# Cost-effectiveness of the coronary sinus Reducer and its impact on the healthcare burden of refractory angina patients

**Running Title**: Results from three European countries' perspective

Guglielmo Gallone MD[1], Patrizio Armeni PhD[2], Stefan Verheye MD[3], Pierfrancesco Agostoni MD[4], Leo Timmers MD[5], Gianluca Campo MD[6], Alfonso Ielasi MD[7], Fabio Sgura MD[8], Giuseppe Tarantini MD[9], Liesbeth Rosseel MD[3], Carlo Zivelonghi MD[4], Geert Leenders MD[5], Pieter Stella MD[5], Matteo Tebaldi MD[6], Maurizio Tespili MD[7], Gianpiero D'Amico MD[9], Luca Baldetti MD[1], Francesco Ponticelli MD[1], Antonio Colombo MD[6], Francesco Giannini MD[6]

*1 Unit of Cardiovascular Interventions, IRCCS San Raffaele Scientific Institute, Milan, Italy*
*2 SDA Bocconi School of Management and CERGAS (Centre for Research on Social and Healthcare Management) Bocconi University, Milan, Italy*
*3 Cardiovascular Center, Ziekenhuis Netwerk Antwerpen Middelheim, Antwerp, Belgium*
*4 Department of Cardiology, Sint Antonius Ziekenhuis, Nieuwegein, The Netherlands*
*5 Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands*
*6 Cardiovascular Institute, Azienda Ospedaliero-Universitaria di Ferrara, Cona, Italy and Maria Cecilia Hospital, GVM Care & Research, E.S: Health Science Foundation, Cotignola, Italy*
*7 Division of Cardiology, ASST Bergamo Est, "Bolognini" Hospital, Seriate, Italy and Interventional Cardiology Unit, Sant'Ambrogio Cardio-Thoracic Center, Milan, Italy*
*8 Institute of Cardiology, Policlinico Hospital, University of Modena and Reggio Emilia, Italy*
*9 Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Padua, Italy*

**Word count: 4134**

**Conflict of interest**: F. Giannini is a consultant for Neovasc Inc. S. Verheye is a consultant for Neovasc Inc. P. Agostoni is a consultant for Neovasc Inc. The other authors have no conflicts of interest to declare.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author(s) 2019.
For permissions please email: journals.permissions@oup.com.



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

**Corresponding Author:**

Francesco Giannini, MD

GVM Care & Research Maria Cecilia Hospital, Cotignola, Italy;

1, Via Madonna di Genova, 48033, Cotignola, Italy

Tel: 0545 217111

E-mail: giannini_fra@yahoo.it

Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

## Abstract

### Aims

The Coronary Sinus Reducer is a percutaneous device proven to improve angina symptoms in refractory angina (RA). We evaluated its potential cost-effectiveness and impact on the healthcare resource use.

### Methods and Results

Angina-related healthcare resource usage and quality-of-life data were collected for 215 consecutive RA patients undergoing Reducer implantion in Belgium, The Netherlands and Italy. Costs were assessed from each country's healthcare system perspective. Data from the date of RA diagnosis to Reducer implantation (Standard-of-Care [SoC]-period) and from Reducer implantation to follow-up (Reducer-period) were compared: during Reducer-period a significant reduction in angina-driven hospitalizations, outpatient vists, coronary angiograms and percutaneous coronary interventions per patient-year was observed, translating into significantly reduced costs per patient-year.

To assess cost-effectiveness, costs and utilities of one-year SoC were compared with those of one-year Reducer-period. Assumptions on Reducer efficacy duration were further explored with modeled projections. Reducer was associated with higher quality-adjusted-life-years (QALYs: 0.665 vs 0.580, $p<0.001$) and incremental costs, yielding incremental cost-effectiveness ratios (ICERs) of 53197, 34948, 63146 €/QALY gained in Belgium, Netherlands and Italy, respectively. Under both the assumptions of 2 and 3 years Reducer effect duration with a 30%-year efficacy decrease, the device yielded ICERs in the range of 1977 - 20796 €/QALY gained.

### Conclusions

In patients with RA, Reducer device decreases healthcare resource use and related costs. In a limited 1-year timeframe, Reducer is consistently cost-effective according to a range of cost-


Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

effectiveness thresholds. Under the explored assumptions, the device yields cost-effectiveness ratios suggesting high-value from all the considered perspectives.

Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

## Key words

chronic refractory angina, coronary sinus reducer, cost-effectiveness, healthcare costs, quality of life

## Introduction

Patients with coronary artery disease (CAD) not amenable to revascularization, who continue to experience angina despite optimal medical therapy may represent up to 10% of all angina patients (1). The number is likely to increase as the population ages and mortality from CAD decreases (2). This population, often described as having refractory angina (RA), does not suffer from excess mortality compared with the overall stable CAD population (3,4), but experiences a significant reduction in quality of life and a substantial increase in the utilization of healthcare resources and related costs (4,5). Several novel therapeuric approaches have been described to address this unmet clinical need. Beyond clinical efficacy, their economic impact on national healthcare systems is key to wide clinical implementation. However, data in this sense are substantially lacking.

The coronary sinus (CS) Reducer (Neovasc Inc., Richmond B.C., Canada) is a stainless steel, ballon-expandable, hourglass-shaped device, which is implanted percutaneously in the CS to create a focal narrowing across it. The subsequent elevation of backward pressure results in redistribution of coronary arterial blood flow from the well perfused epicardium to the ischemic subendocardial layers, thus increasing oxygen supply and leading to symptom relief (6). The clinical evidence has consistently shown the CS Reducer to be a safe and effective treatment to reduce symptoms and to improve quality of life in RA patients (7–10).

In the European Union, € 18.8 billion/year is the estimated total healthcare cost related to coronary heart disease (CHD) (11). In the United States, CHD is one of the 10 most expensive hospital discharge diagnoses accounting for $10.4 billion/year and, as an effect of CAD mortality decline, its costs are estimated to duplicate by the year 2030 (2). As the healthcare burden of CHD is strictly related to unmet symptom control (12), the achievement of the therapeutic symptomatic goal should translate in reduced healthcare costs. Specifically, angina pectoris may account for over 1% of the economic burden of a healthcare system (13), RA representing a considerable proportion of these costs.



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

With these premises, we performed a retrospective evaluation to examine if the CS Reducer, beyond its clinical efficacy may also reduce the healthcare resource used for RA patients and the associated costs, possibly resulting to be a cost-effective solution. This multicenter international registry includes the largest series of patients treated with CS Reducer device to date.

## Methods

This retrospective, observational, multicenter international study included 215 consecutive patients who underwent Reducer implantation for the treatment of RA at eight medical centers in Belgium, The Netherlands and Italy (**Table 1S**) between September 2010 and December 2017.

