ECONOMIC ANALYSIS OF POSTOPERATIVE TROPONIN T SCREENING

MODEL-BASED COST-CONSEQUENCE ANALYSIS OF POSTOPERATIVE TROPONIN T SCREENING IN PATIENTS UNDERGOING NONCARDIAC SURGERY

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TITLE: Model-based cost-consequence analysis of postoperative Troponin T screening in patients undergoing noncardiac surgery

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ABSTRACT

Introduction: Globally, more than 200 million patients undergo major non-cardiac surgery each year and more than 10 million patients will be exposed to postoperative myocardial ischemia, a condition strongly associated with 30-day mortality. The majority of these events go undetected without postoperative Troponin screening.

Methods: We conducted a model-based cost-consequence analysis comparing a postoperative Troponin T screening vs. standard care in patients undergoing noncardiac surgery. In a first model, we evaluated the incremental number of detected perioperative myocardial infarctions and the incremental costs. A second model assessed the effect of the screening and consequent treatment on 1-year survival and the related cost. Model inputs based on the Vascular events In Non-cardiac Surgery patIents cOhort evaluatioN (VISION) Study, a large international cohort. We run probability sensitivity analyses with 5,000 iterations. We conducted extensive sensitivity analyses.

Results: The cost to avoid missing an event amounted to CAD$ 5,184 for PMI and CAD$ 2,983 for isolated Troponin T. The cost-effectiveness of the postoperative Troponin screening was higher in patients' subgroups at higher risk for PMI, e.g. patients undergoing urgent surgery. The incremental costs at 1 year of a postoperative PMI screening by 4 Troponin T measurements were CAD$ 169.20 per screened patient. The cost to prevent a death at 1 year amounted to CAD$ 96,314; however, there was relevant model uncertainty associated with the efficacy of the treatment in the 1-year model.

Conclusion: Based on the estimated incremental cost per health gain, the implementation of a postoperative Troponin T screening after noncardiac surgery seems appealing, in particular in patients at high risk for perioperative myocardial infarction. However, decision-makers will have to consider it in terms of opportunity costs, i.e. in relation to the cost-effectiveness of other potential programs within the broader health care context.

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LIST OF ABBREVIATIONS

ACS: acute coronary syndrome

CABG: coronary artery bypass graft

CADTH: Canadian Agency for Drugs and Technologies in Health

CAD: coronary artery disease

CAD$: Canadian dollars

CBA: cost-benefit analysis

CCA: cost-consequence analysis

CEA: cost-effectiveness analysis

CEAC: cost-effectiveness acceptability curves

CKMB: creatine kinase-MB

CI: confidence interval

CUA: cost-utility analysis

ECG: electrocardiogram

GMP: good modelling practice

HR: hazard ratio

IQR: interquartile range

OCCI: Ontario Case Costing Initiative

PAR: population attributable risk

PCI: percutaneous coronary intervention

PMI: perioperative myocardial infarction

POD: postoperative day

PSA: probabilistic sensitivity analysis

PVD: peripheral vascular disease

QALY: quality-adjusted life years

RCRI: revised cardiac risk inde

RCT: randomized controlled trial

RR: relative risk

VISION: Vascular events In Non-cardiac Surgery patIents cOhort evaluatioN Study

WHO: World Health Organization

1.INTRODUCTION

1.A. ECONOMIC EVALUATIONS OF HEALTH TECHNOLOGIES

1.A.1. Basic concepts

Public health care strives for maximizing health in the population; however the resources available to the provision of health care are limited. Scarcity implies mutually exclusive decisions with regard to resource allocation. The benefits forfeited by other stakeholders in consequence of the allocation decisions are referred to as opportunity costs. The opportunity cost concept can expand across sectors, e.g. health care versus education, or be focused within the health care system, i.e. the allocation of resources to a certain condition will deprive patients affected by other diseases. Under scarcity conditions, decision-making within the health care system will aim at optimizing the balance between health benefits and opportunity cost across patients' population [1]. The goal of economic evaluations of health technologies is to provide decision-makers with "value for money information" [2] through the comparison of health gains and resource consumption of alternative therapeutic, diagnostic or screening interventions [2]. To achieve this objective, a full economic evaluation must fulfill two conditions: compare at least 2 alternatives and address both cost and consequences [3].

In terms of cost, economic evaluations require the identification of consumed resources, their measurement (along a continuum from microcosting to top-down costing) and their valuation. The definition of the perspective and of the time horizon of the analysis is pivotal for resource identification. The broader societal perspective includes direct cost incurred by the public health care system, by other public services (e.g. social services), by the patients, but also indirect cost related to productivity and time losses for the patients, their caregivers (family members or volunteers) and for the training of substitute workers [2, 4]. These resources, in contrast, are not taken into account when a public payer perspective is chosen.

Unresolved methodological questions regarding the use of productivity losses include estimation issues (human capital *versus* friction cost approach), equity concerns, the risk of "double-counting" (productivity gains are taken into account on the cost side as well as implicitly in the valuation of health outcomes), and the differential inclusion of health-specific *versus* non health-specific items on the consequence and on the cost side [3]. In light of these methodological uncertainties, the Canadian Agency for Drugs and Technologies in Health (CADTH) recommends the use of a publicly funded health care system perspective in the reference case or to report productivity-related cost separately if the target audience requires the application of a societal perspective [2].

Over time, costs and health effects of the alternatives may converge, keep parallel or diverge. If they converge or diverge decisions about the time horizon will have major implications on the cost-effectiveness results (over- or underestimation) [3]; as such guidelines on economic evaluation and good modelling practice [2, 5] recommend the use of a long-term time horizon.

Resource valuation in economic evaluations within the health care system often results in a divergence between economic theory and practice. Economic theory requires opportunity cost to be the basis for resource valuation. Market prices correspond, however, to opportunity cost only in a perfectly competitive market. Due to monopoly, cross-subsidization, negotiation of products prices, and fixed professional fees(e.g. independent of actual ability), the health care market does not fulfill the criteria of a free market [3]. Still, common costing practice consists in the use of market prices for resource valuation [3].

In terms of health consequences, the same steps apply (i.e. identification of health consequences , measurement, and valuation). The theoretical framework (constrained maximization in decision making *versus* welfare theory) underlying the various analyses determines the output measure (measurement and valuation) of the health consequences. The unit of measurement applied to the health consequences is used to classify the type of economic analysis.

1.A.1.1. Cost-effectiveness analysis

Cost effectiveness analyses (CEA) and cost-utility analyses (CUA) are both anchored in social decision-making and are conceptually very similar. CEA does not place a value on health states and measures health consequences in natural units, e.g. diagnosed myocardial infarctions or deaths averted. This approach avoids methodological issues related to outcome valuation (see below); however, it restricts results' comparability across conditions and it does not allow for the amalgamation of risk and benefits of a given intervention (e.g. bleeding and stroke in anticoagulation) because the impact of the intervention on life extension and quality of life are not expressed within a single, common metric. Further, CEA assumes rather than explore the desirability or value of the health consequences chosen by the analyst. Cost consequence analyses (CCA) are a variation of CEA that report on several instead of a single clinical endpoint, thus allowing a broader presentation of benefit and risks associated with the intervention.

1.A.1.2. Cost-utility analysis

The health outputs of cost-utilities analyses (CUA) are expressed as preference-weighted life-time, i.e. a measure that merges the duration and the "value" of the gained life relative to a hypothetical reference health state. Death and perfect health are the usual reference anchors (at 0 and 1, respectively) [3]. Quality-adjusted life years (QALY) are the most commonly used unit and they are calculated by the multiplication of the preference weight with the time spent in the state. Health economists measure preferences either directly or indirectly. Direct methods involve interviews with members of the public (after the description of health states) or with patients to elicit their preferences by various approaches, e.g. visual analogues scales, time-trade-off, or standard gamble. Indirect methods classify patients' health status based on multi-attribute functionality (e.g. mobility, self-care, pain) and apply scores previously elicited by direct methods [3].

The use of utility weights and QALY has been criticised for several shortcomings: first, even when elicited by standard gamble (uncertainty-framed method), QALYs represent a von Neumann Morgenstern utility function only under assumption of a) mutual utility independence, b) constant proportional trade-off property, and c) time-linearity of the single attribute utility function [3, 6, 7]. Mutual utility independence assumes that there is no

interaction in the trade-off between the amount of quality and of quantity. The constant proportional trade-off property requires the amount of time sacrificed to achieve a given quality gain to be independent of life-expectancy. Time-linearity of the single attribute utility function (or risk neutrality with regard to time) implies that "for a fixed quality level, one's utilities are directly proportional to longevity" [3]. In reality, these assumptions are frequently not satisfied [6].

Second, the approach of adding the health state utilities over time to generate QALY values implies intertemporal additivity, i.e. the assumption of independence of the utility in a given time period-health state pair from the utilities experienced at all other time-health state pairs [8]. This assumption is not supported by empirical or theoretical evidence [8].

Third, the weights vary depending on a) how they were determined, i.e. by the various direct (e.g. time trade-off, standard gamble) and indirect methods (e.g. Health Utility Index, EQ-5D,..); b) who was asked, e.g. patients or members of the public unfamiliar to the condition, thus relying on the health state description provided during the survey; c) where and when they were determined (different values across cultures); d) if participants are asked to value health states for themselves or for others (integration of equity considerations); and e) the time-horizon they were elicited (time-trade off) over since preferences implicitly includes the time duration[9]. As such, the appraisal of health state valuation requires a detailed description of the setting and methods applied and equating QALY to QALY is misleading.

Fourth, the time implicitly incorporated in the preference raises concerns about "double counting of the time dimension" because a time component is present both in the weight and in the duration multiplicator [9] and about "double counting of time preferences" [8] by the application of discounting to future QALY because the time preference is already integrated in the utility measure. Finally, multi-attribute classification systems assume first-order and mutual utility independence [3], i.e. they do not consider interactions in the preferences across varying levels of impairment on one (first-order) or several (mutual) attributes. The main advantage of CUA over CEA is the comparability of its results across various disease and across treatment with varying side-effects' spectrum. Therefore, in spite of the mentioned methodological concerns, QALY are the most widely used single metric merging duration and quality of life.

1.A.1.3. Cost-benefit analysis

The theoretical framework behind CBA is welfare theory in contrast to constrained maximization as at the basis of CEA and CUA [10]. CEA and CUA provide information on the costs incurred to achieve a given health benefit and do not impute its "societal value" in the analyses, i.e. CEA and CUA expect decision-makers to judge the value of the goal in a separate step (see under Use of economic evaluations). In contrast, CBA incorporate this additional step in the analysis, i.e. CBA appraise the value of the intervention [3] under consideration of the social opportunity costs and they value both health-care and nonhealth-care benefits. Therefore, cost-benefit analyses (CBA) express both cost and health consequences in monetary terms.

Methods to attribute monetary values to health states are the human capital approach, preferences revealed by wage-risk evaluations, and stated preferences in form of willingness-to-pay. Unresolved methodological discussions regarding the human capital approach include issues related to the valuation of leisure time and to the potential for discrimination reflected by wages (e.g. lower wages for women). The use of wage-risk methods is limited by its high setting-specificity resulting in large estimates' variability. The choice of what to include in the valuation (global versus restricted willingness-to –pay, i.e. the use of market prices for benefit where available) and how to include it (degree of uncertainty of the health outcome) make willingness-to –pay difficult to measure. Further, willingness-to-pay interviews are cognitively challenging tasks [3]. Due to these measurement problems, to validation issues, and to ethical concern related to explicitly attaching monetary values to health consequences, the CADTH guidelines [2] do not recommend CBA as a primary approach.

1.A.1.4. Approaches to resources' and health benefit estimation

Economic evaluations apply two main approaches to the estimation of cost and outcomes: first, data collected at the individual level along clinical studies (piggyback economic evaluation) or, less commonly, collected within dedicated pragmatic trials; and second, decision analytic models. The ideal economic evaluation instrument is comprehensive: i.e. it should

include all available evidence, contemplate all relevant decision alternatives, and take into account all the appropriate present and future consequences. Clinical trials do not represent the ideal vehicle for economic evaluation because they include a limited number of options, they address a reduced time horizon, and they may evaluate surrogate outcomes. Further shortcomings include explanatory versus management issues and the use of one source of evidence as opposed to evidence synthesis [3, 10]. Decision analytic models can be designed to respond to those requirements [10].

