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# Impact of Secondary Cardiovascular Events on Health Status

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ABSTRACT

**Objectives:** Estimates regarding the impact of secondary cardiovascular events on health status in patients treated for cardiovascular disease are scarce and of limited accuracy. **Methods:** We obtained individual patient data on health status (EuroQol five-dimensional questionnaire) and secondary cardiovascular events (death, myocardial infarction, cerebrovascular accidents, amputation, extracranial bleeding, and reinterventions) observed during 12 to 36 months of follow-up. Data originated from five completed clinical trials on revascularization in coronary heart disease ($n$ = 2593) or peripheral arterial disease (PAD; $n$ = 1379). We used linear mixed-effects modeling to estimate the acute impact of the initial secondary event and the health status before and after the event. **Results:** A total of 1595 patients had at least one secondary event. Loss of health status just before the event ranged from 0.36 utility score for amputation in women with PAD to zero for cerebrovascular accident in men with PAD. In patients with coronary heart disease, pre-event health status loss ranged from 0.34 for extracranial bleeding in women to 0.10 for myocardial infarction in women. The acute impact of secondary events ranged from minor deterioration for cerebrovascular accident (−0.03) to improvement after all other events, ranging from +0.01 for occlusion to +0.22 for amputation. Women had significantly lower pre-event scores than did men: −0.04 to −0.10 in coronary heart disease and −0.04 to −0.27 in PAD. Older patients had mostly large but insignificantly lower pre-event scores than did younger patients (range +0.04 to −0.67). **Conclusions:** Secondary events after revascularization in patients with cardiovascular disease are associated with health status loss before the event, while acute impact of the events was mostly small.

*Keywords:* cardiovascular events, coronary heart diseases, health status, individual patient data, peripheral vascular disease, outcome assessment (health care), technology assessment.



## Introduction

Patients with advanced cardiovascular disease are often treated with invasive interventions, such as angioplasty or bypass grafting. The short-term efficacy and cost-effectiveness of these interventions is well documented [1–8].

Economic evaluation based on actual long-term individual patient data, however, is both difficult and costly. Generally, estimates of long-term cost-effectiveness are obtained by using a modeling approach where various sources of evidence are integrated. A widely used outcome measure in cost-effectiveness studies is a combination of quantity and quality of life: the well-known quality-adjusted life-year (QALY). One of the challenges in long-term economic modeling is the uncertainty surrounding the estimates that are used in the model. Sources and methods of obtaining the estimates for the input parameters vary. This variability may be associated with lack of accuracy in the estimates, for example, when relatively few events are observed. Clearly, all variability in the model parameters will ultimately add to the overall uncertainty regarding the long-term cost-effectiveness [9]. Among the major drivers of long-term cost-effectiveness is the impact of subsequent adverse health outcomes. Both frequency and (dis)utility will ultimately determine the overall outcome. In cardiovascular disorders, rather accurate and validated estimates of the frequency of subsequent events may be obtained through regression-based prognostic models, for example, based on the Framingham study [10]. Also, clinical studies actually recording clinical outcome have been reported [11,12]. In the absence of accurate data on the effect of secondary cardiovascular events, that is, subsequent events that occur after the intervention, considerable uncertainty in modeling long-term outcome will remain. We found only some estimates for cerebrovascular accidents (CVAs) [13–16], which differed in assessment method and values.

A major reason for this lack of accuracy is that individual studies may be powered on expected differences in event rates but still will rarely observe sufficient numbers of specific secondary cardiovascular events to obtain accurate estimates of their individual impacts. Typically, around 10% to 40% of secondary cardiovascular events are anticipated within 1 year in the patients enrolled in a randomized controlled trial on cardiovascular revascularization [17]. These secondary events comprise several types of events, such as death, myocardial infarction (MI), and reinterventions. Thus, only small numbers of

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**Table 1 – Trial description.**

| Study acronym | Study description | Reference |
|---|---|---|
| ARTS | **A**rterial **R**evascularization **T**herapies **S**tudy: Randomized comparison of coronary artery bypass grafting (CABG) vs. percutaneous transluminal coronary angioplasty (PTCA) with stenting in cardiovascular patients requiring coronary revascularization | 2 |
| BENESTENT | Randomized comparison of PTCA with and without stenting in cardiovascular patients requiring coronary | 1 |
| BOA | **B**ypass, **O**ral anticoagulents or **A**spirin study: Randomized comparison of oral anticoagulant therapy vs. aspirin for the prevention of occlusions of infrainguinal bypasses. Health status data were collected from the start of the trial in 593 patients and in the rest of the patients only after a secondary cardiovascular event ($n = 515$). This caused missing data in the period before the event | 5, 18, 19 |
| DIST | **D**utch **I**liac **S**tent **T**rial: Randomized comparison of primary stent placement vs. primary angioplasty followed by selective stent placement in patients with intermittent claudication or critical ischemia caused by stenosis or occlusion in the iliac arteries | 3, 4, 20 |
| OctoPump | Randomized comparison of on-pump CABG vs. off-pump CABG* in cardiovascular patients requiring coronary revascularization, only eligible for CABG | 6, 8, 17 |
| OctoStent | Randomized comparison of PTCA with stent implantation vs. off-pump† CABG in cardiovascular patients requiring coronary revascularization, eligible for PTCA with stent implantation | 7, 17 |