Patients suffering from severe RA (Canadian Cardiovascular Society [CCS] classes 2-4) despite maximally tolerated medical therapy and considered not amenable for further percutaneous or surgical revascularization procedures by the local Heart Team were treated with Reducer implantation. Pre-implant objective demonstration of myocardial ischemia with either treadmill/pharmacologic stress test, myocardial stress scintigraphy, stress echocardiography or myocardial magnetic resonance was mandatory.

Specific contraindications for implantation (as defined by the manufacturer) were: recent acute coronary syndrome (<3 months), recent coronary revascularization (<6 months) or a mean right atrial pressure higher than 15 mmHg.

The study complies with the Declaration of Helsinki, the locally appointed ethics committee have approved the research protocol and all patients provided written informed consent to Reducer implantation. CS Reducer implantation procedure has been previously described (6).

### Quality of life

Health status related to angina was assessed directly from patients prior to the Reducer implant and from the last face-to-face clinical follow-up. When available, health status data at 6 months and 1 year were also collected. Each assessment was performed with either the use of the



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

Seattle Angina Questionnaire (SAQ) (14) or the EuroQOL health status instrument (EQ-5D)(15), according to each Center's practice.

**Healthcare resource use and costs**

Healthcare resource use associated with the Reducer implantation and with the observation period, lasting from RA diagnosis to last follow-up, were collected retrospectively for all patients by electronic medical records, telephone interview and face-to-face clinical follow-up. Emergency department (ED) admissions, hospitalizations, days of hospitalizations, coronary angiographies, percutaneous coronary interventions (PCI) and outpatient visits, that were driven by angina, were quantified for each patient and reported in 2017 Euro currency.

Costs were assessed adopting a third-party payer perspective, from the viewpoint of each of the healthcare systems of the Centers participating in the study (Belgium, the Netherlands, and Italy). Each event was assigned a cost based on national tariffs associated to the specific Diagnosis Related Group (DRG). The estimated costs for each country are reported in **Table 2S** in the Data Supplement. Reducer device was assigned a cost of 7000 Euro, based on the producer (Neovasc Inc., Richmond B.C., Canada) indication, plus the cost of Reducer implant, estimated as the cost of the DRG for an elective PCI procedure, as in current practice.

**Cost-consequences and cost-effectiveness analyses**

To evaluate the impact of the Reducer on the healthcare burden of RA patients, healthcare resource use and the related costs during the period going from the date of RA diagnosis to Reducer implant (from now on "Standard of Care (SoC) period") and the period going from Reducer implant to last available follow-up (from now on "Reducer period") were compared. Date of RA diagnosis was defined as the first time, in the history of a CAD patient on optimal medical therapy, that revascularization was deemed unfeasible (16). Further elective revascularizations may have happened after RA diagnosis as a consequence of CAD progression or referral to a different center



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

with diverse technical expertise, available technologies or risk-benefit threshold of intervention. We then performed a cost-consequences analysis and a cost-effectiveness analysis (CEA) (17).

*Cost-consequences analysis.* Disaggregated data on healthcare resource use and the related costs are presented in patient-year fashion. Descriptive data are presented for all patients. The comparative analysis was conducted in patients with data of SoC and Reducer periods each of at least 6-month duration in order to avoid analytic biases. Analyses evaluating different observation periods in both patient-year and fixed follow-up fashions were further carried out in order to assess the robustness of data results.

*Cost-effectiveness analysis*. The study population was categorized according to the observation period in the "Reducer group" (post-implant period) and the "SoC group" (pre-implant period), the latter reflecting current clinical practice in RA. The cost-effectiveness of Reducer was assessed using quality-adjusted life years (QALYs) as measures of health benefit, and the expenses of angina-related healthcare resource use as costs. All costs were discounted at 3% annually, as currently recommended (18). A decision-tree analysis was applied to model the events (probabilities), costs and QALYs in the first 12 months, for which we had recorded data **(Figure 1)**. A Markov model-based extrapolation was then run, conceptualizing the course of the disease in terms of mutually exclusive health states (alive / dead) and the possible transitions among them, for obtaining data at 24 and 36 months according to the different explored assumptions. The rate of failed Reducer implant was considered and included in the analysis according to the intention-to-treat. The 1-year mortality rate was estimated using the Kaplan-Meier method on the observed data, for the Reducer group, and from the widest available contemporary registry reporting RA patient mortality rates, for the SoC group (3). QALYs were derived from angina-related quality of life as assessed by the SAQ or the EQ-5D instrument. Utility weights (range 0 to 1, higher=better health) from SAQ were obtained using a mapping algorithm developed to translate SAQ scores in EQ-5D utilities and validated in CHD populations with a wide range of disease severity and following various interventions (19,20). Utility weights from EQ5D were obtained using an algorithm



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

developed from the Dutch population (21). In the SoC group, only SAQ at baseline was available for most patients. Based on the assumption that SAQ scores of RA patients on SoC treatment tends to remain steady over a 1-year horizon (22–24), QALYs of the SoC group were estimated as the time-weighted average of the baseline utility value. In the Reducer group, when SAQ at 1 year was unavailable, SAQ at 6 months was used to estimate utilities at 1 year. This was based on the observation of steady score improvement from baseline between the 6-month and 1-year timepoints assessments in our cohort (**Figure 1S**, Data Supplement). A utility value of 0 was applied to patients who died. Utility weights for the Markov model were obtained for the two groups as marginal effects of a linear regression on longitudinal data (pre-post) were the dependent variable was utility weight and the independent variable was the treatment status (equivalent to the pre-post period). The marginal effect estimated in the pre-implant period was used as a proxy for the utility scores of SOC patients, while the marginal effect estimated in the post-implant period was applied to Reducer patients. Total costs for both health states were computed as the sum of expected costs (resource use weighted by their probability) generated by a patient during one cycle of the model (1 year).

Costs and utilities between the groups were compared, and the cost-effectiveness of Reducer was expressed as incremental cost-effectiveness ratio (ICER), defined as the difference in cumulative costs of Reducer and SoC groups divided by the difference in cumulative QALYs of Reducer and SoC groups. Fixed observation periods of 1 year starting from the Reducer implant and going forward (Reducer group) and backward (SoC group) were considered in the analysis. Patients with available data satisfying either or both time-period requirements were included in either or both groups, respectively.

The cost-effectiveness of Reducer was assessed over several time-from-implant-horizons, exploring different assumptions on the duration of Reducer efficacy on both QALY and healthcare resources use: (a) for the base case (observed data at 1 year); (b) at 2 and (c) at 3 years from implant,

Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

assuming the observed Reducer effect at 1 year on costs and utilities to decrease at a 30%/year rate and to vanish after 2 and 3 years from implant, respectively.