1.A.2. Decision-analytic models in economic evaluations

Decision analysis provides a controlled structure for decision-making under explicit consideration of uncertainty [10]. Its goal is to inform which is the preferred alternative based on the expected costs and consequences associated with various allocation alternatives. Decision-analytic models are the mathematical tools applied in decision analysis and they display the expected financial and health-related consequences resulting from the alternative decisions.

The design of a decision analytic model implies choices about the degree of complexity versus parsimony necessary to accurately depict reality without oversimplification, about the model structure (e.g. included health states, comparators, time horizon), about the sources and the modelling of parameter data, and about how to address uncertainty. These choices are at the discretion of the modeller with an inherent risk of bias, e.g. by the omission of relevant comparators or adverse treatment effects [2, 11].

The vulnerability of models to choices that may be biased generated a need for good modelling practice (GMP) guidelines. GMP practice guidelines [5, 12] address 3 main topics: model structure, data identification and handling (including sensitivity analysis), and model validation. The acronym SAVED was proposed for the appraisal of decision analytic model [11]:

- Structural integrity,
- Appropriateness of input data and calculation methods,
- Validation of the model output,
- Extensive use and reporting of sensitivity analysis, and

- Detailed and unbiased reporting of the findings.

Structural integrity requires the model to reflect the condition with regard to health states, natural course, and treatment alternatives at the clinical level (face validity) [5, 11, 12] and at the design level (e.g. time horizon, structure, cycle length).

In terms of data sources the various guidelines agree [5, 12] that lack of data fulfilling the "ideal standards of scientific rigor" [5] should not prevent modelling because "Decisions will be made, with or without the model. To reject the model because of incomplete evidence would imply that a decision with neither the data nor the model is better than a decision with the model but without the data" [5]. The CADTH guidelines [2] also discuss the issue of the timing of the evaluation: on one side early evaluations, i.e. shortly after introduction of a new product when effectiveness data may be limited, will suffer from high degrees of uncertainty; on the other side, late evaluations bear the risk of being uninformative to decision-makers because of obsolete results, e.g. if the decision already occurred [13-16] or in presence of uncontrolled diffusion [2, 17]. In response to this difficult balance, guidelines [2, 5] encourage the continuous reassessment and updating of the models. An additional relevant advantage of early modelling is the assessment of expected value of perfect information to determine the need and to guide the type of additional research [2, 10].

A pivotal step in data handling is the assessment of uncertainty [5, 12]. Uncertainty in economic models arises from variability, heterogeneity, model uncertainty, and parameter uncertainty. Variability refers to random outcome differences among patients with the same profile [10]. In contrast, heterogeneity describes systematic differences resulting from defined characteristics, e.g. low versus high risk patients. Modellers deal with heterogeneity by reporting the results by subgroups [5], e.g. as multiple cost-effectiveness acceptability curves (CEAC) [10], or by hierarchical models [5]. A crucial distinction in the use of subgroups between clinical and economic evaluations is that clinical trial typically focuses on relative effects (i.e. expressed as experimental event rate/control event rate), whereas economic analyses concentrate on absolute effects (expressed as experimental event rate – control event rate). Therefore, heterogeneity modelling by subgroups does not assume subgroup interaction on the (relative) treatment effect, i.e. it is consistent with the concerns raised about subgroup analyses in clinical trials [18, 19].

Choices about model design, e.g. inclusion or omission of health state, and about methodological issues, e.g. discounting approach, generate model uncertainty. GMP guidelines [5, 12] recommend deterministic sensitivity analysis to address model uncertainty. Parameter inputs are typically estimates and do not represent "true" values. Probabilistic sensitivity analysis takes into account this parameter uncertainty by populating the model with parameter distributions (instead of point estimates) and running second-order Monte Carlo simulations. Uncertainty in the model results, reflected by their distribution, is the source of decision uncertainty, i.e. uncertainty if the preferred option according to the model actually is the more desirable. CEAC address decision uncertainty by plotting the probability that the preferred alternative is the more cost-effective [3, 10].

The use of probabilistic analysis with CEAC also mediates the long-standing divergence between the common clinical-epidemiological approach to hypothesis testing and the expected-value prospective advocated by decision analysts. Clinical trials typically reject the null hypothesis and infer a significant effect based on an alpha error probability of 0.05. Decision analysts argue that expected values should drive resource allocation [3, 20] and they oppose limiting models to interventions that comply with the usual statistical inference threshold [5]. The transparent, explicitly acknowledged inclusion of interventions independent of the p-value with the consequent representation of decision uncertainty by CEAC offers the option to the decision-makers to follow the statistical inference or the expected-value approach [3, 5]. Further, the evaluation of interventions not fulfilling the inference threshold and the evaluation of the resulting decision uncertainty in an expected value of perfect information analysis may direct future research [3].

Model validation involves several steps, the most basic one being the assessment of its computational reliability indirectly by extreme values [5]. Other modellers suggest the addition of the more time-consuming reproduction in alternative software [11] to debugging by extreme values to ensure mathematical reliability of the model. Internal validity depends on calibration, i.e. the congruency of the model results with the empirical data inputs used in the model and on reproducibility in addition to computational reliability [5].

The model is reproducible if an independently designed model with the same parameter inputs reaches similar findings. Methods of external validation include verification,

corroboration, and prediction [11]. Verification evaluates the model results based on external data [11], i.e. it represents an "external" calibration. Corroboration refers to results' congruency between the current and prior models. Limited data availability may hamper efforts to external validation, e.g. if there is no independent data set or alternative model to verify and corroborate the model output, or if prediction cannot be assessed because the models reflect obsolete evidence and clinical practice once data to test its predictive ability are available [5, 11].

1.A.3. Use of economic evaluations in decision-making

Economic evaluations do not make the decision, rather they are an instrument to inform and therefore support decisions about drug or devices reimbursement, about planning of infrastructure within the health care system (e.g. number of coronary angiography laboratories, or neonatal tertiary care centres), about cost-sharing and pricing of medical products, or about drug listing and budget plans at an institutional level. They can also inform national clinical guidelines or institutional practice standard, and governmental research funding [2, 3].

In spite of this broad spectrum of possible applications, economic evaluations frequently do not impact decision-making. Galani and coworkers [14] systematically reviewed data from surveys of decision-makers on their application of economic evaluations. Of the 51 included studies, 36% found that economic evaluations' results had a major impact on decision-makers at national and regional level. In 28% of the surveys, physicians reported a major impact of economic evaluations on their decisions. As expected, the higher the centralization of the health care system the higher the impact of economic evaluations exhibited on decision-making [14].

Barriers to the application of the economic evaluations' results arise from several sources. Decision-makers tend to view economic evaluation results with suspicion because of extensive assumption (e.g. time-horizon extrapolation), of poor reporting of methods and results (transparency issues), of industry sponsorship [21], and of inadequate training in the appraisal of the quality of economic evaluations and in the interpretation of their results [13-16].

Further, stakeholders may not perceive the results as relevant due to a lag between results and the timing of the decision, to inflexibility in resource allocation across budgets (silo-effect), to setting specificity (impact of e.g. prevalence or differences in standard care on cost-effectiveness), and because economic evaluations do not address affordability, i.e. the budget impact of the intervention. Also, CEA and CUA do not include societal values such as equity or other ethical considerations in their assessment [16, 21-23]. Equal weighting of a given unit of health improvement, e.g. QALY, independent of the attributes of affected population (e.g. children) and of the disease (e.g. perceived severity) may not reflect societal preferences [16, 21].

Tensions in decision-making will arise when there are discrepancies between cost-effectiveness and social value [21]. Drummond and coworkers [21] exemplified such situations: drugs for erectile dysfunction show high cost-effectiveness but are associated with low societal value which results in their exclusion from reimbursement in most jurisdictions. In contrast, treatment of disease with high societal value may be considered for funding in spite of low cost-effectiveness, e.g. rare genetic diseases or rare malignancies. Finally, political aspects, e.g. public pressure and lobbying, are likely to impact decision-making [22, 23]. Decision-making researchers advocated for structured strategies to solve these contrasts, including the generation of disease-specific references [21] or the explicit assessment of the various components of decision making, e.g. budget impact, equity and political considerations, in addition to efficacy and efficiency, in multicriteria decision analysis frameworks [22, 23].

1.B. PRINCIPLES OF SCREENING

Screening refers to "the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly" to "sort out apparently well persons who probably have a disease from those who probably do not"[24]. Screening programs are classified according to their goal in case-finding and epidemiological survey. The goal of the first being "to detect disease and bring patients to treatment", as opposed "to elucidate the prevalence, incidence and natural history of the variable or variables under study" as in epidemiological survey. Throughout this manuscript, screening will refer to case finding unless stated otherwise.

In 1968, the World Health Organization (WHO) proposed a set of criteria to assess the appropriateness of a screening program [24]. An ideal screening program satisfies the following requirements:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease with evidence that early treatment leads to better outcomes than late treatment
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population. This requirement may be expanded to include the acceptability of the diagnostic procedures and the treatment triggered by a positive screening test [25].
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

A crucial condition for appropriateness not listed in the original WHO publication [24], is the need of evidence of the screening effect on patient-important outcomes in screened versus

not screened individuals generated in a randomized controlled trial (criterion 11) [26, 27]. This addition derives from the recognition that observational data tend to overestimate the protective effect of screening programs due to biases typically encountered in cohorts of screened and unscreened individuals: lead time bias and some characteristic forms of selection biases.

Lead time bias refers to the overestimation of the screening effect due to early detection of the cases without any effect on survival, i.e. the patient is just "labelled" longer as diseased. Characteristic forms of selection bias reported to affect the effect size estimation of preventive programs in observational studies include: length time bias, healthy user/adherer bias, confounding by functional status, and by selective prescribing.

Length time bias occurs when cases with a poorer prognosis become symptomatic earlier and multiple (repeated) screening preferentially detects cases with a longer latent phase, i.e. the cases with a better prognosis. Healthy user bias refers to the propensity of individuals that participate to a screening program to take advantage of other preventive measures, including a healthier lifestyle [28], and it is conceptually similar to the healthy adherer bias, i.e. the tendency of patients adherent to placebo [29] to experience better outcomes.

At the other end of the spectrum, patients with low functional status may not be able to take part to preventive programs leading to a underrepresentation of sick individuals in the group exposed to such services [28, 30] (confounding by functional status). Confounding by selective prescription is a related bias, generated by the non-prescription of preventive measures to individuals with a high expected mortality [28].

The next section 1.C. will outline the rationale of screening for perioperative myocardial infarction, i.e. in how far a screening program by postoperative Troponin T measurement complies with the requirements for appropriateness of a screening intervention. Section 1.C.1 discusses the criteria related to the PMI condition (criteria 1, 4, 7), section 1.C.2. addresses the criteria related to the screening intervention itself (criteria 5, 6, 11; criterion 10 is not discussed as the concept of a "screening drive" does not apply to an acute condition; thus, criterion 10. is fulfilled a priori), and section 1.C.3. focuses on the criteria related to the treatment triggered by positive screening (criteria 2,3,8,9).

