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## Long-term Cost-effectiveness of Endoscopic vs Open Vein Harvest for Coronary Artery Bypass Grafting

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### Abstract

**Background:** The greater saphenous vein is frequently used as a conduit for coronary artery bypass grafting (CABG). Previously, veins were most often harvested using open vein harvesting (OVH), however, endoscopic vein harvesting (EVH) techniques have become increasingly popular. Nevertheless, the long-term cost-effectiveness of EVH remains unknown. The present study estimated the long-term cost-effectiveness of EVH versus OVH for CABG.

**Methods:** A Markov model was developed to estimate life-time costs (UK Pounds Sterling) and quality adjusted life-years (QALYs) with comparative results presented as incremental cost-effectiveness ratios (ICERs). Costs and probabilities of events in the OVH group were mainly drawn from a previously published study. Resource consumption and event probabilities in the EVH group were estimated using a meta-analysis to reflect the best available evidence. Parameter uncertainty was assessed using both one-way sensitivity analyses and probabilistic sensitivity analyses.

**Results:** The life-time cost/QALY was £8219 rendering EVH cost-effective compared to OVH. Sensitivity analyses showed that EVH was cost-effective in 60.4% of simulations at a threshold of £30 000/QALY, reflecting a large uncertainty in the point estimate of the ICER. The main causes of uncertainty were the time-horizon and the event rates of major clinical events in the treatment groups.

**Conclusions:** Current evidence indicates that EVH is cost-effective for harvesting saphenous vein segments for CABG compared to OVH. Further studies on long-term clinical outcomes are needed to reach a more precise cost-effectiveness estimate.

**Keywords:** CABG; Venous grafts; Endoscopy/endoscopic procedures; Health economics; Quality of life; Postoperative care

### Introduction

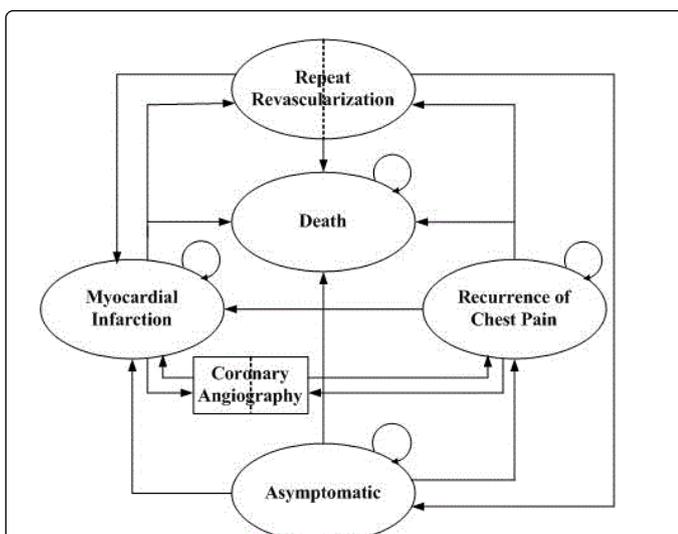
The short-term effectiveness and long-term safety of endoscopic vein harvesting (EVH) versus traditional open vein harvesting (OVH) of saphenous vein conduits for coronary artery bypass grafting (CABG) has been investigated rigorously. Meta-analysis of the clinical evidence show that EVH is a short-term benefit as leg wound morbidity, infections, and pain is reduced without compromising the long-term safety as no differences were observed in the recurrence of chest pain, myocardial infarctions, and all-cause mortality [1-3]. Previous economic evaluations of EVH versus OVH have looked at costs and outcomes five to six weeks postoperatively [4,5]. Such a short time-horizon is suitable for an economic evaluation if costs and outcomes can be considered equal between treatment groups after the period in which they are compared [6]. Still, no studies have estimated the long-term (e.g. life-time) cost-effectiveness of EVH compared to OVH although several reviews have called for a more rigorous cost-effectiveness analysis [1,7,8]. Therefore, the present study estimated both the short-term and the life-time cost-effectiveness of EVH of saphenous vein as a conduit for CABG using total endoscopic methods

compared to OVH using a single continuous incision. This was done to provide essential information for the decision about vein harvesting method and to exemplify the importance of choosing the appropriate time horizon in cost-effective analysis.