Uncertainty due to parameter estimation was demonstrated by calculation of cost-effectiveness acceptability curves (CEACs). The curve plots the probability that Reducer is cost-effective, compared with SoC, against any given cost-effectiveness or societal willingness to pay (WTP) threshold for 1 QALY gain. Specifically, we considered the cost-effectiveness threshold, defined by the World Health Organization (WHO) (25), of an ICER less than 3 times the gross domestic product (GDP) per capita for each country (2016 GDP estimates) , and the Dutch societal WTP threshold estimated for our RA population as 50000 €/QALY gained, based on the economic model of the Institute for Medical Technology Assessment Disease Burden and calculated with their online toll (26), which takes into account the burden of disease as expressed by the proportion of normal quality-adjusted life expectancy lost because of the condition related to the disease as currently treated in daily practice (27). No formal specific WTP thresholds are provided by Italian and Belgian health economic guidelines (28,29), based on the principle that thresholds are subject to the available health care budget and the interventions already financed in a country.

**Statistical analysis**

Categorical variables are reported as frequencies. Continuous variables are described as mean and standard deviations or as median and interquartile ranges, as appropriate. Normality was checked by the Kolmogorov-Smirnov test. The baseline and follow-up measurements were compared using t-tests and the two-sided Wilcoxon Rank Sum or Signed Rank tests, as appropriate. In the CEA, unit costs were multiplied times the predicted frequency of healthcare resource use-related events. For obtaining the CEACs we conducted a probabilistic sensitivity analysis using Monte-Carlo simulations (5000 scenarios). We assumed a uniform distribution for survival, a

Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

lognormal distribution for utility weights and a gamma distribution for costs (30). Ranges, confidence intervals and standard errors were derived from our database.

All analyses were performed using STATA (version SE 15, StataCorp LLC, College Station, Texas) , SPSS Statistics (version 20, IBM Corporation, Armonk, NY, USA), and Excel (2016, Microsoft, Redmond, Washington, USA).

## Results

### Baseline characteristics

A total of 215 patients underwent Reducer implantation procedure. Baseline characteristics are summarized in **Table 1**. Median age was 68 (63-75) years with 56.3% males. CAD risk factors were highly prevalent. Of all patients, 70.1% had history of coronary artery by-pass grafting (CABG) and 80.5% of PCI. There was a high prevalence of 3-vessel CAD (68.2%).

All patients experienced disabling angina symptoms, with 11.2% patients in CCS class 2, 67.4% in CCS class 3 and 21.4% in CCS class 4. Patients were treated according to maximally indicated/tolerated number of drugs or doses, with 53.4% of patients in therapy with at least three anti-ischemic medications.

### Clinical outcomes

Procedural success was achieved in 211 (98.1%) patients. Reducer implantation was not achieved in 4 (1.9%) patients because of CS unfavorable anatomy, device migration occurred in one of these cases, treated by successful snaring and no adverse clinical events. No other intra-procedural or follow-up adverse events associated with Reducer implantation occurred.

A median 15 months (range 8-23 months) follow-up was available for the 211 patients with successful Reducer implantation. Overall, a total of 15 (7.1%) non-fatal myocardial infarction (MI)



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

and 21 (9.9%) deaths were recorded, among which 10 (4.7%) were of cardiovascular origin (3 fatal MI, 1 arrhythmic, 6 end-stage heart failure).

Baseline and follow-up information regarding CCS angina class was available for all patients. Compared to baseline, angina severity at follow-up was significantly reduced (CCS: 3 [3-3] to 2 [1-2], p<0.001). Among 117 (55.5%) patients with available SAQ (median time of last SAQ assessment from baseline: 13 [8-18] months), an improvement in all five domain scores was observed (physical limitation: 47 [35-55] to 57 [47-52], p<0.001; angina stability: 40 [25-43] to 60 [40-80], p<0.001; angina frequency: 50 [40-63] to 61 [50-83], p<0.001; treatment satisfaction: 48 [34-73] to 80 [70-82], p<0.001; quality of life: 29 [17-40] to 62 [47-75], p<0.001) (**Figure 2**). This benefit was reflected in a significant reduction of the number of anti-ischemic drugs prescribed for patient (3 [2-3] vs. 2 [2-3]; *p*<0.001).

**Cost-consequences analysis**

Healthcare burden-related data were available for 321.2 patient-years of SoC period (9 months, interquartile range 3-24) and 519.2 patient-years of follow-up after Reducer implantation (15 months, interquartile range 8-23). Overall, during the SoC and Reducer periods 1.3 and 0.2 hospitalizations occurred for angina per patient-year (3.4 and 1.0 total hospitalization days per patient-year), 0.2 and 0.1 ED admissions for angina per patient-year, 1.0 and 0.2 coronary angiographies for angina per patient-year, 0.3 and 0.1 PCI for angina per patient-year, 2.1 and 0.7 outpatient visits for angina per patient-year, respectively. This translated into healthcare costs for patient-year of 6255 and 1467 € (Belgian perspective), 3888 and 946 € (Dutch perspective), 7159 and 1403 € (Italian perspective) during the SoC and Reducer periods, respectively.

Healthcare burden-related events and the associated costs were compared in patients with at least 6-month SoC and Reducer observation periods (n=119; SoC period: 203.5 patient-years, Reducer period: 469.2 patient-years) (**Figure 3**). A reduction in healthcare burden-related events was observed: hospitalization for angina per patient-year 1.0 (0.0-2.0) vs 0.0 (0.0-0.5), p<0.001



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

(total hospitalization days per patient-year 3.6 (1.3-7.8) vs 0.0 (0.0-1.7), p<0.001); ED admissions for angina per patient-year 0.0 (0.0-0.0) vs 0.0 (0.0-0.0), p=ns; coronary angiographies for angina per patient-year 0.8 (0.3-1.5) vs 0.0 (0.0-0.0) p<0.001, PCI for angina per patient-year 0.0 (0.0-0.4) vs 0.0 (0.0-0.0), p=0.029; outpatient visits for angina per patient-year 2.1 (1.1-3.3) vs 1.3 (0.4-2.3), p<0.001.

This translated into a significant reduction of the associated costs from all the three healthcare system perspectives: Belgian, 4143 (1970-9347) € vs 312 (97-3209) €, p<0.001; Dutch, 3079 (1441-6990) € vs 121 (37-2342) €, p<0.001; Italian, 4175 (2009-3210) € vs 194 (58-2786) €, p<0.001.

Similar results were displayed when the analysis was limited to fixed 6-month pre- vs 6-month post-implantation periods, when only patients with at least 12-month pre-implant and post-implant periods were considered, and when, in this subgroup, the analysis was limited to the year pre- vs the year post-implantation (**Table 3S**, Data Supplement).