1.C. RATIONALE OF POSTOPERATIVE SCREENING FOR PERIOPERATIVE MYOCARDIAL INFARCTION

1.C.1. Perioperative Myocardial infarction

1.C.1.1. Magnitude of the problem

Worldwide, over 200 million major surgical procedures take place annually corresponding to 1 procedure for every 25 human beings [31]. This annual rate increases to nearly 1 procedure for every 10 adults in developed countries[31]. Most of these procedures are noncardiac [32]. In the POISE Trial [33], a large international randomized controlled trial (RCT)(>8,000 patients in 23 countries) that included patients aged ≥45 years with known cardiovascular disease or at risk for it, 1.8% of patients undergoing noncardiac surgery who required hospitalization died of a cardiovascular cause within 30 days of the procedure. The most frequent perioperative cardiovascular complication was perioperative myocardial infarction (PMI) (5.1% nonfatal PMI within 30 days after surgery) [33]. In the Vascular events In Non-cardiac Surgery patIents cOhort evaluatioN (VISION) Study, that internationally enrols unselected, i.e. independent of the cardiovascular risk level, patients aged ≥45 years undergoing noncardiac surgery with overnight hospitalization, the cardiovascular mortality at 30 days was 0.84%. Increased postoperative Troponin T concentration suggestive of ischemic myocardial damage was found in 8.35% [34]. Extrapolating these findings under the assumption of half of the global surgical volume taking place in patients ≥45 years, over 800,000 patients annually die due to cardiovascular complications within 30 days of noncardiac surgical procedures and 10 million suffer myocardial ischemia.

1.C.1.2. Natural history and manifestations of PMI

PMI is associated with a poor prognosis; in the POISE Trial, the 30-day mortality after PMI was 12% and PMI increased the adjusted hazard of 30-day mortality by a factor 4 independent of the presence of ischemic symptoms [35]. Data generated in the same

population [35] also suggested a high incidence of congestive heart failure, cardiac arrest, and stroke after PMI.

In spite of their poor outcomes, only a minority of patients suffering a PMI experience ischemic symptoms such as chest or epigastric pain or dyspnea. These findings suggested by several smaller samples [36-38], were confirmed both by the POISE Trial [35] and the VISION study [34] (Appendix 1). The majority of PMIs occurs within the first 48 hours after surgery [35, 39], i.e. during a period of extensive use of opioids and of epidurals for postoperative pain control. This likely explains why a substantial proportion of patients will not experience any ischemic symptoms. An additional factor that results in the underdetection of PMI is the attribution of suggestive signs, like tachycardia, hypotension, or of clinical symptoms, such as nausea, to alternative conditions frequently encountered in the perioperative period, e.g. hypovolemia, anemia, or postoperative nausea and vomiting secondary to volatile anesthetics and opioids [40]. Similarly, early signs of congestive heart failure may be misinterpreted as volume overload related to aggressive intraoperative fluids administration. PMI thus represents a condition that is clinically often missed.

A concern commonly raised in relation to screening tests is the risk of overdetection. This concept refers to the detection of latent cases that will never affect prognosis or become symptomatic [26, 27, 41]. However, the POISE Trial and the VISION Study [34] suggest that asymptomatic PMI are clinically relevant events. The crude 30-day mortality of PMI was 9.7% in patients with and 12.5% in patients without ischemic symptoms in the POISE trial; the corresponding adjusted HR were 4.76 (95%CI 2.68-8.43) and 4.0 (95%CI 2.65-6.06)[35]. Thus, given the close temporal relation to mortality (30 days) and the strength of the association, the risk of overdetection does not appear relevant.

As suggested in previous studies [35, 39, 42] (Appendix 2), the VISION Study[34] established that a peak postoperative 4th generation Troponin T concentration was an independent predictor of 30-day mortality. The VISION Study [34] measured postoperative 4th generation Troponin T in 15,133 patients who experienced inhospital noncardiac surgery internationally and evaluated the association of postoperative peak Troponin T values with 30-day all-cause mortality (282 deaths, 1.9% [95%CI 1.7-2.1]) independent of 24 preoperative and surgical variables. The analysis included a minimal p-value approach to establish 4th generation

Troponin T thresholds associated with a significant impact on 30-day mortality. Peak 4th generation Troponin T exceeded 0.02 μg/L in 1,757 patients (11.6% [95%CI 11.1-12.2]). The model showed that postoperative Troponin elevation (Appendix 2), the indication for surgery (urgent/emergent vs nonurgent) (adjusted hazard ratio [HR] 3.73 [95%CI 2.88-4.82]), and age ≥75 years (adjusted HR 2.37 [95%CI 1.75-3.23] were among the strongest predictors of 30-day mortality after noncardiac surgery.

The population attributable risk (PAR) considers the strength of the adjusted association with the prevalence of the risk factor (PAR=proportion of exposed cases x (relative risk-1)/relative risk)) [43] and generates a measure of the proportion of incident events, here 30-day mortality, that would be prevented by the "elimination" of the risk factor under the assumption of causality. In the VISION Study the PAR of 30-day mortality was 42.1% (95%CI 34.8-49.3) for peak postoperative 4th generation Troponin T concentration ≥0.02 μg/L. This suggests the possibility that 2 in 5 deaths at 30-days after noncardiac surgery may be prevented by the elimination of this risk factor.

The timeline between detection and death is of particular interest for a proposed screening intervention. The VISION data suggest that elevated Troponin T measurements during the first 3 days after surgery typically represent a warning myocardial event at a stage where the initiation of therapeutic interventions is still possible. The median times from the peak Troponin T measurement to death were 13.5 days (IQR 8.5-20) in patients with a peak of 0.02 μg/L, 9.0 days (IQR, 3.5-16) in those with a peak of 0.03-0.29 μg/L, and 6.5 days (IQR, 1.5-15) in those with a peak ≥0.30 μg/L [34].

1.C.2. PMI screening by Troponin T measurement

1.C.2.1. Validity of Troponin T for the detection of perioperative myocardial infarction

The biomarker-based diagnosis of myocardial infarction requires the detection of cardiac biomarkers above the 99th percentile and ischemic symptoms, or ECG changes, or new wall motion abnormalities [44]. Cardiac Troponins are preferred over creatine kinase-MB (CKMB)

because of their higher tissue-specificity, sensitivity, and longer half-life [44, 45]. Adams and coworkers [46] validated these advantageous test characteristics for the detection of myocardial infarction by Troponin I in noncardiac-surgery patients. The advantage of measuring Troponin T over Troponin I relies on the existence of a single commercially available Troponin T assay for a given generation. This reduces confusion regarding the concentrations considered the upper limit of the norm [47].

For the 4th generation Troponin T assay (Roche Diagnostics, Elecsys2010), the International Federation of Clinical Chemistry and Laboratory Medicine endorses a cut-off concentration at ≥0.03 μg/L for the diagnosis of myocardial infarction. This relies on a coefficient of variation of 10% [48]. The VISION study [34] demonstrated the independent association (HR 5.07 [95%CI 3.85-6.72]) between this cut-off value and 30-day mortality, thus validating this cut-off in patients undergoing noncardiac surgery. Further, using a minimal p-value approach, the VISION study detected 0.02 μg/L as a Troponin T concentration associated with an independent increase in 30-day mortality (HR 2.41 [95%CI 1.34-3.73]).

1.C.2.2. Acceptability of Troponin T measurements and of diagnostic procedures triggered by positive screening

There is no formal evidence of the extent to which patients would be comfortable with the measurement of postoperative Troponin T test; however, we expect patients' acceptance to postoperative Troponin measurement to be high because: 1) the inconvenience of the screening test itself is limited, as it requires only postoperative blood sampling that occurs regularly in routine clinical care independent of a Troponin T screening; 2) patients are in hospital, i.e. it could be viewed as a special form of opportunistic screening; and 3) the strong association of Troponin T to death in the coming weeks after surgery. In their systematic literature review on barriers and facilitators to screening uptake, Jepson and coworkers [30] found empirical evidence suggesting that less invasive screening strategies and opportunistic screening-improved screening uptake. The extrapolation of those principles to postoperative Troponin measurements appears plausible in spite of the limitation of the generalization from a chronic to an acute condition that impact short-term outcome and across screening modalities.

Follow-up diagnostics in positive patients include additional Troponin T sampling, ECG, echocardiography and potentially coronary angiography. In Canadian VISION centres, 0.6% of the patients underwent a coronary angiogram (0.1% of the patients with negative Troponin, 12.7% of the patients with PMI). All-cause mortality in over 88,000 Canadians with CAD undergoing coronary angiogram between 1996 and 2004 amounted to 2.1% [49]. This figure does not represent mortality directly linked to the coronary angiogram but all-cause 30-day mortality. In 40.9% of the evaluated population, the indication for coronary angiography was acute coronary syndrome (ACS). Further, 35.3% and 14.7% of the patients underwent PCI within 7 days and CABG within 30 days, respectively (proportion of patients undergoing PCI at 30 days not reported) [49]. Therefore, the estimate of 2.1% mortality after coronary angiogram also includes deaths related to the ACS itself and coronary revascularisations. This figure however, in spite of not being specific to angiogram-induced mortality, may be more relevant for patients when balancing risk and benefits [50] of a potentially positive postoperative Troponin screening, given that they would undergo angiography under acute conditions. The 30-day all-cause mortality after PMI was 11.6% in an international trial [35] and 12.9% (95%CI 10.1-16.4) in the VISION study.

We can obtain an approximation of patients' and physicians' acceptance of medical treatment triggered by the Troponin screening and consequent PMI detection in Canada by the discharge medication after nonoperative ACS. The Canadian ACS Registries were multicenter cohort studies that enrolled adults hospitalized with an ACS. In the Canadian ACS Registry II (2002-2003), 94.3% of the patients were discharged on aspirin or oral anticoagulation, 85.3% on B-Blockers, 67% of ACE-inhibitors, and 83.5% on statins [51]. These proportions likely represent a conservative estimate given that they reflect implementation, i.e. acceptance that has overcome multiple knowledge translation barriers. Of note, discharge use does not equate with continued adherence. The methods section reports the estimates for treatment adherence assumed in the model given that the model applied a third-payer perspective.

1.C.2.3. Trial-generated evidence for the effectiveness of postoperative Troponin T screening on patient-important outcomes

There is currently no evidence from RCTs that measuring Troponin concentrations to detect PMI reduces mortality or morbidity. Further, the VISION study is a cohort study that measures Troponin T concentrations in all patients, and thus does not provide observational estimates for the effect of a Troponin T screening on outcomes. The methods section describes how we approached this limitation.

However, there is clinically a compelling logic for identifying postoperative Troponin elevations that would otherwise be missed; thus, the goal of proceeding to the present early economic evaluation is to see if the logic survives testing by rigorous modelling. Further arguments in favor of early evaluation are the avoidance of a delay between decision and provision of information to direct the decision (i.e. avoidance of the generation of obsolete, useless information) and the possibility of quantification of the need of additional research by expected value of perfect information [2, 5].

1.C.3. Treatment of PMI

1.C.3.1. Treatment effect, treatment indications, and treatment availability

The optimal PMI treatment and secondary prophylaxis after PMI is not established. However, the large effect size of aspirin administration for myocardial infarction in the nonoperative setting [52, 53] and the promising perioperative observational results with aspirin and statins [35] suggest that the outcome of patients with an elevated postoperative Troponin is likely modifiable.

Supply (not use) of cardiovascular medications is not limited in Canada. The postoperative screening of Canadian patients undergoing noncardiac surgery resulted in a limited number of coronary angiograms (<1% of the screened patients) and of revascularisation procedures (PCI 0.2%, CABG 0.1% of the screened patients) within 30-day of surgery. Even assuming the 30-day coronary catheterisation rate (61.5%) reported in nonoperative MI across 77 hospital in Ontario in 2005-2006 [54] and a 3% incidence of PMI (see below), the screening of

10,000 noncardiac surgery patients will result in less than 200 coronary angiograms. Therefore, the requirement of the availability of treatment facilities is satisfied.

1.C.3.2. Benefit and cost of postoperative Troponin T screening

Scarcity of resources calls for a balance in benefit and cost (including both financial and health-related adverse implications) of a screening program [24, 50], i.e. "The cost of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole" [24]. The goal of this project is to provide information for the appraisal of how far a postoperative Troponin T screening test complies with this criterion.