### Materials and Methods

#### Model overview

A decision-analytic model was developed to estimate costs and quality adjusted life-years (QALYs) from the perspective of the Danish Healthcare System. The model was constructed as a Markov model with a cycle length of three months, see Figure 1 and the figure legend for a description of the model (Figure 1). The cohort was CABG patients aged 65 years and 80% male gender. The base-case model captured life-time costs and QALYs while an alternative scenario considered costs and QALYs within three months postoperatively. All costs and QALYs accrued beyond the first year were discounted using an annual rate of 3.5% [9].



**Figure 1:** Structure of decision-analytic model. The postoperative course for patients treated with coronary artery bypass grafting using the saphenous vein as a conduit harvested by endoscopic or open technique is modelled in this Markov model. All patients enter the model in the health state “Asymptomatic” symbolizing that the symptoms of coronary artery disease disappeared following surgery. Cycles represent health states while boxes represent events which may occur in the health state which has an arrow leading to it. The health state “Repeat Revascularization” does not have an arrow leading back into the health state which means that patients only stay in this health state for a single cycle (three months). The stippled lines indicate that patients exit to the side where they entered.

### Event probabilities

As recommended by international guidelines for cost-effectiveness analysis [10]; the estimates of treatment effectiveness are based on the formal evidence syntheses of a meta-analysis [1]. Event probabilities for the Markov model are shown in Table 1. A Danish randomized trial was used to calculate event probabilities in the OVH group [11]. Event probabilities in the EVH group were then estimated by utilizing the odds ratios and rate ratios from a meta-analysis [1]. The 95% confidence intervals (CIs) of the odds ratios and rate ratios were utilized to estimate the parameter uncertainty. The mortality rate for the patients in the health state “Asymptomatic” was modelled using Danish life tables while patients in health states “Recurrence of Chest Pain”, “Myocardial Infarction” and “Repeat Revascularization” were assumed to have a higher mortality rate [12-16]. In both treatment groups it was assumed that patients with recurrence of chest pain had a hazard ratio for all-cause mortality of 1.29 (95% CI 0.89 to 1.87) compared to asymptomatic CABG patients [12,15]. Likewise, it was estimated that patients experiencing a myocardial infarction or a repeat revascularization had a hazard ratio for all-cause mortality of 7.82 compared to asymptomatic CABG patients [12,16].

### QALYs

All health states in the Markov model were assigned a health-related quality of life (HRQoL) value and the time spent in each health state

was multiplied with the HRQoL value to calculate QALYs. To estimate HRQoL values for patients during the first three months postoperatively, a mapping model was utilized [17]. Pain intensity and mobility problems measured on visual analogue scales (VASs) were drawn from the best available evidence and mapped to Danish EQ-5D-3L index scores to obtain the difference in HRQoL [1,18]. The input for estimating short-term effectiveness, i.e. during the first cycle of the Markov model, is summarized in Table 2. In the Markov model the HRQoL values for the chronic conditions were drawn from Danish and American community based preference weights [19,20]. Temporary HRQoL decrements for repeat revascularization were drawn from a previous cost-effectiveness comparing CABG and stenting [21]. In the Markov model the HRQoL for health states other than “Asymptomatic” were estimated using the decrements shown in Table 3. For an example, the mean HRQoL in the health state “Myocardial Infarction” in the 20th cycle, i.e. five years postoperatively, would be  $0.87-5 \times 0.0008-0.148 = 0.718$ .

### Costs

The mean resource consumption was combined with the unit costs to estimate the total cost per patient. The resource consumption in the OVH group was mainly estimated from a Danish randomized trial [11]. The summary statistics from a meta-analysis was used to estimate the resource consumption in the EVH group [1]. The base-case analysis assumes that surgeons are trained in EVH and that the wards have already purchased the video-equipment. As such, the base-case analysis views the cost of video equipment and training as sunk costs and does not include these in the analyses. To estimate the unit costs of repeat revascularizations it was assumed that 42.9% of these were performed as CABGs and the remaining as percutaneous coronary interventions. Estimates of resources consumed are summarized in Table 4.

All costs were measured in 2014 values of Danish Crowns and subsequently reported in Great British Pound Sterling (£1 GBP = 9.16 DKK). In the absence of information about the parameter uncertainty in unit costs an alpha and a beta were approximated assuming a standard error of  $\pm 10\%$  of the mean. Unit costs drawn from previous studies were inflated to 2014 values using a yearly inflation rate of 2%. All unit costs are shown in Table 5.