**Cost-effectiveness analysis**

One-hundred-three and 143 RA patients with available healthcare resource use data for at least 1 year of SoC and 1 year following Reducer implantation were included in the CEA and formed the SoC group and Reducer group, respectively. Seventy-eight patients with available data for both the SoC and Reducer time periods were included in both groups. No differences in baseline characteristics were observed between groups (**Table 4S**, Data Supplement). Utility values were available for 76 (73.8%; n=54 SAQ-derived, n=22 EQ-5D derived) and 97 (67.8%; n=75 SAQ-derived; n=22 EQ5D-derived) patients of the SoC and Reducer groups, respectively.

Cost-effectiveness results are summarized in **Table 2.** At 1 year from baseline QALY and costs were higher in the Reducer group (QALY: 0.594 vs 0.456; p<0.001, Costs: 15179 vs 7540 € [Belgium], 10008 vs 5185 € [Netherlands], 15702 vs 6988 € [Italy]; p for all <0.001), resulting in ICERs for Reducer implant over SoC treatment of 55356 €/QALY gained (Belgium), 34948



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

€/QALY gained (Netherlands), 63146 €/QALY gained (Italy). The associated simulations under the WHO cost-effectiveness thresholds were 99.9%, 100.0% and 93.3%, respectively, and under the cost-effectiveness threshold of 50000 €/QALY gained were 40.0%, 96.0% and 16.0%, respectively **(Figure 4)**.

When the observed Reducer effect on costs and QALY at 1 year was assumed to decrease of 30%/year and to vanish after 2 and 3 years from implant, the respective resulting ICERs were 14905 and 1977 €/QALY gained (Belgium), 10169 and 2968 €/QALY gained (Netherlands), 20796 and 6614 €/QALY gained (Italy). The associated simulations under the WHO and 50000 €/QALY gained cost-effectiveness thresholds were 100% in all cases **(Figure 4)**

## Discussion

The main findings of the study are that: (1) Reducer device reduces the healthcare burden of RA patients and the associated costs across a range of European healthcare system perspectives; (2) despite the limited 1-year timeframe of our analysis, Reducer appears to be cost-effective according to the WHO cost-effectiveness thresholds, and, in the Netherlands, also according to the Dutch societal WTP threshold. If the 1-year observed effect of Reducer on costs and QALY is assumed to last for 2 or 3 years with a 30%-year effect reduction on costs and utilities, the device yields cost-effectiveness ratios suggesting high-value from all the considered perspectives.

RA incidence is estimated to be in the range of 50000-100000 new cases/year in United States and 30000-50000 new cases/year in Europe (1,31) representing a substantial public and social health issue. In our analysis, RA patients produced extremely high healthcare resource use despite 85.8% were on at least two anti-ischemic drugs and 53.4% on at least three. Our observations are consistent with previous reports of RA populations, that show similar amounts of angina-related hospitalizations (4,5,32,33).



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

After Reducer implantation, a significant and consistent decrease in angina-driven hospitalizations, coronary angiographies, PCI and outpatient visits occurred, translating into reduced healthcare costs from the Belgian, Dutch and Italian healthcare system perspectives. In our cohort, 43% of the patients underwent Reducer implantation within 6 months from RA diagnosis. While providing overall descriptive data, these patients were not included in the comparative cost-consequences analysis due to their short, non-representative period under SoC treatment. The results of the cost-consequences analysis were robust and remained significant in the analyses with fixed observation periods of 6 and 12 months, and in patients with at least 12-month SoC and Reducer observation periods, standing for a sustained Reducer effect over time on the healthcare resource use. Moreover, the previously described clinical efficacy in terms of anginal symptoms burden reduction and quality of life improvement (7,34,35) was confirmed in our cohort, which includes the largest series of patients treated with Reducer to date.

In our study, the RA diagnosis date was defined as the first time, in the history of a CAD patient on optimal medical therapy, that revascularization was deemed unfeasible. This was based on the practical view that, provided widespread availability of the Reducer treatment option across interventional cardiology units, its implant would be considered in this clinical setting. The concept of non-eligibility for revascularization is challenging, and consensus is often difficult (36,37). In our RA population, we found that 11.4% patient-year underwent PCI during the overall observation period. This observation reflects, beyond acute coronary syndromes, the progressive nature of CAD, which may lead to new treatable lesions, and RA diagnosis subjectivity (38). While a definition of RA diagnosis that takes into account specific anatomical and clinical criteria may better suit studies designed to investigate other research issues (36), we believe that the adopted pragmatic definition is the most appropriate for an economic evaluation, reflecting potential Centers' preference for a device with high feasibility and procedural safety in RA patients (34,35), who are often characterized by complex coronary anatomy and high-risk clinical features. Furthermore, our study design appears very conservative for the purpose of the economic



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

evaluation. The nature of CAD, its clinical manifestation and the associated healthcare resource use are progressive (5). Accordingly, the economic benefit showed in our analysis would have likely been greater if Reducer was implanted at the time of RA diagnosis, as it may happen with a wider diffusion of the device utilization.

Using a cost of 7000 € for the Reducer device as indicated by the producer, plus the procedural cost of an elective PCI, this study estimated 1-year ICERs for Reducer versus SoC of 55356 €/QALY gained (Belgium), 34948 €/QALY gained (Netherlands), 63146 €/QALY gained (Italy).

These ICERs are all well below three times the national annual GDP per capita, thus representing cost-effectiveness according to WHO guideline definition. The Dutch guideline for economic evaluations in healthcare (27) recommend a WTP threshold based on the burden of disease, calculated for our RA population as 50000 €/QALY gained. Reducer resulted to be cost-effective in Netherlands also according to this internally defined threshold.

In the CEA, we limited the observation period to 1 year due to substantial lack of cost and utility data beyond this moment. This timeframe may not fully capture the Reducer's effect on costs and QALYs, which may last longer, thus affecting cost-effectiveness. Because there is no clinical evidence to inform the long-term outcomes of Reducer compared with SoC, we explored two different assumptions regarding Reducer effect, in a time-horizons of 2-3 years from implant. Under both, the device yielded ICERs in the range of 1977 €/QALY gained - 20796 €/QALY gained suggesting high-value across all the considered perspectives. Studies reporting on longer-terms Reducer efficacy are warranted to clarify which assumption best suit reality.

Despite far from conclusiveness, our analysis gives insight on the potential of a new device to bring clinical and healthcare value in the disabling and onerous condition of RA and enables assessment of convergent validity of results across different countries and healthcare systems.

Of note, only one small randomized sham-controlled study supporting the clinical efficacy of Reducer has been carried to date (7). Even if real-word experience appears very consistent, further evidence in this sense is advisable.



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

Several limitations of this CEA will need to be addressed in future studies. First, we did not consider drug costs, indirect costs and the broader effects of Reducer from a societal perspective (18). Accounting for these variables would have likely demonstrated further benefit: a reduction in the number of prescribed anti-ischemic drugs was observed following Reducer implant, and the reported reduction in hospitalizations, invasive procedures and outpatient visits would have probably translated in reduced transportation, patient-time and unpaid lost productivity costs, largely counterbalancing those related to Reducer implant.