2. OBJECTIVES

The objectives of this project are:

1) To evaluate the incremental cost and incremental number of detected PMI and of detected isolated Troponin T elevation resulting from a postoperative Troponin T screening consisting in 4 Troponin T tests in patients ≥ 45 years who undergo noncardiac surgery requiring hospitalization;

2) To establish the most cost effective approach to a postoperative Troponin T screening to detect PMI with regard to the number of the Troponin T sampling;

3) To evaluate the incremental cost and incremental number of detected PMI and of detected isolated Troponin T elevation in patients subgroups defined by preoperative characteristics

4) To explore the incremental cost and incremental number of deaths by any cause at 1 year resulting from a postoperative Troponin T screening in patients ≥ 45 years who undergo noncardiac surgery requiring hospitalization;

5) To explore cost and number of events at 1 year in patients' subgroups defined by preoperative characteristics.

3. METHODS

3.A. OVERVIEW

The basis for this project is the Vascular events In Non-cardiac Surgery patIents cOhort evaluatioN (VISION) Study, a large, multicentre, international prospective cohort of patients undergoing noncardiac surgery. The VISION study initially measured postoperative 4th generation Troponin T concentrations, then switched to the measurement of 5th generation TroponinT. These analyses are based on the cohort of patients in which 4th generation Troponin T measurement occurred. The VISION study measured Troponin T in all patients; thus, it did not provide estimates for the effect of a Troponin T screening on outcomes. Further, it did not collect data on costs. Therefore, the estimates of the treatment effect and of the cost rely on external data and this CCA was model-based.

As mentioned there are no randomized data quantifying the treatment effect of a postoperative Troponin T screening program. Given the uncertainty on the effect size, we opted for a 2-step approach: the first step consisted in the modelling of the number of detected PMI and the related diagnosis costs. This model did not impute any effect of the screening on the outcomes; therefore, the results were not limited by assumptions regarding screening and treatment effect.

The second step consisted in a more sophisticated model that imputed an effect of the screening, i.e. of the detection PMI and its treatment, on outcome. We assumed PMI patients to be treated as patients suffering a MI in the nonoperative setting, i.e. by a combination of aspirin, B-blocker, ACE-inhibitor and statins. The combination of drugs currently recommended for MI developed over the years, and the placebo arm of the randomized controlled trials that established “optimal medical treatment” did not represent patients naive to all drugs, as we assumed missed PMI patients to be. Further, “optimal medical treatment” is not established for PMI. Therefore, we populated the model with hypothetical treatment effects for the 4-drug combination and performed sensitivity analyses.

We preferred a CCA over a CEA as the primary form of the results presentation as it has been reported as the preferred approach by decision-makers given that it allows decision-makers the assessment and valuation of the disaggregated results [13]. We avoided the use of a CUA because we considered that the pooling of the patients with heterogeneous underlying diseases and disabilities (for which they underwent noncardiac surgery) violates the assumptions at the basis of the QALY approach (e.g. mutual utility independence) whose applicability has been questioned even for more homogeneous patient' populations [6]. Further, we judged that the use of preference weights not specific to events acquired in the perioperative setting might misrepresent the actual preferences in the operative setting.

3.A.1. Population

Canadian patients enrolled in the VISION study screened by a 4th generation Troponin T assay represent the population for this analysis, i.e. we included patients that:

- were aged ≥45 years
- underwent noncardiac surgery that required postoperative hospitalization of at least 1 night
- underwent their procedure under general or regional anesthesia (neuro-axial or nerve block)
- were enrolled in Canadian VISION sites.

To achieve a representative sample of hospitalized patients undergoing noncardiac surgery the VISION Study protocol implemented only few exclusion criteria. The VISION Study excluded patients who received procedures performed with topical or infiltrative anesthesia only, that refused participation, or that had been previously enrolled. For this analysis, we also excluded patients who had elevated Troponin T in the 7 days prior to surgery, as the screening concept did not apply to them.

Additional strategies to obtain a representative sample implemented in the VISION study consisted in 1) a board screening approach including identification in the preoperative assessment clinic, preoperative holding area, emergency department, intensive care unit, in surgical wards (patients were included up to 24 hours after surgery); 2) enrolment not only of

elective day-procedures but also of emergent or urgent night- or weekend-cases. Informed consent by next of kin or delayed consent allowed the inclusion of severely-ill patients and of emergent cases. In case of surgical volumes exceeding the research personnel resources at the centre, the VISION study project office randomly assigned enrolment weeks and categories of surgery to be enrolled according to the local surgery-type distribution. This process was monitored by weekly screening logs that reported the number of eligible patients and the number of enrolled patients. The Canadian VISION study centres enrolled 70.3% of the eligible patients (Figure 1).

The patients were enrolled between September 2007 and October 2010 at Hamilton Health Sciences, Hamilton, at St. Joseph Hospital, Hamilton, at Health Sciences Centre Winnipeg, Winnipeg, and at University of Alberta Hospital, Edmonton.

3.A.2. Postoperative follow-up in the VISION study

The study protocol mandated 4 measurements of Troponin T in all patients: between 6 and 12 hours after surgery, on postoperative day (POD) 1, 2, and 3. Local laboratories measured Troponin T concentrations by an immunoassay (Elecsys 2010, 4th generation, Roche Diagnostics). The lower limit of detection of the assay was 0.01 µg/L, the 99th percentile cut-off point concentration <0.01 µg/L and the coefficient of variation <10% at 0.03 µg/L. Health care providers and research personnel were not blinded to postoperative Troponin T concentrations.

In the presence of elevated Troponin T concentrations, research staff searched the clinical notes for indication of ischemic symptoms and 12-lead ECGs. If patients did not report clinical symptoms and the ECG did not demonstrate ST-segment changes, T-wave abnormalities, or Q-wave development (for details see Appendix 3), the VISION protocol recommended conducting an echocardiogram to assess potential regional wall motion abnormalities.

Research personnel assessed the hospitalization notes and laboratory results for the following endpoints: percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), myocardial infarction, congestive heart failure, stroke, cardiac arrest, bleeding and death (definitions in Appendix 3). At 30 days and 1 year, the follow-up occurred by phone. If patients reported an event during the phone interview, research personnel contacted their

physicians or relevant institutions to obtain appropriate source documentation. After review of all collected data by local physicians, case report forms and source document were faxed directly into the data management system (iDataFax™, Clinical DataFax Systems Inc., Hamilton, Canada) of the coordinating centre (McMaster University, Hamilton, Ontario, Canada).

3.A.3. Adjudication of PMI in the VISION study

The VISION study definition of PMI required any of the following:

1. A typical rise of Troponin or a typical fall of an elevated Troponin detected after surgery in a patient without a documented alternative explanation for an elevated Troponin (e.g., pulmonary embolism) AND one of the following:

a. ischemic signs or symptoms (i.e. chest, arm, or jaw discomfort, shortness of breath, pulmonary edema) within 24 hours of Troponin T elevation;

b. development of pathologic Q waves present in any two contiguous leads that are > 30 milliseconds;

c. ECG changes indicative of ischemia (i.e. ST elevation [≥ 2mm in leads V1, V2, or V3 and ≥ 1mm in the other leads], ST segment depression [≥ 1mm], or symmetric inversion of T waves ≥ 1mm in at least two contiguous leads, or development of LBBB. ST-depression/elevation and LBBB development had to occur within 3 days of Troponin T elevation or ischemic symptoms. T-wave inversion had to occur within 5 days of Troponin T elevation or ischemic symptoms;

d. coronary artery intervention (i.e. PCI or CABG surgery) within 2 weeks of Troponin T elevation or ischemic symptoms; or

e. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging;

OR

2. Pathologic findings of an acute or healing myocardial infarction

OR

3. Development of new pathological Q waves on an ECG if Troponin levels were not obtained or were obtained at times that could have missed the clinical event.

The PMI adjudication followed a multi-step process: central adjudicators, previously trained, reviewed all events reported by the local investigators as PMI or as elevated Troponin T. Adjudicators were blinded to the classification by the local investigators. If the adjudicator agreed with the investigator's report of the event, the event was classified accordingly in the database and the adjudication was considered completed. If the adjudicator disagreed with the investigator's decision, a second central adjudicator, unaware of both the decision of the investigator and of the first adjudicator, reviewed the source documents. If the second adjudicator agreed with the first, the event was assigned accordingly. If the second adjudicator agreed with the investigator's report and disagreed with the first adjudicator, the 2 adjudicators discussed the case to resolve disagreement. If disagreement persisted, the Chair or Co-chair of the Adjudication Committee reviewed the case and reached the final decision.

3.A.4. Data quality in the VISION study

Review of all collected data by local physicians, central consistency check, statistical monitoring and on-site monitoring in all centres ensured data quality. On-site monitoring consisted in the audit of case report forms and source documentation in a random sample of patients that included patients with and without events. Consistency check, statistical monitoring, and on-site audits did not suggest any irregularity. Follow-up at 30 days was 99.3% complete.

3.A.5. Ethical considerations

The Research Ethics Board at each site approved the protocol prior to recruitment start. Research personnel obtained written informed consent by all patients or their families. The VISON study included vulnerable patients, because incapable to give informed consent, e.g. severely-ill patients, demented patients, and emergent cases. In accordance to the Draft Second Edition of the Tri-Council Policy Statement: Ethical Conduct for Research involving Humans (revision December 2009), for legally competent patients that were unable to provide

informed consent, research personnel informed and obtained consent from a family member. In case of legal incompetence, research personnel informed and obtained consent from the patient's authorized representative. The cost, treatment effect, and adherence parameters of the cost-consequence analyses based on published data; as such we did not seek approval for the models.

3.B. COST-CONSEQUENCE ANALYSIS OF TROPONIN T SCREENING ON THE DETECTION OF PMI

3.B.1. Overview

We conducted a CCA of the systematic measurement of Troponin T concentrations (screening) after noncardiac surgery requiring overnight hospitalisation compared with current standard care (i.e. Troponin measurement triggered by suggestive potential myocardial ischemic symptoms). We applied the perspective of the Canadian publicly funded health care. We measured the health consequences as the number of detected PMIs and of perioperative Troponin elevations during the screening period. We expressed cost as 2011 Canadian dollars (CAD$).

3.B.2. Model structure and computer simulation

The reference model considered the following alternatives: 1) the determination of 4th generation Troponin T concentrations at 6 to 12 hours after surgery, and on postoperative days 1, 2, and 3 versus standard care, or 2) the reliance of suggestive myocardial ischemic symptoms or signs (e.g. angina, dyspnea, or pulmonary edema) to trigger evaluation for potential PMI.

The model was structured as a decision tree (Figure 2) and it included the following health states at the end of the screening period: “true positive” (detected PMI), “true negative” (no PMI), “false negative” (missed PMI), and “false positive” and “isolated Troponin T elevation” for the clinical symptoms-based (noncardiac chest pain) and for the screening alternative, respectively. Isolated Troponin T elevation was considered a distinct state because of its independent prognostic impact, and therefore did not fit the false positive state. Appendix 4 reports the detailed definitions of the various health states.

The reference analysis was a probabilistic sensitivity analysis (PSA) generated by a second order Monte Carlo simulation with 5,000 iterations. The results are the means over 5,000 iterations of the expected cost and consequences. We ran the model in Microsoft Excel spreadsheets with corresponding macros. We internally validated the model by extreme values.

3.B.3. Data inputs

3.B.3.1 Probabilities of the health states

Data generated in 6,149 Canadian VISION patients fulfilling the criteria mentioned above informed the probabilities of the health states in the Troponin T screening alternative (Table 1). There were no clinically relevant differences in outcomes across centres (Appendix 4). Since the VISION Study did not include a standard care alternative, we estimated the number of detected PMI after standard care by the number of symptomatic PMI and the number of missed PMI by the number of asymptomatic PMI in the VISION cohort. The VISION study did not collect information on clinical symptoms in patient without Troponin T elevation. The estimates of the incidence of false positive in the standard care, i.e. the proportion of noncardiac chest pain and dyspnea, relied on expert opinion that was not elicited in a Delphi panel. Table 2 summarizes the model parameters and their distributions.