### Analyses

Two scenarios were constructed to investigate the cost-effectiveness of EVH compared to OVH. The two scenarios were based on two different interpretations of the long-term clinical outcomes following EVH and OVH. The base-case analysis applied a Bayesian interpretation of the uncertainty in the data. This interpretation of clinical evidence is the default in health economic evaluations [22]. It entails perceiving the point estimate as our best available guess of the parameter value and the CI as a range which the parameter has a 95% probability of lying within. The alternative scenario assumes that the existing evidence confirms non-inferiority of EVH compared to OVH regarding the long-term clinical endpoint considered in Table 2. In this alternative scenario the model assumes no long-term differences in the recurrence of chest pain, myocardial infarction, repeat coronary angiography, repeat revascularization, or death; i.e. odds ratios and rate ratios presented in Table 1 are replaced by 1.00 (95% CI: 1.0; 1.0). The alternative scenario is therefore a comparison of costs and QALYs within the first three month postoperatively.

In each scenario the cost-effectiveness of EVH compared to OVH was calculated as the incremental cost-effectiveness ratio (ICER). The ICER expresses the expected additional cost of obtaining one additional QALY. To capture the uncertainty in the estimation of the ICER, one-way sensitivity analyses were conducted. The five most important parameters in the one-way sensitivity analyses were presented in Tornado diagrams. To assess the joint uncertainty in all parameters, probabilistic sensitivity analysis was conducted using

second order Monte Carlo simulation. Based on the output cost-effectiveness acceptability curves (CEACs) were drawn. The CEACs were used to assess the probability of EVH being cost-effective compared to OVH at increasing threshold values [22]. The UK threshold of £30 000/QALY was used to assess the cost-effectiveness of EVH compared to OVH [9]. The decision-analytic model was developed in Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA).

Probability(transition to  transition from)	Expected Value in OVH group [Source]	Expected Value in EVH group (95% CI) [Source]	Distribution*
P(Chest pain   Asymptomatic) until 5 years	0.0286 [28]	0.0280 (0.0180; 0.0436) [1]	Lognormal
P(Chest pain   Asymptomatic) after 5 years	0.0028 [28]	0.0028 (0.0018; 0.0044) [1]	Lognormal
P(MI   Asymptomatic) until 0.25 years	0.0292 [29]	0.0328 (0.0215; 0.0496) [1]	Lognormal
P(MI   Asymptomatic) from 0.25-5 years	0.0029 [15,29]	0.0033 (0.0022; 0.0051) [1]	Lognormal
P(MI   Asymptomatic) after 5 years	0.0011 [15]	0.0012 (0.0008; 0.0019) [1]	Lognormal
P(MI   Chest pain) until 5 years	0.0083 [15]	0.0093 (0.0061; 0.0142) [1]	Lognormal
P(MI   Chest pain) after 5 years	0.0033 [15]	0.0037 (0.0024; 0.0057) [1]	Lognormal
P(Death   Asymptomatic) until 0.25 years	0.0317 [11]	0.0293 (0.0244; 0.0352) [1]	Lognormal
P(Death   Asymptomatic) after 0.25 years	Life-table [12]	RR of all-cause mortality applied to life-table [1]	Lognormal
P(Repeat Revascularization   Chest pain)	0.0124 [15]	0.0150 (0.0127; 0.0176) [1]	Lognormal
P(Repeat Revascularization   MI)	0.0310 [30]	0.0373 (0.0316; 0.0439) [1]	Lognormal
P(Coronary Angiography   Chest pain)	0.0070 [30]	0.0074 (0.0047; 0.0117) [1]	Lognormal
P(Coronary Angiography   MI)	0.0070 [30]	0.0074 (0.0047; 0.0117) [1]	Lognormal

CI = confidence interval; EVH = endoscopic vein harvesting; MI = myocardial infarction; OVH = open vein harvesting; P = probability; RR = rate ratio; \*The distribution is the distribution applied to the odds ratios and rate ratios from the meta-analysis.