* See Table 2 for study characteristics.

† Off-pump CABG uses the Octopus Tissue Stabilizer, which allows revascularization on the beating heart without needing cardiopulmonary bypass.

specific secondary events are observed, resulting in considerable uncertainty (wide confidence intervals) regarding the estimates of the impact of new events on health status from a single trial.

To overcome this barrier and accurately estimate the impact of secondary cardiovascular events, we set out to pool individual patient data from completed clinical trials on interventions aimed at revascularization in patients with cardiovascular diseases (see trial descriptions in Table 1). The trials were selected to include patients with coronary heart disease (CHD) or peripheral artery disease (PAD).

We report here both the acute impact of having a secondary event and the overall impact, that is, the loss of health status compared with patients without an event.

## Methods

Individual patient data on health status, secondary cardiovascular events, and patient characteristics were obtained from five trials (see Table 1 for full names and descriptions of trials). Three trials recruited patients with CHD: Benestent II [1], ARTS [2], and Octopus [6–8,17]. Two trials included patients with PAD: BOA [5,18,19] and DIST [3,4,20]. All cardiovascular events after the vascular intervention under study are regarded as secondary events. We distinguished the initial secondary event and subsequent events. As there were insufficient further events to fit statistical models, we chose to confine the analyses to the first event after the vascular intervention.

Health status was measured with the EuroQol five-dimensional (EQ-5D) questionnaire [21], once before the vascular intervention and several times after the intervention. The EQ-5D health status instrument comprises five questions—each with three levels—representing five health domains: pain, mood, mobility, self-care, and daily activities. This results in 243 health states. The EQ-5D utility score was computed by using the MVH-A1 algorithm [22]. This algorithm yields a score ranging from −0.594 to +1.00 (full health). A value of zero represents death; negative values imply a health state worse than death. An interaction term adjusts for an extra decrease in utility when one of the dimensions is at the most severe level.

Secondary cardiovascular events included death, MI, CVA, amputation, infrainguinal-vein-graft occlusion, extracranial bleeding, and reinterventions. The latter comprised percutaneous transluminal coronary angioplasty, percutaneous transluminal angioplasty, and coronary artery bypass grafting.

The number of measurements and the length of follow-up were different for the included trials (Table 2). The length of follow-up was between 12 and 36 months.

**Table 2 – Trial characteristics.**

| Trial name | Trial arm | Patient type | N patients | Age | Gender (% male) | Follow-up months |
|---|---|---|---|---|---|---|
| ARTS | CABG | CHD | 600 | 61.2 (9.3) | 76.0 | 1, 6, 12, 36 |
| | PTCA + stent | | 605 | 60.7 (9.6) | 77.0 | |
| BENESTENT | PTCA | CHD | 414 | 58.4 (10.5) | 77.3 | ½, 1, 6, 12 |
| | PTCA + stent | | 413 | 58.1 (10.5) | 80.0 | |
| BOA | Aspirin | PAD | 545 | 67.9 (10.0) | 63.7 | 3, 9, 15, 21, 27, 33 |
| | OAC | | 555 | 68.4 (9.9) | 64.0 | |
| DIST | PTA + primary stent | PAD | 128 | 57.9 (10.2) | 72.7 | 3, 12, 24 |
| | PTA + selective stent | | 121 | 57.9 (10.6) | 71.3 | |
| OctoPump | On-pump CABG | CHD | 123 | 61.2 (9.1) | 70.2 | 1, 3, 12 |
| | Off-pump CABG | | 137 | 60.3 (8.9) | 66.2 | |
| OctoStent | PTCA | CHD | 132 | 60.3 (9.1) | 70.3 | 1, 6, 12 |
| | Off-pump CABG | | 132 | 58.8 (9.9) | 71.8 | |

For abbreviations and acronyms of trial names, see Table 1. CABG, coronary artery bypass grafting; CHD, coronary heart disease; OAC, oral anticoagulant; PAD, peripheral artery disease; PTCA, percutaneous transluminal coronary angioplasty.