3.B.3.2. Cost estimates

The VISION Study did not collect cost or resource use data. We estimated the cost of the intervention based on predefined diagnostic algorithms to confirm or exclude PMI in presence of positive Troponin screening or suggestive symptoms in the standard care group. The algorithms included the following resources: 4th generation Troponin T measurements as screening and as serial follow-up in case of positivity or clinical symptoms (triggered Troponin measurements), resultant cardiology consultations, serial ECG, echocardiography, and coronary angiography (Appendix 6). Canadian VISION data were the source for the following probabilities used to estimate the costs: probability that the diagnosis of PMI relied on the echocardiographic detection of wall motion abnormalities, that the PMI diagnosis based on Q-wave development only, that the Troponin T concentrations only exceeded the upper limit of the norm on the last day of the scheduled Troponin T sampling, and the probability of a coronary angiogram in

patients in the various states. Table 2 reports the unit costs and their sources. The model did not include costs related to the surgical procedure itself, because these resource items were identical in both alternatives [2]. Costs were inflated by the Canadian healthcare consumer price index as necessary.

3.B.4. Sensitivity analysis

To explore the impact of the expert-based diagnostic algorithms on the model estimates, we carried out a one-way deterministic sensitivity analysis. The worst case scenarios assumed a 25% increase and a 25% reduction in resource utilisation in the screening and in the standard care alternative, respectively. The best case scenario assumed the inverse. The utilisation of the following resources was accounted for: triggered Troponin measurements, cardiology consultations, serial ECG, echocardiography, and coronary angiography. A second sensitivity analysis, applied a false positive rate of 0% and of 10% in the standard care alternative.

3.B.5. Exploration of heterogeneity

We calculated cost and consequences of a Troponin T screening for the 4 measurements approach separately in populations at various levels of PMI risk and presented the results as disaggregated cost and consequences (probabilistic sensitivity analysis, mean over 5,000 simulations) and as multiple cost-effectiveness acceptability curve. We predefined the following heterogeneity analyses: a) aged ≥65 years, ≥75years; b) orthopedic surgery; c) urgent/emergent surgery; d) major general surgery; e) history of CAD f) history of peripheral vascular disease (PVD); g) history of congestive heart failure; h) history of diabetes; and j) revised cardiac risk index score of ≥1, ≥2, ≥3. We focused on orthopedic and major general surgery as those were the most frequent procedures in the VISION study population.

3.B.6. Exploration of various screening protocols

We calculated cost and consequences of a Troponin T screening based on a single measurement 6 to 12 hours postoperatively and of 2 and 3 measurements (probabilistic sensitivity analysis, mean of 5,000 simulations).

3.C. COST-CONSEQUENCE ANALYSIS OF TROPONIN T SCREENING ON 1-YEAR SURVIVAL

3.C.1. Overview

We conducted a cost-consequence analysis of the systematic measurement of Troponin T concentrations (screening) after noncardiac surgery requiring overnight hospitalisation compared with current standard care (i.e. Troponin measurement triggered by suggestive potential myocardial ischemic symptoms). We applied the perspective of the Canadian publicly funded health care. We measured the health consequences as the number of all-case death at 1 year. The noncardiac surgery population consists in a heterogeneous population, e.g. patients with various cancer types, acute infections, and elective joint surgery. This precluded a common projection of long-term survival. Therefore, the assessment of potential health benefit after 1 year would lack clinical face validity. We expressed cost as 2011 Canadian dollars (CAD$).

3.C.2. Model structure and computer simulation

The reference model considered the following alternatives: the determination of 4th generation Troponin T concentrations at 6 to 12 hours after surgery, and on postoperative days 1, 2, and 3 versus standard care vs. the reliance of suggestive myocardial ischemic symptoms or signs (e.g. angina, dyspnea, or pulmonary edema) to trigger evaluation for potential PMI- and consequent treatment of detected events. We assumed all patients, independent of the methods of PMI detection – screening or symptom triggered- to undergo the same treatment. Treatment applied both for patients with PMI and with isolated Troponin T elevation and it

consisted in a combination of aspirin, B-blocker, ACE-inhibitor and statin, i.e. as in patients suffering a MI in the nonoperative setting.

The model was structured as a decision tree (Figure 3) and it included the following health states at the end of the screening period: detected and missed PMI, detected and missed isolated Troponin elevation, and no PMI. The no-PMI state included true negative patients and the false positive patients. However, we assumed the last to have incurred additional costs to rule out the PMI.

At 30 days, patients were categorized as having suffered either a nonfatal re-infarction, a nonfatal cardiac arrest, a nonfatal congestive heart failure, a nonfatal stroke, a nonfatal bleeding requiring transfusion, to have undergone coronary revascularisation (PCI or CABG), to have died, or not to have suffered any complications. The model assumed the events to be mutually exclusive. PCI and CABG at 30 days represented health states but were not considered as outcomes subjected to a treatment effect because of the short time-window between the index event and revascularisation (30 days); therefore, there was a high probability of the revascularisation to be triggered by the index PMI and not by subsequent events or disease progression. The heath states at 1 year were survival after the various cardiovascular complications or all-cause death.

The reference analysis was a probabilistic sensitivity analysis (PSA) generated by a second order Monte Carlo simulation with 5,000 iterations. The results are the means over 5,000 iterations of the expected cost and consequences. We ran the model in Microsoft Excel spreadsheets with corresponding macros. We internally validated the model by extreme values.

3.C.3. Data inputs

3.C.3.1. Probabilities of the health states

Data generated in 11,251 international VISION patients informed the incidence estimates of 30-day and 1-year events in the missed PMI and missed isolated Troponin elevation patients, respectively. The event incidence in the detected PMI was reduced by the treatment

effect size estimates (see below). We opted for this approach even if clinicians were not blinded to Troponin T results in VISION given that VISION data on drug use suggest that in a substantial proportion of cases PMI did not trigger treatments. We tested this assumption in sensitivity analysis (see Natural course assumption sensitivity analysis). We applied the treatment effect to patients with detected PMI, detected isolated Troponin T elevations (in the screening arm), and to all patients who suffered a cardiovascular complication (re-infarction, congestive heart failure, cardiac arrest, stroke, PCI, CABG) at 30 days independent of the initial detection of the PMI, given that patients developing complications became clinically manifest. Table 3 summarizes the model parameters and their distributions.

3.C.3.2. Estimates of the treatment effect and of adherence

We based the estimation of the treatment effect on the effect size of aspirin and we assumed additional 15% relative risk reduction for the combination of all 4 drugs in the reference model. We opted to base the effect estimate on the aspirin effect, because it was established early [52], ISIS-2 participants were not administered ACE-inhibitors or statin, and only a minority (6.4%) of them were planned to receive inhospital intravenous B-Blocker [52]. Given that the RR for each single other component of the assumed 4-drug combination varied between 0.8 and 0.95 (depending on endpoint, follow-up duration and drug, see Appendix 7 and 8) [52, 55-64], we considered additional 15% relative risk reduction by the combination of aspirin with all 3 B-blocker, statin, and ACE-inhibitors as a plausible estimate (see below for sensitivity analyses).

For the treatment effect on the short-term incidence of congestive heart failure, we opted for the treatment effect of ACE-inhibitors, given that the effect of the other drugs is less well established. For congestive heart failure, the reference model assumed the treatment effect of ACE-inhibitors only in spite of a 4-drug treatment.

The PEP trial [53] informed the estimates for the treatment effect of aspirin on postoperative bleeding requiring transfusion. Appendix 7 and 8 summarizes the effect size estimates of the single components of the 4-drug combination therapy reported in RCT or RCT meta-analyses.

We assumed the same standard error for the 4-drug combination as for the aspirin estimates generated in the ISIS-2 trial [52] for short-term all-cause mortality, and nonfatal re-MI, cardiac arrest, and stroke, respectively. For the estimates of the treatment effect on 1-year mortality, we applied the SE of aspirin reported by the ATT collaboration 2009 meta-analysis [58]. The SE for congestive heart failure based on the standard error of the estimate of ACE-inhibitors from the ACEI-MI Collaborative Group MA [57] (Appendix 7 and 8). We decided to apply the same distribution width, centred on the various effect size estimates in the sensitivity analyses to avoid artificially inflating uncertainty across sensitivity analyses with various effect sizes. Treatment effects were not assumed in patients with preoperative drug intake.

3.C.3.3. Estimates of adherence

The reference model assumed 75% adherence to the 4-drug combination in patients with detected PMI or isolated Troponin T elevation and in patients developing a cardiovascular complication at 30 days without intake prior to surgery. This estimate based on the adherence rate observed in the Canadian ACS Registry I and II [51]. The ACS Registries were multicenter cohort studies that enrolled adults hospitalized with an ACS in Canada in 1999-2001 and 2002-2003. Patient-reported adherence was assessed at 1-year. Of the 5,833 patients without contraindications to recommended drugs, 6.8% discontinued the aspirin/oral anticoagulants, 21.1% the B-blocker, 10.8% the lipid-lowering treatment, and 24.2% the ACE-inhibitors. Adherence at 19 months varied from 91% (ACE-inhibitors) to 78% (lipid-lowering treatment) in the control arm of a RCT that allocated 2,643 patients hospitalized on a cardiology ward to a program to improve long-term adherence versus standard care [65], We conducted a high-adherence sensitivity analysis with 90% of the patients continuing drug intake at 1 year. We hypothesized that all patients with preoperative drug intake would stay on the treatment (100% adherence), given that they reported to be adherent prior to surgery and the model did not assume any additional effect in those patients.

3.C.3.4. Cost estimates

Intervention-related costs include the costs incurred to diagnose or exclude PMI and isolated Troponin T (Table 3) as determined in first model with the addition of the costs generated by the administration of enteric-coated aspirin 81 milligrams daily, metoprolol 50 milligrams twice daily, ramipril 10 milligrams daily and atorvastatin 80 milligrams [66] daily. Clopidogrel is not commonly initiated in PMI, as such the reference model did not assume PMI patients do be administered clopidogrel (see sensitivity analysis). Drug-related costs based on generic products and included mark-ups and the average dispensing fees in Ontario [67]. We assumed patients with detected PMI and patients who suffered a cardiovascular event at 30 days, thus becoming clinically manifest, to be prescribed the 4-drug combination. The source of PCI cost [68] included the cost of clopidogrel administration. The model did not include costs related to the noncardiac surgical procedure itself, because these resource items were identically incurred in both alternatives [2]. We did not include unrelated health care cost incurred during gained lifetime, e.g. adjuvant chemotherapy.

To obtain estimates for the costs incurred by patients suffering the various events, we conducted a focused search of published data. We searched the Ontario Case Costing Initiative (OCCI) (www.occp.com), PubMed ([(cost OR economic) AND Canada AND "each specific event"]), and the CEA Registry (https://research.tufts-nemc.org/cear4/). We selected reports based on the following criteria hierarchy: event specificity over location, e.g. US perioperative bleeding costs were preferred over Canadian bleeding cost estimates in anticoagulated patients, and location over data collection period, i.e. Canadian data were preferred over more recent data generated outside Canada. We choose sources with a broad perspective that reported disaggregated costs and we applied the costs of specific items to avoid double counting (e.g. medication cost) as well as to adapt the estimates to the third-payer prospective (e.g. exclusion of productivity loss).

We approximated 30-day event costs for nonfatal re-infarction, nonfatal congestive heart failure, nonfatal stroke and nonfatal cardiac arrest by the hospitalization cost reported in the OCCI. The OCCI generates estimates in a dedicated costing database that merges statistical and financial hospital information in a case costing framework. The estimates report inhospital

cost incurred by case-mix groups and they consider personnel (nursing, Allied Health providers, and physicians), tests and procedures, drugs, patient-care specific and non-patient-care-specific overhead cost. For the 30-day event costs after PCI, CABG, and perioperative bleeding, we applied hospitalization cost retrieved from the literature [68, 69].

The estimates for the events cost at 1 year were literature-based (see above) and included cost incurred as outpatients (e.g. follow-up visits, outpatients procedures) and costs due to rehospitalizations. The model assumed that all PCI patients received a bare metal stent (see sensitivity analysis) and that 44% of the cardiac arrest survivors underwent internal cardiac defibrillator implantation [70]. Costs were inflated by the relevant consumer price index as necessary. Appendix 9 summarizes the methods and estimates (in 2011 CAD$) reported by the cost sources.