**Table 1:** Transition probabilities for the Markov model

Quality of life outcome	Expected Value in OVH group (95% CI) [Source]	Expected Value in EVH group (95% CI) [Source]	Distribution
<b>Non-preference-based measures of health mapped</b>			
Pain on a VAS at day 5, mm	28.7 [17]	13.9 (4.2; 23.7) [1,17]	Normal
Mobility on a VAS at day 5, mm	36.0 [18]	12.0 [18]	Fixed
Pain on a VAS at day 30, mm	16.1 [17]	13.3 (10.1; 16.5) [1,17]	Normal
Mobility on a VAS at day 30, mm	30.0 [18]	2.0 [18]	Fixed
<b>Health-related quality of life estimates for patients in the "Asymptomatic" health state</b>			
Baseline	0.756 (0.727; 0.785) [17]	0.756 (0.727; 0.785) [17]	Normal
Postoperative day 5	0.636 (0.607; 0.665) [17]	0.685 (0.655; 0.715) [1,17,18]	Normal
Postoperative day 30	0.785 (0.756; 0.815) [17]	0.809 (0.780; 0.840) [1,17,18]	Normal
Three months postoperative	0.87 [31]	0.87 [31]	Fixed

CI = confidence interval; Endoscopic vein harvesting; OVH = open vein harvesting; VAS = visual analogue scale

**Table 2:** Health-related quality of life estimates during the first cycle of the Markov model

Health states	Expected Value in both group (95% CI)[Source]	Distribution
Reduction for myocardial infarction	-0.148 (-0.186; -0.109) [20]	Normal
Reduction for chest pain	-0.168 (-0.205; -0.130) [20]	Normal
Reduction per additional year	-0.0008 (-0.001; -0.0006) [19]	Normal
Temporary reduction for repeat revascularization by percutaneous coronary intervention	-0.04 (-0.05; -0.03) [21]	Normal
Temporary reduction for repeat revascularization by coronary artery bypass grafting	-0.09 (-0.12; -0.07) [21]	Normal

CI = confidence interval

**Table 3:** Health-related quality of life decrements used in health states of the Markov model

Type of resource consumption	Expected Value in OVH group[Source]	Expected Value in EVH group (95% CI)[Source]	Distribution
P(Single use equipment)	0	1	Fixed
Duration of surgery, minutes	216 [11]	231 (219; 243) [1,11]	Normal
Length of stay in intensive care unit, days	2.79 [1]	2.84 (2.57; 3.10) [1,11]	Normal
Length of stay in ward, days	11.5 [4]	11.0 (10.5; 11.4) [1,4]	Normal
P(Beside leg wound revision)	0.020 [11]	0.009 (0.005; 0.015) [1,11]	Lognormal
P(Leg wound revision in operating room)	0.010 [11]	0.004 (0.003; 0.007) [1,11]	Lognormal
P(Visit from home care nurse)	0.063 [11]	0.006 (0.003; 0.014) [1,11]	Lognormal
No. of visits per patient	7.5 [11]	7.5 [11]	Fixed
P(Visit to general practitioner)	0.143 [11]	0.046 (0.028; 0.074) [1,11]	Lognormal
No. of visits per patient	4.3 [11]	4.3 [11]	Fixed
P(Antibiotic treatment)	0.095 [11]	0.026 (0.020; 0.034) [1,11]	Lognormal
P(Readmission)	0.016 [11]	0.010 (0.007; 0.014) [1,11]	Lognormal

CI = confidence interval; EVH = Endoscopic vein harvesting; OVH = open vein harvesting; P() = probability of resource being consumed

**Table 4:** Resource consumption

Description of resource	Mean [Source]	Distribution (Alpha; Beta)
Single use equipment	£504 [4]	Gamma (100; 5.04)
Duration of surgery, per minute	£14.6 [5]	Gamma (100; 0.15)
Length of stay in intensive care unit, per day	£2550 [32]	Gamma (100; 25.5)
Length of stay in ward, per day	£569 [32]	Gamma (100; 5.69)
Leg wound revision without general anesthesia	£147 [4]	Gamma (100; 1.47)
Leg wound revision in general anesthesia	£643 [4]	Gamma (100; 6.43)
Readmission	£2509 [33,34]	Gamma (100; 25.1)
Visit from home care nurse	£52.5 [4,35,36]	Gamma (100; 0.53)
Visit to general practitioner	£41.5 [37]	Gamma (100; 0.42)
Course of antibiotic treatment	£48.5 [4]	Gamma (100; 0.49)
Transition cost to the "Myocardial Infarction" state	£6861 [33,34]	Gamma (100; 68.6)
Transition cost to the "Coronary Angiography" state	£334 [38]	Gamma (100; 3.34)
Transition cost to the "Repeat Revascularization" state	£13 880 [33,34]	Gamma (100; 139)
Transition cost to the "Death" state	£1556 [33,34]	Gamma (100; 15.6)
Three month healthcare costs in the "Asymptomatic" state	£344 [39]	Gamma (136; 2.35)
Three month healthcare costs in the "Myocardial Infarction" state	£939 [39]	Gamma (17; 51.2)
Three month healthcare costs in the "Recurrence of Chest Pain" state	£779 [40]	Gamma (6.24; 125)