Second, we assessed Reducer cost-effectiveness against the SoC of patients from the same cohort prior to Reducer implant, rather than using a formal control group as it is customary in CEA.

However, this approach (driven by the limited data existing on healthcare resource use of RA patients) allows to consider groups with homogeneous baseline characteristics, and is also rather conservative in estimating cost-effectiveness: indeed, it compares two consecutive periods of the natural history of RA, being Reducer follow-up the more advanced. Third, data were collected retrospectively. Because of this reason, we had incomplete information regarding the elective/urgent nature of PCI procedures. We thus estimated PCI costs on the basis of the elective procedure DRG, possibly causing slight underestimation of the overall costs. However, this is unlikely to have favored Reducer cost-effectiveness estimate, as Reducer is not associated with excess urgent revascularizations (7,34,35), and urgent revascularization rates are likely to have been similar between the SoC and Reducer groups.

## Conclusions

In patients with severe angina refractory to optimal medical therapy and not amenable for further revascularization, the Reducer device reduces the healthcare resource use and the associated costs. In a limited 1-year timeframe, Reducer is consistently cost-effective across the considered countries and range of cost-effectiveness thresholds. Under both the assumptions of a Reducer



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

effect duration for 2 and 3 years from implant with a 30%-year efficacy decrease, the device yields cost-effectiveness ratios suggesting high-value from all the considered perspectives.

Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

## References


1. Mannheimer C, Camici P, Chester MR, Collins A, DeJongste M, Eliasson T, et al. The problem of chronic refractory angina: Report from the ESC Joint Study Group on the treatment of refractory angina. Eur Heart J. 2002;23(5):355–70.

2. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart Disease and Stroke Statistics'2017 Update: A Report from the American Heart Association. Vol. 135, Circulation. 2017. 146-603 p.

3. Henry TD, Satran D, Hodges JS, Johnson RK, Poulose AK, Campbell AR, et al. Long-term survival in patients with refractory angina. Eur Heart J. 2013;34(34):2683–8.

4. Povsic TJ, Broderick S, Anstrom KJ, Shaw LK, Ohman EM, Eisenstein EL, et al. Predictors of long-term clinical endpoints in patients with refractory angina. J Am Heart Assoc. 2015;4(2):1–12.

5. Yu W, Maru F, Edner M, Hellstrom K, Kahan T, Persson H. Spinal cord stimulation for refractory angina pectoris: a retrospective analysis of efficacy and cost-benefit. Coron Artery Dis. 2004;15(1):31–7.

6. Konigstein M, Giannini F, Banai S. The Reducer device in patients with angina pectoris: mechanisms, indications, and perspectives. Eur Heart J. 2017;

7. Verheye S, Jolicœur EM, Behan MW, Pettersson T, Sainsbury P, Hill J, et al. Efficacy of a Device to Narrow the Coronary Sinus in Refractory Angina. N Engl J Med. 2015;372(6):519–27.

8. Abawi M, Nijhoff F, Stella PR, Voskuil M, Benedetto D, Doevendans PA, et al. Safety and efficacy of a device to narrow the coronary sinus for the treatment of refractory angina: A single-centre real-world experience. Netherlands Hear J. 2016;24(9):544–51.

9. Benedetto D, Abawi M, Stella PR, Nijhoff F, Lakemeier MDM, Kortlandt F, et al. Percutaneous Device to Narrow the Coronary Sinus: Shifting Paradigm in the Treatment of Refractory Angina? A Review of the Literature. Front Cardiovasc Med. 2016;3.

10. Giannini F, Baldetti L, Konigstein M, Rosseel L, Ruparelia N, Gallone G, et al. Safety and efficacy of the reducer: A multi-center clinical registry - REDUCE study. Int J Cardiol. Elsevier B.V.; 2018;269:40–4.

11. Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, et al. European Cardiovascular Disease Statistics 2017. Eur Hear Netw. 2017;192.

12. Arnold S V., Morrow DA, Lei Y, Cohen DJ, Mahoney EM, Braunwald E, et al. Economic impact of angina after an acute coronary syndrome insights from the merlin-timi 36 trial. Circ Cardiovasc Qual Outcomes. 2009;2(4):344–53.

13. Stewart S, Murphy NF, Walker a, McGuire a, McMurray JJ V. The current cost of angina pectoris to the National Health Service in the UK. Heart. 2003;89(8):848–53.

14. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonnell M, et al. Development and evaluation of the Seattle Angina questionnaire: A new functional status




Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

measure for coronary artery disease. J Am Coll Cardiol. 1995;25(2):333–41.

15. https://euroqol.org.

16. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease - addenda. Eur Heart J. 2013;34(38):2949–3003.

17. NeumannPJ, SandersGD, RussellLB, SiegelJE, Ganiats TG E. Cost-Effectiveness in Health and Medicine. 2nd ed. Oxford University Press. 2016;

18. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. Vol. 316, JAMA - Journal of the American Medical Association. 2016. p. 1093–103.

19. Wijeysundera HC, Tomlinson G, Norris CM, Ghali WA, Ko DT, Krahn MD. Predicting EQ-5D utility scores from the Seattle Angina Questionnaire in coronary artery disease: A mapping algorithm using a Bayesian framework. Med Decis Mak. 2011;31(3):481–93.

20. Wijeysundera HC, Farshchi-Zarabi S, Witteman W, Bennell MC. Conversion of the Seattle Angina questionnaire into EQ-5D utilities for ischemic heart disease: A systematic review and catalog of the literature. Clin Outcomes Res. 2014;6(1):253–68.

21. Matthijs M. Versteegh, PhD1,*, Karin M. Vermeulen, PhD2, Silvia M. A. A. Evers, PhD3, 4, G. Ardine de Wit, PhD5, 6, Rilana Prenger, PhD7, Elly A. Stolk P. Dutch Tariff for the Five-Level Version of EQ-5D. VALUE Heal. 2016;

22. Burkhoff D, Schmidt S, Schulman SP, Myers J, Resar J, Becker LC, et al. Transmyocardial laser revascularisation compared with continued medical therapy for treatment of refractory angina pectoris: a prospective randomised trial. Lancet. 1999;354(9182):885–90.

23. Oesterle SN, Sanborn TA, Ali N, Resar J, Ramee SR, Heuser R, et al. Percutaneous transmyocardial laser revascularisation for severe angina: The PACIFIC randomised trial. Lancet. 2000;356(9243):1705–10.

24. Khan TZ, Hsu L-Y, Arai AE, Rhodes S, Pottle A, Wage R, et al. Apheresis as novel treatment for refractory angina with raised lipoprotein(a): a randomized controlled cross-over trial. Eur Heart J. 2017;38(20):1561–9.

25. WHO-CHOICE. Making choices in health: WHO guide to cost-effectiveness analysis. Glob Program Evid Heal Policy ,World Heal Organ Geneva. 2003;71.