3.C.4. Sensitivity analysis

Given the uncertainty around the effect of the Troponin T screening and of the consequent treatment on outcome, we explored various treatment effect sizes (Table 4).
To explore the impact of adherence to the prescribed treatment, we predefined the following scenarios: a) 100% adherence in patients with preoperative intake of the 4-drug combination and 50% adherence in patients with administration start after PMI detection, b) 100% adherence in patients with preoperative intake of the 4-drug combination and 90% adherence in patients with administration start after PMI detection. The reference case assumed a100% adherence in patients with preoperative intake of the 4-drug combination (no additional effect was assumed in these patients) and 75% adherence in patients with administration start after PMI detection

In the reference model, we assumed that the event rate in VISION represented the natural course in spite of the fact that the health care providers are not blinded to the Troponin T concentrations. Therefore, the event rate in the patients with detected PMI/isolated Troponin T elevations was the VISION event rate*Relative Risk. In a sensitivity analysis, we assumed the VISION event rate to be the event rate in the treated, i.e. detected patients, and the event rate in the missed cases was estimated by VISION event rate*(1/Relative Risk). We calculated cost

and consequences of a Troponin T under the various assumptions and presented the results as disaggregated cost and consequences (probabilistic sensitivity analysis, mean over 5,000 simulations) and as multiple cost-effectiveness acceptability curves. The unit of the x-axis in the CEAC was incremental averted deaths per CAD$.

In terms of cost, we assessed a scenario with additional clopidogrel administration in patients with PMI and isolated Troponin elevations and a scenario in which drug eluting stents were implanted in all patients undergoing PCI.

As mentioned above, the noncardiac surgery population is heterogeneous and therefore the reference model assessed 1-year survival. In a sensitivity analysis, we assessed a scenario with a 5-year time horizon by a Markov model with 4 cycles after the 1 year after surgery. For patients without PMI or isolated Troponin elevation, we assumed the mortality of the general population [71] (age- and sex-specific for a cohort of 65-year old with a male proportion of 48%) and the mortality of patients after the first year after myocardial infarction in the nonoperative setting [72] for patients with PMI or isolated Troponin T elevations. After the first year, the model assumed a treatment effect on survival but not on the incidence of cardiovascular complications (e.g. strokes). The model assumed a stable adherence at 75% to the combined 4-drug medication. The cost after the first year consisted in the drug cost in both arms, given that event-related costs were considered to equally apply to both groups (no treatment effect on cardiovascular events). We applied a 5% discounting.

3.C.5. Exploration of heterogeneity

We ran the model in populations at various levels of PMI risk and presented the results as disaggregated cost and consequences and their incremental and as multiple CEAC. We predefined the following heterogeneity analyses: a) aged ≥65 years, ≥75years; b) orthopedic surgery; c) urgent/emergent surgery; d) major general surgery; e) Revised Cardiac Risk Index (RCRI) score of ≥1, ≥2, ≥3.

4. RESULTS

4.A. BASELINE CHARACTERISTICS

The data forming the basis for the effectiveness (probability, sensitivity, specificity) of postoperative Troponin T screening were generated in 6,149 Canadian VISION patients. Nearly half of the patients were men (47.7%) and 73.2% of the patients were aged ≥65 years. Cardiovascular risk factors included arterial hypertension in 53.9%, diabetes in 18.6%, and CAD in 16.9%. The most common types of surgery were low-risk surgery (32%), major orthopedic surgery (27%) and major general surgery (15.3%). The surgery was classified as urgent or emergent- i.e. within 72hours or less of the acute event- in 10.3%. Table 1 reports the details of demographics, preoperative risk factors and type of surgery.

The estimates of the 30-day events and of 1-year mortality after noncardiac surgery were generated in 13,871 and 11,251 international patients, respectively. Nearly half of the patients were men (48.4%) and 49.0% of the patients were aged ≥65 years. Cardiovascular risk factors included arterial hypertension in 50.9%, diabetes in 19.5%, and CAD in 12.1%. The most common types of surgery were low-risk surgery (40.8%), major orthopedic surgery (19.6%) and major general surgery (20.2%). The surgery was classified as urgent /emergent in 14.1%.

4.B. COST-CONSEQUENCE ANALYSIS OF TROPONIN T SCREENING ON THE DETECTION OF PMI

4.B.1. Reference model

The incremental costs of a postoperative PMI screening by 4 Troponin T measurements was CAD$ 99.45 per screened patient, including follow-up diagnostics and consultations in patients with elevated Troponin T measurements. The cost to avoid missing an event amounted to CAD$ 5,184 for PMI and CAD$ 2,983 for isolated Troponin T (Table 5). Figure 4a and 4b show the distribution of the simulations in the incremental cost-effectiveness plan and the

corresponding cost-effectiveness acceptability curve. Under assumption of a volume of 100,000 noncardiac surgery procedures per year the annual budget impact of a postoperative PMI screening program amounted to CAD$ 9.94 million with the incremental detection of 1,918 PMI and of 3,334 isolated Troponin T elevations. The absolute 30-day mortality was 12.9% (95%CI 10.1-16.4) in patients who suffered a PMI, 7.7% (95%CI 5.7-10.3) in patients with isolated Troponin T, and 1.1% (95%CI 0.9-1.2) in the patients without any of the two.

4.B.2. Sensitivity analysis

The incremental cost to avoid missing a PMI amounted to CAD$ 5,565 under assumption of 25% increase in resource utilisation in the screening and 25% reduction in resource utilisation in the standard care alternative (worst case) and to CAD$ 4,362 under assumption of 25% reduction in resource utilisation in the screening and 25% increase in resource utilisation in the standard care alternative (best case). Under assumption of a 0% and 10% false positive rate in the standard care, the detection of a PMI cost CAD$ 5,053 and CAD$ 4,697, respectively (Table 6).

4.B.3. Exploration of heterogeneity

The cost-effectiveness of the postoperative Troponin screening was higher in patients' subgroups at higher risk for PMI, i.e. elderly, patients with higher RCRI-score and in patients undergoing urgent/emergent surgery (Figure 5, Table 7). The incremental costs to avoid missing a PMI were less than CAD$ 3,000 in patients aged ≥75 years, those undergoing urgent/emergent surgery, in patient with at least RCRI ≥2, and with a history of CAD or of PVD. The cost-effectiveness ratio range between CAD$ 3,000 and CAD$ 4,000 per detected PMI in patients undergoing orthopedic surgery, those with a history of diabetes mellitus, those aged ≥ 65 years, and in presence of a RCRI ≥ 1.

4.B.4. Exploration of various screening protocols

The 1st measurement detected 34.6%, the 2nd measurement 22.9%, the 3rd measurement 26%, and the 4th measurement 16.5% of the PMI (Table 8). A screening protocol consisting of 3 measurements appeared the most cost-effective with CAD$ 5,142 per detected PMI and CAD$ 2,802 per detected isolated Troponin T (Table 9). The marginal cost from 3 to 4 measurements amounted to CAD$ 5,142 per additionally detected PMI and 5,184 per additionally detected isolated Troponin T elevation.

4.C. COST-CONSEQUENCE ANALYSIS OF TROPONIN T SCREENING ON 1-YEAR SURVIVAL

4.C.1. Reference model

The incremental costs at 1 year of a postoperative PMI screening by 4 Troponin T measurements were CAD$ 169.20 per screened patient. The cost to prevent a death at 1 year amounted to CAD$ 96,314 (Table 10). Figure 6 shows the distribution of the simulations in the incremental cost-effectiveness plan (6a) and the corresponding cost-effectiveness acceptability curve (6b). Under assumption of a volume of 100,000 noncardiac surgery procedures per year the annual budget impact of a postoperative PMI screening program and consequent treatment amounted to CAD$ 16.8 million and prevented 175 deaths in the first 1 year after noncardiac surgery.

4.C.2. Sensitivity analysis

The incremental cost varied from CAD$ 62,728 per averted death under the best case scenario with respect to treatment effect (effect of aspirin with additional 25% relative risk reduction through the combination of 4 drugs) to CAD$ 196,566 in the worst-case, i.e. the assumption of a treatment effect as reported for the isolated use of aspirin (Table 11, Figure 7).

Under assumption of a treatment adherence of 50% the prevention of a death at 1 year generated cost of CAD$ 154.195. Under assumption of a high adherence (90%) the corresponding amount was CAD$ 82,310 per averted death (Table 11, Figure 8).

The reference case assumed the event rate in VISION to represent the untreated patients. If the VISION incidence of cardiovascular events represented the treated course rather than the natural course, the prevention of one death at 1 year after noncardiac surgery would require CAD$ 59,213 (Table 11, Figure 9).

Under assumption of clopidogrel administration in patients with PMI or isolated Troponin elevation the costs amounted to CAD$ 102,493 per averted death. The treatment by drug-eluting stent in all patients undergoing PCI increased the cost per averted death to CAD$ 99,519. The cost per life-year saved in a 5-year horizon model was CAD$ 23,281.

4.C.3. Exploration of heterogeneity

The incremental costs to prevent a death at 1 year was less than CAD$ 80,000 in patients ≥ 65 years and less than CAD$ 60,000 in patients aged ≥ 75 years and in those undergoing urgent/emergent surgery (Figure 10 and 11). With increased RCRI score the cost to avert a death decreased from CAD$ 65,407 (RCRI ≥1) to 31,800 (RCRI ≥1) (Table 12, Figure 12)

5. DISCUSSION

5.A. MAIN RESULTS

This analysis suggests that the incremental cost to avoid missing a PMI after noncardiac surgery in unselected patients aged ≥45 years through troponin screening (compared with no screening) would be CAD$ 5,184. The estimated incremental costs to detect an isolated Troponin elevation after noncardiac surgery would amount to CAD$ 2,983. Both conditions are associated with a high mortality within 30 days and together may account for 42% of the 30-day deaths after noncardiac surgery [34]. The estimated incremental cost to avoid missing a PMI was less than CAD$ 3,000 in selected populations, e.g. patients aged ≥75 years, patients undergoing urgent/emergent surgery, patients with a history of cardiovascular disease, or patients with a Revised Cardiac Risk score ≥2 risk factors. By way of comparison, the cost of cancer screening programs amounted to 2011-US$ 12,580 per detected breast, 2011-US$ 15,885 per detected cervical [73] and 2009-US$ 10,086 per detected prostate cancer [74]. Furthermore, the risk of death related to PMI or isolated Troponin elevation is much more immediate (i.e., within 30-days) compared to cancer screening, which may range from years to decades.

Among the screening protocol tested, the more cost-effective approach appeared to be a screening consisting in 3 Troponin T measurements, i.e. at 6 to 12 hours, on postoperative days 1 and 2. Under assumption of a surgical volume of 100,000 noncardiac procedures, a budget of CAD$ 8.43 million would allow physicians to identify an additional 3,649 patients (1,640 PMI and 3,009 isolated Troponin T elevations) with perioperative myocardial ischemia, offering an opportunity to intervene with treatment.

To date, the optimal treatment and secondary prophylaxis after PMI and Troponin elevation has not been established in a randomized controlled trial. Observational data reported an adjusted odds ratio of 0.52 (95%CI 0.29-0.99) for aspirin and 0.26 (0.13-0.54) for statin treatment after PMI [35], thus supporting the assumption of beneficial interventions for

these patients. A strategy of postoperative Troponin T screening therefore, has the potential to improve survival in patients after noncardiac surgery.

Our model of 1-year survival after noncardiac surgery suggest that the cost to prevent a death within the 1st year after noncardiac surgery through postoperative Troponin T screening amounted to CAD$ 96,314. Under the assumption of a volume of 100,000 noncardiac surgery procedures per year, the annual budget impact of a postoperative PMI screening program and consequent treatment amounted to CAD$ 16.8 million and prevented 175 deaths. These estimates, however were sensitive to the assumed treatment effect, with CAD$ 196,566 per prevented death under assumption of the same effect size as for aspirin only by the 4-drug combination. Further, there was relevant model uncertainty associated with the efficacy of the treatment in the 1-year model.