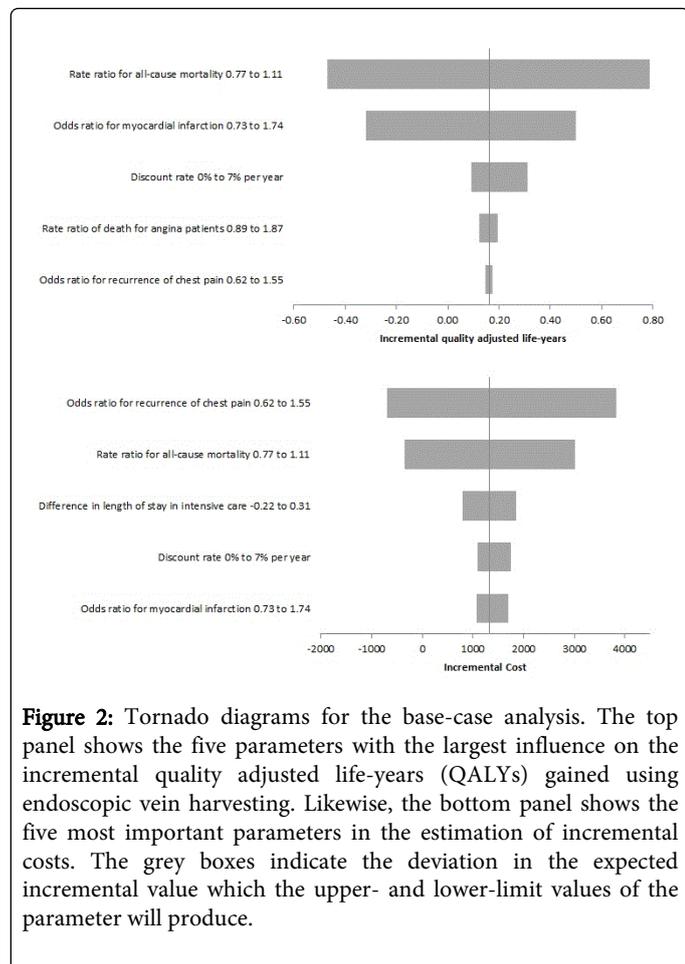
**Table 5:** Unit costs of resources consumed

## Results

In the base-case analysis, EVH was cost-effective compared to OVH. EVH had an estimated incremental cost of £1325 per patient and an incremental effectiveness of 0.1612 QALY per patient, i.e. the ICER was £8219/QALY. The probabilistic sensitivity analysis revealed that the cost-effectiveness results from the base-case analysis contained a large uncertainty around the ICER. In the base-case analysis, EVH had a 60.4% probability of being cost-effective at £30 000/QALY threshold. The probability of EVH being cost-effective becomes 63.2% at a threshold of £100 000/QALY. One-way sensitivity analyses showed that the rate ratio for long-term all-cause mortality was the most important parameter for the incremental effectiveness of treatments. Likewise, the odds ratio of recurrence of chest pain was the parameter with the largest influence on the incremental cost of treatments. The remaining parameters identified as important for incremental cost and effectiveness are shown in the Tornado diagrams in Figure 2.

In the alternative scenario the ICER was £93 419/QALY and probabilistic sensitivity analysis showed a 20.2% probability of EVH

being cost-effective at the £30 000/QALY threshold. The alternative scenario showed an incremental QALY gain of 0.0048 QALY per patient within three months postoperatively. The incremental cost at three months postoperatively was £444 per patient.



**Figure 2:** Tornado diagrams for the base-case analysis. The top panel shows the five parameters with the largest influence on the incremental quality adjusted life-years (QALYs) gained using endoscopic vein harvesting. Likewise, the bottom panel shows the five most important parameters in the estimation of incremental costs. The grey boxes indicate the deviation in the expected incremental value which the upper- and lower-limit values of the parameter will produce.