26. Institute for Medical Technology Assessment. The iMTA Disease Burden Calculator (iDBC) for proportional shortfall and fair innings for The Netherlands [Internet]. [cited 2018 May 20]. Available from: www.imta.nl/idbc

27. Zorginstituut Nederland. Guidelines for economic evaluations in healthcare. 2016.

28. Cleemput I, Neyt M, Van de Sande S, Thiry N. BHCKC. Belgian guidelines for economic evaluations and budget impact analyses: second edition. Heal Technol Assess (HTA) KCE Rep 183C D/2012/10273/54. 2012;1–94.

Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

29. Fattore G. Proposta di linee guida per la valutazione economica degli interventi sanitari in Italia. PharmacoEconomics Ital Res Artic. 2009;11(2):83–93.

30. Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, et al. Probabilistic sensitivity analysis for NICE technology assessment: Not an optional extra. Vol. 14, Health Economics. 2005. p. 339–47.

31. Mukherjee D, Bhatt DL, Roe MT, Patel V, Ellis SG. Direct myocardial revascularization and angiogenesis--how many patients might be eligible? Am J Cardiol. 1999;84(5):598–600, A8.

32. Williams B, Menon M, Satran D, Hayward D, Hodges JS, Burke N, et al. Patients with coronary artery disease not amenable to traditional revascularization: Prevalence and 3-year mortality. Catheter Cardiovasc Interv. 2010;75(6):886–91.

33. Lawson WE, Hui JCK, Kennard ED, Linnemeier G. Enhanced External Counterpulsation is Cost-Effective in Reducing Hospital Costs in Refractory Angina Patients. Clin Cardiol. 2015;38(6):344–9.

34. Giannini F, Baldetti L, Ponticelli F, Ruparelia N, Mitomo S, Latib A, et al. Coronary Sinus Reducer Implantation for the Treatment of Chronic Refractory Angina: A Single-Center Experience. JACC Cardiovasc Interv. 2018;11(8):784–92.

35. Konigstein M, Bazan S, Revivo M, Banai S. Coronary Sinus Reducer implantation improves symptoms, ischemia and physical capacity in patients with refractory angina unsuitable for myocardial revascularization: A single center experience. EuroIntervention. 2018;

36. Jolicoeur EM, Cartier R, Henry TD, Barsness GW, Bourassa MG, McGillion M, et al. Patients With Coronary Artery Disease Unsuitable for Revascularization: Definition, General Principles, and a Classification. Can J Cardiol. Elsevier Inc.; 2012;28(2 SUPPL.):S50–9.

37. Kornowski R. Refractory myocardial angina and determinants of prognosis. Catheter Cardiovasc Interv. 2010;75(6):892–4.

38. Jolicoeur EM, Ohman EM, Temple R, Stockbridge N, Smith S, Mark D, et al. Clinical and research issues regarding chronic advanced coronary artery disease Part II: Trial design, outcomes, and regulatory issues. Am Heart J. 2008;155(3):435–44.

Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

## Figure legends

**Figure 1 -** Schematic representation model to inform the cost-effectiveness analysis. The transition probabilities between health states (alive/dead) are Kaplan-Meier estimates derived from the observed data of our registry (Reducer group) and from the greatest and more recent registry of RA patients available (SoC group) (3). The rate of failed Reducer implant was considered and included in the analysis according to the intention-to-treat. ICER, incremental cost-effectivenes ratio; QALY, quality-adjusted life-year; SoC, Standard of Care.

**Figure 2 –** CCS class and SAQ score variations after Reducer implantation. CCS, Canadian Cardiovascular Society; SAQ, Seattle Angina Questionnaire.

**Figure 3 -** Healthcare burden-related events of refractory angina patients and associated costs with Standard of Care treatment and after Reducer implantation. ED, emergency department; PCI, percutaneous coronary intervention.

**Figure 4 -** Cost-Effectiveness of the Reducer in refractory angina patients. Joint distribution of incremental costs and quality-adjusted life years for Reducer versus Standard of Care (first line) and cost-effectiveness acceptability curves (second line) for the base case (blue) and under different assumptions: Reducer efficacy at base case decreases at 30%/year rate and there is no effect beyond 2 years from implant (red); Reducer efficacy at base case decreases at 30%/year rate and there is no effect beyond 3 years from implant (green).
The dashed red line represents World Health Organization cost-effectiveness threshold for each country estimated as three times the GDP per capita (GDP estimates 2016: Belgium 37274 €, Netherlands 41259 €, Italy 27363 €); the dashed blue line represent Dutch guideline cost-effectiveness threshold (50000 €/QALY gained). Abbreviations as in Figure 1.



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

# Tables

**Table 1 -** Baseline clinical characteristics

| | Number of patients (total = 215) |
|---|---|
| **Patient characteristic** | |
| Age – years (IQR) | 68 (63-75) |
| Male – no (%) | 121 (56.3) |
| Arterial hypertension – no (%) | 180 (80.9) |
| Diabetes mellitus – no (%) | 91 (42.4) |
| Dyslipidemia – no (%) | 184 (85.6) |
| Current or previous smoking – no (%) | 64 (29.7) |
| Familial coronary artery disease – no (%) | 93 (43.3) |
| Atrial fibrillation – no (%) | 28 (13.0) |
| Previous pacemaker – no (%) | 20 (9.3) |
| Glomerular filtration rate– ml/min (IQR) | 69 (54-84) |
| Chronic obstructive pulmonary disease (%) | 22 (10.0) |
| 3-vessel coronary artery disease – no (%) | 147 (68.2) |
| Previous MI – no (%) | 122 (56.8) |
| Previous PCI – no (%) | 173 (80.5) |
| Previous CABG – no (%) | 150 (70.1) |
| Previous stroke – no (%) | 18 (8.4) |
| Previous PAD – no (%) | 44 (20.4) |
| **CCS angina class** | |
| 2 – no (%) | 24 (11.2) |
| 3 – no (%) | 145 (67.4) |
| 4 – no (%) | 46 (21.4) |
| **Quality of life scores** | |
| SAQ Physical limitation- points (IQR) | 47 (35-55) |
| SAQ Angina stability – points (IQR) | 40 (25-43) |
| SAQ Angina frequency – points (IQR) | 50 (40-63) |
| SAQ Treatment satisfaction – points (IQR) | 48 (34-73) |
| SAQ Quality of life – points (IQR) | 29 (17-40) |
| EQ-5D index (IQR) | 0.449 (0.235-0.774) |
| **Baseline therapy** | |
| Beta blockers (%) | 168 (78.2) |
| Calcium channel blockers (%) | 117 (54.5) |
| Nitrates (%) | 143 (66.5) |
| Ivabradine (%) | 39 (18.1) |
| Ranolazine (%) | 69 (31.9) |
| Number of anti-ischemic drugs (IQR) | 3 (2-3) |

CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; EQ-5D = EuroQOL health status instrument; IQR = interquartile range; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SAQ = Seattle angina questionnaire.

Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

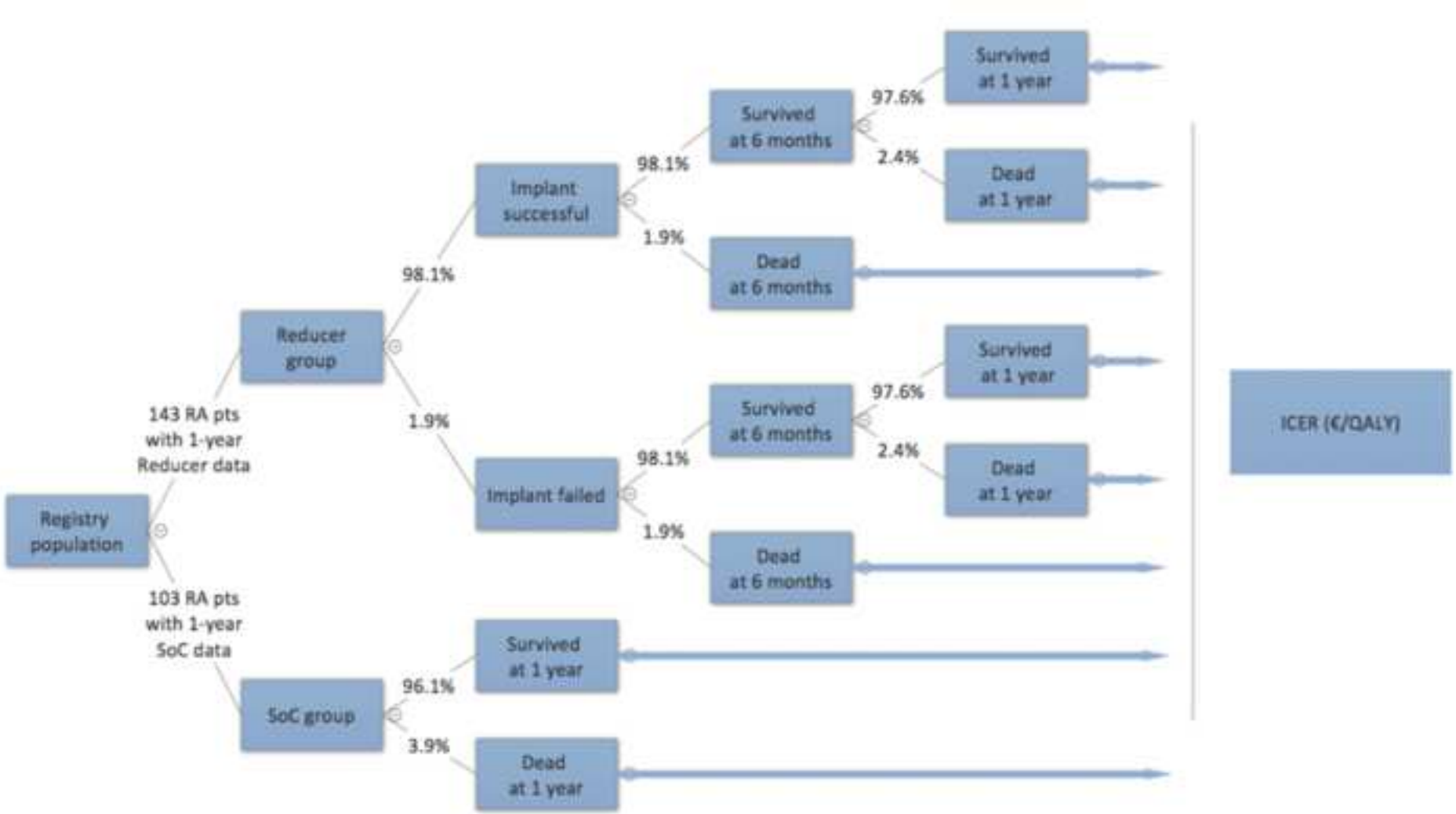
**Table 2 -** Cost-effectiveness results

| | Cost with Reducer (€) | Cost with SoC (€) | Δ cost (€) | QALY with Reducer | QALY with SoC | Δ QALY | ICER (€/QALY) | %< WHO thresholds | %< Dutch threshold |
|---|---|---|---|---|---|---|---|---|---|
| **Base case** (1-year observation) | | | | | | | | | |
| Belgium | 15179 | 7540 | 7639 | | | | 53197 | 99.9 | - |
| Netherlands | 10008 | 5185 | 4823 | 0.594 | 0.456 | 0,138 | 34948 | 100.0 | 96.0 |
| Italy | 15702 | 6988 | 8714 | | | | 63146 | 93.3 | - |
| **2 years** (30%/yr effect reduction on costs and utilities) | | | | | | | | | |
| Belgium | 18577 | 15081 | 3497 | | | | 15053 | 100.0 | - |
| Netherlands | 12755 | 10369 | 2386 | 1.147 | 0.912 | 0.235 | 9554 | 100.0 | 100.0 |
| Italy | 18854 | 13975 | 4879 | | | | 23641 | 100.0 | - |
| **3 years** (30%/yr effect reduction on costs and utilities) | | | | | | | | | |
| Belgium | 23300 | 22621 | 679 | | | | -10071 | 100.0 | - |
| Netherlands | 16754 | 15554 | 1020 | 1.712 | 1.368 | 0.344 | -6291 | 100.0 | 100.0 |
| Italy | 23235 | 20963 | 2273 | | | | -2862 | 100.0 | - |

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted-life-year; SoC = standard of care.

Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

Figure 1

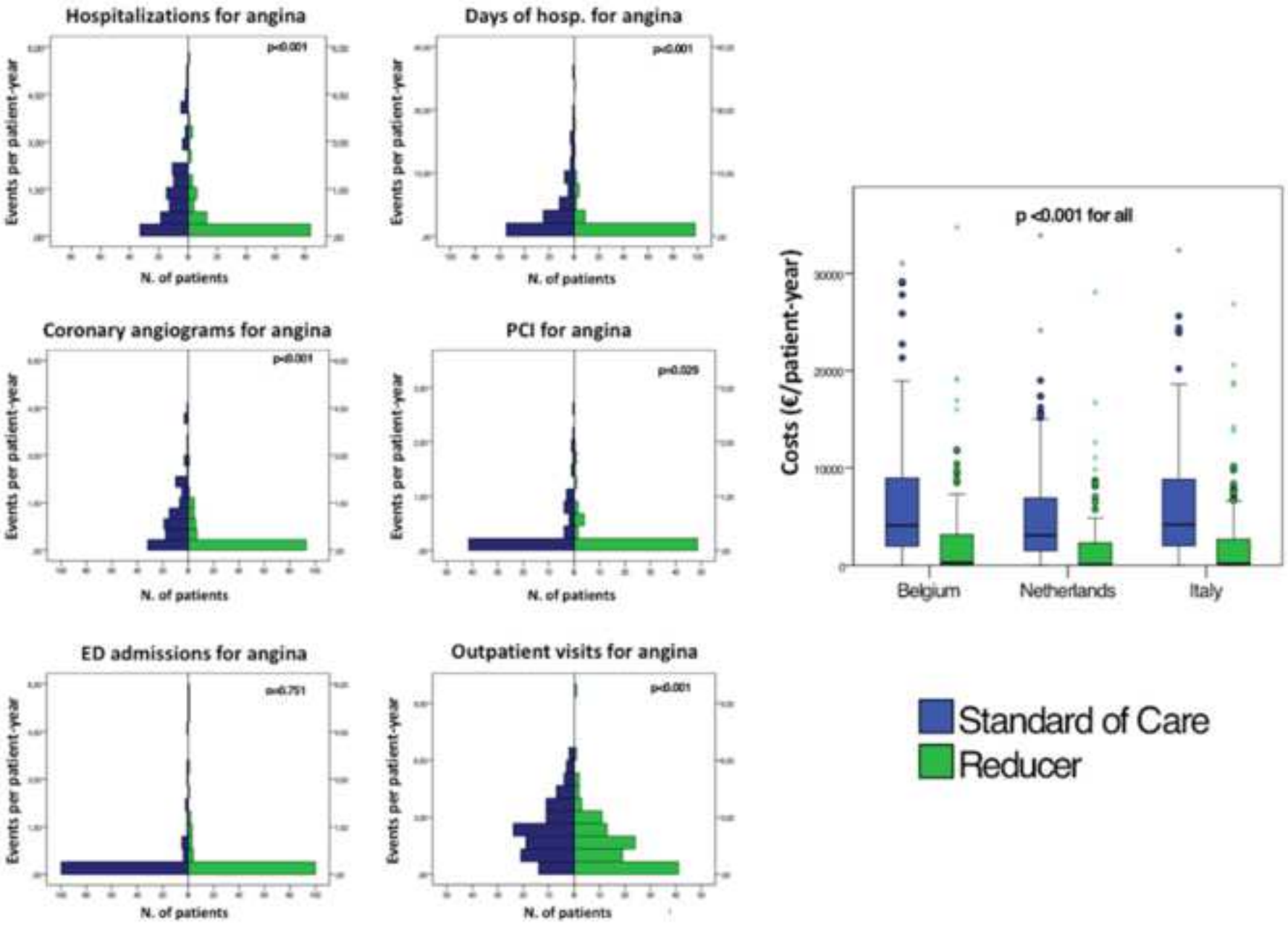



Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

Figure 2

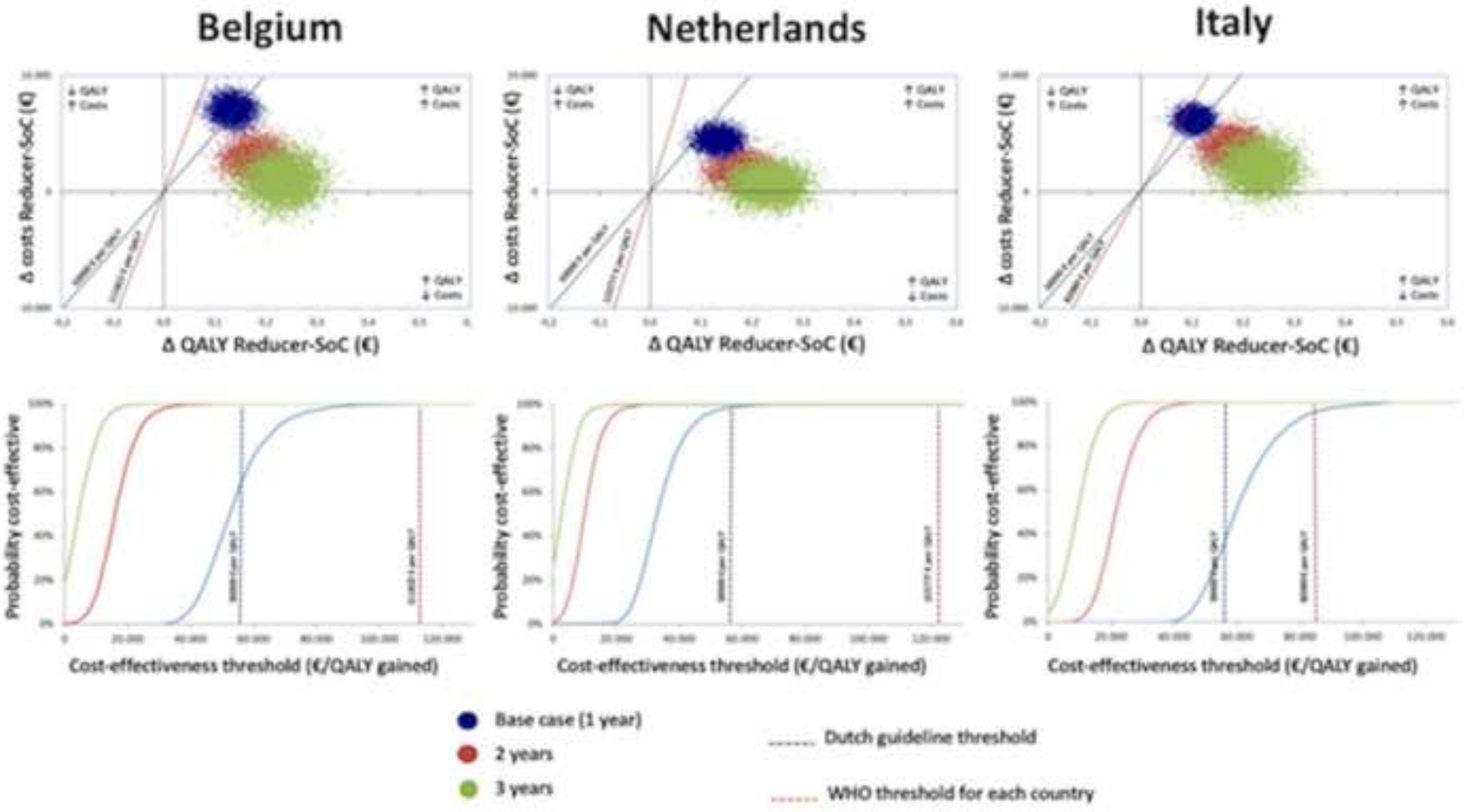

Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

Figure 3




Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019

Figure 4




Downloaded from https://academic.oup.com/ehjqcco/advance-article-abstract/doi/10.1093/ehjqcco/qcz027/5498149 by Stockholm University Library user on 28 May 2019