In high-risk populations, e.g. patients aged ≥75 years, patients undergoing urgent/emergent surgery or those with 2 or more risk factors (RCRI), the estimates were less than CAD$ 60,000 per averted death. The costs per life-year gained in a sensitivity analysis with a 5-year horizon were less than CAD$ 25,000.

5.B. STRENGTHS AND LIMITATIONS

Our study's strengths consist in the large, representative sample of patients (> 6,000 patients, broad inclusion criteria) undergoing noncardiac surgery in Canada for the estimates of postoperative Troponin T screening results. PMI and isolated Troponin T elevation underwent central adjudication. The estimates of the 30-day and 1-year event rate based on a representative sample of >10,000 patients after noncardiac surgery. The large sample size allowed for the exploration of the cost-effectiveness both in terms of PMI detection and of 1-year survival in relevant subgroups. Further, we did not focus on cost-effectiveness only but also addressed affordability, i.e. the budget impact associated with a Troponin T screening in patients undergoing surgery [13]. Finally, we conducted extensive sensitivity and scenario analyses.

This cost-consequence analysis has limitations. The VISION Study did not collect resource utilisation data. Therefore, for the estimation of resource utilisation in presence of elevated Troponin concentrations, we applied diagnostic algorithms (both for the Troponin T screening and for the standard care alternative) based on expert opinion. However, sensitivity analyses suggest that the assumptions made only small differences in the cost-effectiveness estimates. Further, we retrieved the cost estimates for the various events, e.g. stroke, congestive heart failure, from the literature, i.e. they were not specific for events acquired in the postoperative setting. Given that the VISION Study did not have a standard care alternative, the model relied on the following assumptions with regard to the health states: first, that the proportion of detected and missed PMI by clinical assessment corresponded to the symptomatic and asymptomatic PMI diagnosed in VISION. Second, VISION did not collect ischemic symptoms in Troponin-negative patients, and we estimated the proportion of false positive (i.e. noncardiac chest pain) based on expert opinion. Sensitivity analyses suggest a very limited impact of this parameter on the cost-effectiveness estimates.

There is no RCT-generated evidence of the effectiveness of Troponin screening after noncardiac surgery on patient-important outcomes, as such we populated the model with hypothetical treatment effect sizes and adherence estimates. However, we extensively explored the impact of our assumptions in sensitivity analyses. Further, various modelling guidelines agree [5] that lack of data fulfilling the "ideal standards of scientific rigor" should not prevent modelling because "Decisions will be made, with or without the model. To reject the model because of incomplete evidence would imply that a decision with neither the data nor the model is better than a decision with the model but without the data" [5]. The CADTH guidelines [2] also discuss the issue of the timing of the evaluation: on one side early evaluations (i.e. shortly after introduction of a new strategy when effectiveness data may not be available), will suffer from high degrees of uncertainty; on the other side, late evaluations bear the risk of being uninformative to decision-makers because of obsolete results, e.g. if the decision already occurred [13-16] or in presence of uncontrolled diffusion [2, 17].

Health care providers were not blinded to Troponin T results in the VISION study; therefore, the event rate occurring in VISION might not represent the natural course of PMI after noncardiac surgery but the course after treatment initiation triggered by the Troponin T

measurements mandated by the study. We explored the impact of this assumption in a scenario analysis.

We assessed a time horizon of 1 year. Good modelling practice guidelines encourage the use of life-long horizons [2, 5]. However, given the heterogeneous long-term prognosis of patients undergoing noncardiac surgery, we considered a common projection after 1 year most appropriate for the reference model. Further, we reported the results as cost per averted death within the first year. This measure does not represent one life-year, because the majority of incremental survivors will continue to survive beyond the 1-year cut. We conducted a sensitivity analysis over a 5-

Finally, the proposed models did not integrate potential psychological harms resulting from "labelling" [75] and the negative effects of false negative results [76]. Anxiety, distress and absenteeism have been reported after positive screening for chronic conditions [75]. Shaw and coworkers systematically reviewed and meta-analysed randomized trials and observational studies that addressed the psychological consequences of positive screening results. Their findings suggest an increase of short-term anxiety and short-term depression after positive screening that however did not persist in the long-term. Absenteeism increased after positive screening in 2 of 7 studies [75]. We consider the results on the psychological effects of positive screening in conditions with an extended timeline between diagnosis and clinical manifestation to be of limited applicability to the acute condition "PMI" that is associated with a 12.9% 30-day mortality in these data. Similarly, we did not take into account the psychological and legal consequences of false negative screening, i.e. false reassurance, the demotivation to engage in healthier life-styles, or potential litigation [76]. Data on these effects are scarce and addressed other settings, e.g. antenatal or and breast cancer screening [76]; as such they appear of limited applicability to case detection of PMI.

5.C. COMPARISON WITH PRIOR STUDIES

Mantha and coworkers [77] evaluated the cost-effectiveness of a postoperative Troponin I screening (4 measurements) strategy to initiate PMI-reducing measures (heart rate

control and surveillance in a coronary care unit) in patients aged ≥65 years undergoing open abdominal aortic aneurysm repair. They populated their model based on literature data and assumed a 4.9% PMI-probability and a hypothetical RR of 0.55 by the application of the mentioned strategies. They measured health benefit as QALY projected over a life-time horizon and concluded that a postoperative Troponin I screening after abdominal aortic aneurysm repair was cost-effective by an incremental cost-effectiveness ratio of 2003-US $12,641/QALY.

Our model was populated by a large contemporary cohort of patients undergoing a broad spectrum of noncardiac surgery procedures and it was not limited by the use of QALY not specific for postoperative events. In spite of these differences in methods, both evaluations support that there are health gains achievable by a Troponin T screening after noncardiac surgery within commonly applied ceiling ratios. Under the sole focus of the estimated incremental cost per health gain, the implementation of a postoperative Troponin T screening after noncardiac surgery seems appealing, in particular in patients at high risk for PMI. However, decision-makers will have to consider it in terms of opportunity costs, i.e. in relation to the cost-effectiveness of other potential programs within the broader health care context.

5.D. CLINICAL IMPLICATIONS

Globally, more than 200 million patients undergo major non-cardiac surgery each year [31] and more than 10 million patients will be exposed to postoperative myocardial ischemia (PMI or isolated Troponin elevation). This condition is strongly associated with 30-day mortality, but 4 in 5 patients will be deprived of potentially effective treatment because the lack of ischemic symptoms results in the majority of these events going undetected without a Troponin screening program. Based on the estimated incremental cost per health gain, the implementation of a postoperative Troponin T screening after noncardiac surgery seems appealing, in particular in patients at high risk for PMI, e.g. elderly patients, patients undergoing urgent or emergent surgery, and patients with known or with risk factors for atherosclerotic disease. However, decision-makers will have to consider it in terms of opportunity costs, i.e. in

relation to the cost-effectiveness of other potential programs within the broader health care context.

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7. TABLES

Table 1. Baseline characteristics overall and by health state. Patients with asymptomatic PMI are included in the detected PMI (TP) in the Troponin T screening alternative and classified as missed PMI(FN) in the standard care alternative (*).

	All n=6149	no PMI (TN) n=5746	symptomatic PMI (TP) n=70	asymptomatic PMI (TP/FN)* n=118	Isolated Troponin elevation n=205	False negative Troponin screening n=10
Age, mean (SD), years	64.9 (11.6)	64.4 (11.3)	74.6 (12.1)	74.4 (10.8)	70.1 (12.5)	73.3 (7.6)
Age ≥ 65 years	3050 (49.6)	2758 (48.0)	55 (78.6)	95 (80.5)	133 (64.9)	9 (90)
Age ≥ 75 years	1453 (23.6)	1256 (21.9)	41 (58.6)	64 (54.2)	86 (42.0)	6 (60.0)
Male	2932 (47.7)	2712 (47.2)	35 (50.0)	58 (49.2)	121 (59.0)	6 (60.0)
History of CHF	205 (3.3)	160 (2.8)	10 (14.3)	13 (11.0)	22 (10.7)	0
History of CAD	1042 (16.9)	893 (15.5)	35 (50.0)	50 (42.4)	59 (28.8)	5 (50.0)
PCI/CABG < 1 year	85 (1.4)	70 (1.2)	4 (5.7)	4 (3.4)	7 (3.4)	0
History of cerebrovascular event	442 (7.2)	379 (6.6)	15 (21.4)	12 (10.2)	35 (17.1)	1 (10.0)
History of PVD	300 (4.9)	238 (4.1)	16 (22.9)	16 (13.6)	29 (14.1)	1 (10.0)
History of hypertension	3316 (53.9)	3027 (52.7)	55 (78.6)	85 (72.0)	139 (67.8)	10 (100)
History of diabetes	1144 (18.6)	1024 (17.8)	24 (34.3)	35 (29.7)	58 (28.3)	3 (30.0)
History of or current AF	469 (7.6)	403 (7.0)	13 (18.6)	18 (15.3)	35 (17.1)	0
Urgent/emergent surgery	631 (10.3)	554 (9.7)	12 (17.1)	30 (25.4)	33 (16.1)	2 (20.0)
Vascular surgery	232 (3.8)	200 (3.5)	12 (17.1)	9 (7.6)	11 (5.4)	0
Major general surgery	940 (15.3)	862 (15.0)	13 (18.6)	21 (17.8)	40 (19.5)	4 (40.0)
Thoracic surgery	153 (2.5)	143 (2.5)	1 (1.4)	2 (1.7)	7 (3.4)	0
Major urogynecologic	775 (12.6)	728 (12.7)	6 (8.6)	15 (12.7)	26 (12.7)	0
Major orthopedic	1690 (27.5)	1563 (27.2)	22 (31.4)	47 (39.8)	55 (26.8)	3 (30.0)
Neurosurgery	390 (6.3)	370 (6.4)	3 (4.3)	4 (3.4)	12 (5.9)	1 (10)
Low risk surgery	1969 (32.0)	1880 (32.7)	13 (18.6)	20 (16.9)	54 (26.3)	2 (20.0)
RCRI ≥ 1	2196 (35.7)	1942 (33.8)	53 (75.7)	75 (63.6)	120 (58.5)	6 (60.0)
RCRI ≥ 2	624 (10.1)	496 (8.6)	26 (37.1)	39 (33.1)	61 (29.8)	2 (20.0)

RCRI ≥ 3	160 (2.6)	109 (1.9)	11 (15.7)	14 (11.9)	25 (12.2)	1(10.0)

Vascular surgery included thoracic aorta or aorto-iliac reconstructive procedures, peripheral vascular reconstruction without aortic cross-clamping, extracranial cerebrovascular surgery and endovascular abdominal aortic aneurysm repair. Major general surgery included complex visceral resection, partial or total colectomy or stomach surgery, other intra-abdominal surgery, and major head and neck resection for tumor. Neurosurgery included craniotomy and spine surgery involving multiple levels of the spine. Major Orthopedic Surgery included major hip or pelvis surgery (hemi or total hip arthroplasty, internal fixation of hip, pelvic arthroplasty). Major Urology or Gynecology Surgery included visceral resection (i.e., nephrectomy, ureterectomy, bladder resection, retroperitoneal tumor resection, radical procedure for cancer [i.e. exenteration], hysterectomy). Low-Risk Surgery included parathyroid, thyroid, breast, hernia, local anorectal procedure, radical prostatectomy, transurethral prostatectomy, oopherectomy, salpingectomy, endometrial ablation, peripheral nerve surgery, ophthalmology, ears/nose/throat surgery, vertebral disc surgery, spinal fusion, knee arthroplasty, hand surgery, cosmetic surgery, arterio-venous access surgery for dialysis, other surgery not fulfilling the major criteria as above. Revised Cardiac Risk Index ≥ 1, ≥ 2, and ≥ 3 included at least 1, 2, and 3 of the following: history of coronary artery disease, of congestive heart failure, of cerebrovascular accident, diabetes mellitus requiring insulin-treatment, preoperative creatinine concentrations > 2 mg/dL.