## Discussion

The present study showed that EVH of saphenous vein segments for CABG was cost-effective compared to OVH. Although the economic evaluation is based on the best evidence currently available, i.e. a meta-analysis, the result is uncertain [1]. The base-case showed a large uncertainty in the cost-effectiveness result which was mainly attributed to the uncertainties in differences of long-term event-rates of major clinical event. To accommodate that some clinicians assume that the harvesting methods are completely equal in terms of long-term event-rates of major clinical events; an alternative scenario only considered costs and QALYs within three months postoperatively. Under this assumption, EVH was not cost-effective compared to OVH. The main difference between the base-case and the alternative scenario is that the QALY gain is much larger in the base-case than in the alternative scenario. The best evidence currently available on long-term outcomes show a slight survival benefit of using EVH compared to OVH. Although this difference is not statistically significant, the base-case applies the point-estimate as it is the current best evidence [1].

While the present study investigated the cost-effectiveness of EVH from the Danish health system's perspective, many European cardiothoracic wards might be more concerned with the question of how technologies such as EVH impact their budget. We found no evidence that costs, at a departmental level, are reduced by using EVH rather than OVH. As such, EVH will increase spending at departments of cardiothoracic surgery. However, the additional money spent on EVH can be considered 'good value for money' as our analysis showed that EVH is cost-effective compared to OVH from the Danish healthcare system's perspective. To assess whether this result is transferable to other jurisdictions it is ideal to perform a formal evaluation using one of several tools to assess transferability [23-25]. It should be noted that the decision analytic model was informed with data from a meta-analysis which included published data from a variety of countries and that the results of the present economic evaluation therefore is likely to be generalizable to a number of jurisdictions.

Two studies have investigated the short-term cost-effectiveness of EVH or minimal invasive vein harvesting compared to OVH [4,5]. Rao et al. performed decision analytic modeling and estimated that minimal invasive vein harvesting was cost-effective compared to conventional harvesting within six weeks postoperatively [5]. In a cost-effectiveness analysis alongside a randomized trial, Oddershede et al. concluded that EVH was not cost-effective compared to OVH within the first five weeks postoperatively [4]. Both previous studies estimated the short-term QALY gain using mapping methods which were not based on a statistical algorithm. As such, large differences in short-term incremental QALYs could be expected. Rao et al. estimated a gain of 0.0232 QALY within six weeks postoperatively and Oddershede et al. estimated a gain of 0.0027 QALY within five weeks postoperatively. The present study estimated the incremental QALY within three months postoperatively using a published mapping algorithm and found an incremental gain of 0.0048 QALY. These inconsistent estimates illustrate the need for trial-based investigations of short-term QALY gains. Fortunately, two forthcoming randomized controlled trials will be collecting information on HRQoL until two years postoperatively [26,27].

## Limitations

Although the present study is based on the current best available evidence, it would have benefitted greatly from more data on the long-term occurrence of major clinical events. The uncertainties in the odds ratios and rate ratios for occurrence of major clinical events were the main reasons for the uncertainties in incremental costs and QALYs.

In addition, the economic evaluation performed in this study did not include costs of training surgeons in the use of EVH and the cost of the video equipment. This means that the analyses inform the decision of whether a Danish ward for cardiothoracic surgery should continue to use EVH or switch back to OVH. If decision makers are interested in assessing the cost-effectiveness of changing from their current use of OVH to EVH, an additional cost of \$93.21 US dollar should be expected in the EVH group [4].

Furthermore, the present study is limited by the fact that it did not consider costs from a societal perspective. The narrow healthcare sector perspective means that potential saving for the patients on analgesics, transportation, etc. have been overlooked. More so, it is reasonable to believe that EVH might enable some patients to return to work a bit sooner than OVH. Any difference in productivity is not

included in the analysis when a healthcare sector perspective is applied. It is, however, unlikely that these matters would have a large impact on the results.

Another important limitation in the present study is the fact that extrapolations had to be performed to estimate life-time costs and QALYs. One of the important implications of such extrapolations is that is based on the best current knowledge about the long-term patency of grafts harvested by EVH and OVH. Although, some studies have published results on long-term outcomes following EVH and OVH most were not RCTs and none had more than 5 years follow-up [1]. As such, more RCT designed to provide long-term data are needed to assess if there are equivalency patency of graft following EVH and OVH. In addition, this will help to reduce the uncertainty in the extrapolations that must be performed. Extrapolation is a necessary evil in cost-effectiveness research and we based our assumptions on the best available evidence [1], as recommended by current guidelines for economic evaluations [10].

In conclusion, the current evidence indicates that EVH is the cost-effective method for harvesting saphenous vein segments for CABG. However, if equivalency in long-term clinical outcomes between harvesting methods is assumed, EVH is unlikely to be cost-effective compared to OVH. As such, further studies on long-term clinical outcomes are needed to reach a more precise cost-effectiveness estimate.

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