Table 2. Parameters and their distributions of the model of Troponin T screening on the detection of PMI.

Health states	Distribution	Point estimate	α/β	Source
TN Troponin screening	beta	0.934	5746/403	VISION study
TP Troponin screening	beta	0.031	188/5961	VISION study
FN Troponin screening	beta	0.002	10/6139	VISION study
Isolated Troponin elevation*	beta	0.033	205/5944	VISION study
TN standard care	beta	0.909	5592/557	residual
TP standard care	beta	0.011	70/6079	VISION study**
FN standard care (PMI)	beta	0.019	118/6031	VISION study**
FN standard care (isolated Troponin elevation)*	beta	0.035	215/5934	VISION study**
FP standard care	beta	0.025	154/5995	expert-based
Cost parameters	Distribution	Point estimate	α/β or SE	Source
ECG	NA	16.65		Ontatio Health Insurance (OHIP) Schedule of Benefit, Diagnostic and Therapeutic procedures[78]
Echocardiography	NA	131.85		Ontatio Health Insurance (OHIP) Schedule of Benefit, Diagnostic and Therapeutic procedures[78]
Troponin T measurement (per measurement)	NA	18		Personal communication, Laboratory Reference Centre affiliated to Hamilton Health Sciences (www.hrlmp.ca)
Cardiologist's consultation	NA	148.95		Ontario Health Insurance (OHIP) Schedule of Benefits and Fees, Consultations and Visits[78]
Cardiologist's partial assessment	NA	36.20		Ontario Health Insurance (OHIP) Schedule of Benefits and Fees, Consultations and Visits[78]
Coronary angiogram	NA	1727.88		Ontatio Health Insurance (OHIP) Schedule of Benefit, Diagnostic and Therapeutic procedures[78]+ Overhead cost based on unpublished data calculated for Wang X et al. J Med Econ. 2008.[68]

Probability of FN Troponin screening with case detection not based on autopsy findings	beta	1	10/0	VISION study
Probability of PMI diagnosis based on echocardiography only	beta	0.080	15/173	VISION study
Probability of Troponin turning positive in the last scheduled measurement	beta	0.141	57/346	VISION study
Probability of angiogram in patients with symptomatic PMI	beta	0.186	13/57	VISION study
Probability of angiogram in patients with asymptomatic PMI	beta	0.128	24/164	VISION study
Probability of angiogram in patients with isolated Troponin elevation	beta	0.010	2/203	VISION study
Probability of angiogram in FN-screened patients	beta	0.100	1/9	VISION study
Cost Troponin screening TN	log normal	72	3.60	
Cost Troponin screening TP	log normal	700.080593	35.00	
Cost Troponin screening FN	log normal	541.892562	27.09	
Cost Troponin screening isolated Troponin T elevation	log normal	487.833009	24.39	
Cost standard care TN	NA	0		expert-based diagnostic algorithms, calculated by the parameter cost listed above
Cost standard care TP	log normal	832.10177	41.61	
Cost standard care FN (PMI)	NA	0		
Cost standard care FN (isolated Troponin elevation)	NA	0		
Cost standard care FP	log normal	69.3	3.47	

FN: false negative; FP false positive; NA: not applicable; PMI: perioperative myocardial infarction; SE: standard error; TN: true negative; TP: true positive

Table 3. Parameters and their distributions of the model of Troponin T screening on 1-year survival

Health states	Distribution	Point estimate	α/β or SE	Source
Detected PMI (Troponin screening)	beta	0.0306	0.0022	modelled based on VISION data (Table2)
Missed PMI (Troponin screening)	beta	0.0016	0.0005	modelled based on VISION data (Table2)
Isolated Troponin elevation (Troponin screening)	beta	0.0333	0.0023	modelled based on VISION data (Table2)
Detected PMI (Standard care)	beta	0.0114	0.0014	modelled based on VISION data (Table2)
Missed PMI (Standard care)	beta	0.0192	0.0018	modelled based on VISION data (Table2)
Missed isolated Troponin elevation (Standard care)	beta	0.0350	0.0024	modelled based on VISION data (Table2)
False positive (Standard care)	beta	0.0250	0.0020	modelled based on VISION data (Table2)
Probability of 30-day ReMI without PMI/ isolated Troponin elevation	beta	0.0035	20/5729	VISION study
Probability of 30-day PCI without PMI/ isolated Troponin elevation	beta	0.0002	3/13868	VISION study
Probability of 30-day CABG without PMI/ isolated Troponin elevation	beta	0.0001	1/13870	VISION study
Probability of 30-day CHF without PMI/ isolated Troponin elevation	beta	0.0099	138/13733	VISION study
Probability of 30-day cardiac arrest without PMI/ isolated Troponin elevation	beta	0.0006	8/13863	VISION study
Probability of 30-day stroke without PMI/ isolated Troponin elevation	beta	0.0042	58/13813	VISION study
Probability of 30-day bleeding without PMI/ isolated Troponin elevation	beta	0.0225	128/5572	VISION study

Probability of 30-day death without PMI/ isolated Troponin elevation	beta	0.0106	147/13724	VISION study
Probability of 30-day ReMI with PMI	beta	0.0068	1/146	VISION study
Probability of 30-day PCI with PMI	beta	0.0352	15/411	VISION study
Probability of 30-day CABG with PMI	beta	0.0188	8/418	VISION study
Probability of 30-day CHF with PMI	beta	0.1737	74/352	VISION study
Probability of 30-day cardiac arrest with PMI	beta	0.0164	7/419	VISION study
Probability of 30-day stroke with PMI	beta	0.0235	10/416	VISION study
Probability of 30-day bleeding with PMI	beta	0.0827	11/122	VISION study
Probability of 30-day death with PMI	beta	0.1291	55/371	VISION study
Probability of 30-day ReMI with isolated Troponin elevation	beta	0.0057	1/173	VISION study
Probability of 30-day PCI with isolated Troponin elevation	beta	0.0019	1/517	VISION study
Probability of 30-day CABG with isolated Troponin elevation	beta	5.127E-07	2.652E-05	VISION study
Probability of 30-day CHF with isolated Troponin elevation	beta	0.0618	32/486	VISION study
Probability of 30-day cardiac arrest with isolated Troponin elevation	beta	0.0019	1/517	VISION study
Probability of 30-day stroke with isolated Troponin elevation	beta	0.0116	6/512	VISION study
Probability of 30-day bleeding with isolated Troponin elevation	beta	0.0941	16/154	VISION study
Probability of 30-day death with isolated Troponin elevation	beta	0.0772	40/478	VISION study
Probability of 1-year death after no complications after no PMI	beta	0.0359	253/6785	VISION study
Probability of 1-year death after ReMI	beta	0.1888	151/649	VISION study
Probability of 1-year death after PCI	beta	0.0909	1/10	VISION study
Probability of 1-year death after CABG	beta	4.6353E-06	1.877E-04	VISION study

Probability of 1-year death after CHF	beta	0.2340	44/144	VISION study
Probability of 1-year death after cardiac arrest	beta	1.6025E-06	6.109E-05	VISION study
Probability of 1-year death after stroke	beta	0.2115	11/41	VISION study
Probability of 1-year death after bleeding	beta	0.0886	336/3456	VISION study

Treatment effect-releted parameters	Distribution	Point estimate	SE	Source
Relative risk for ReMI	log normal	0.4165	0.1398	assumption (see Appendix 7 and 8)
Relative risk for PCI	log normal	1.0000		assumption (see Appendix 7 and 8)
Relative risk for CABG	log normal	1.0000		assumption (see Appendix 7 and 8)
Relative risk for CHF	log normal	0.9650	0.0161	assumption (see Appendix 7 and 8)
Relative risk for cardiac arrest	log normal	0.7616	0.0883	assumption (see Appendix 7 and 8)
Relative risk for stroke	log normal	0.4505	0.2522	assumption (see Appendix 7 and 8)
Relative risk for bleeding	log normal	1.2510	0.1053	assumption (see Appendix 7 and 8)
Relative risk for 30-day mortality	log normal	0.6715	0.0453	assumption (see Appendix 7 and 8)
Relative risk for 1-year mortality	log normal	0.7650	0.0481	assumption (see Appendix 7 and 8)
Adherence to treatment initated after PMI/isolated Troponin T elevation detection		0.7500		assumption based on Yan et al, 2007[51]
Probability of preoperative drug intake in patients without PMI/isolated Troponin T elevation	beta	0.1392	1928/13854	VISION study
Probability of preoperative drug intake in patients with PMI/isolated Troponin T elevation	beta	0.265	318/1200	VISION study
Adherence to preoperative treatment		1		assumption

Cost parameters		Point estimate	SE	
Cost of Troponin T screening in patients without PMI	gamma	73.77	15.78	modelled (Table2)
Cost of Troponin T screening in patients with PMI	gamma	797.24	275.12	modelled (Table2)
Cost of Troponin T screening in patients with missed PMI	gamma	724.19	301.57	modelled (Table2)
Cost of Troponin T screening in patients with isolated Troponin elevation	gamma	496.99	158.58	modelled (Table2)
Cost of standard care in patients without PMI		0.00		assumption
Cost of standard care in patients with PMI	gamma	859.03	314.76	modelled (Table2)
Cost of standard care in patients with missed PMI		0.00		modelled (Table2)
Cost of standard care in patients with isolated Troponin elevation		0.00		modelled (Table2)
Cost of standard care in patients with FP Troponin screening	gamma	71.23	15.42	modelled (Table2)
30-day cost in patients with no complications		0.00		assumption
30-day cost in patients with ReMI	gamma	9,580.76	205.74	OCCI fiscal year 2009-2010, subendocard M (code I214)[79]
30-day cost of pat who underwent PCI	gamma	9,648.05	42.05	Wang, J Med Econ 2008, probabilistic results BMS [68]
30-day cost of pat who underwent CABG	gamma	15,673.82	28.32	Wang, J Med Econ 2008, probabilistic results onpump CABG
30-day cost in patients with CHF	gamma	10,100.25	183.76	OCCI fiscal year 2009-2010, congestive HF (code I500) [79]
30-day cost in patients with cardiac arrest	gamma	33,783.29	6448.57	OCCI fiscal year 2009-2010,cardiac arrest with successful resuscitation (code I460) [79]

30-day cost in patients with stroke	gamma	15,295.19	608.38	OCCI fiscal year 2009-2010, cerebral infarction unspecified (code 1639) [79]
30-day cost in patients with bleeding	gamma	4,051.31	202.57	according to distribution of surgical type in overall VISION, based on Stokes, BMC HealthServices Res 2011 [69]
1-year cost in patients with no complications		0.00		
1-year cost in patients with ReMI	gamma	4,364.58	328.50	Frasure Smith, Psychosom Res 2000 [80]
1-year cost of pat who underwent PCI	gamma	2,635.38	10.71	Wang, J Med Econ 2008 [68]
1-year cost of pat who underwent CABG	gamma	1,137.46	2.01	Wang, J Med Econ 2008 [68]
1-year cost in patients with CHF	gamma	21,832.98	1091.65	Wijeysundera H, Val Health 2010[81]
1-year cost in patients with cardiac arrest	gamma	37,940.93	1897.05	Nichol Ann Emerg Med 2009, [70]
1-year cost in patients with stroke	gamma	28,738.21	1436.91	Goeree J Med Econ 2005 [82]
Cost Aspirin		0.028		Ontario drug benefit formulary, version Jan 19th 2012 [66]
Cost B-Blocker		0.1415		Ontario drug benefit formulary, version Jan 19th 2012 [66]

Cost Statine	0.559	Ontario drug benefit formulary, version Jan 19th 2012 [66]
Cost ACE-Inhibitor	0.2533	Ontario drug benefit formulary, version Jan 19th 2012
Dispensing fees and markup factor	1.232	Canada Statistics [67]

ACE: angiotensin converting enzyme; CABG: coronary artery bypass graft; CHF: congestive heart failure; OCCI: Ontario Case Costing Initiative; PCI: percutaneous coronary intervention; PMI: perioperative myocardial infarction; SE: standard error

Table 4. Treatment effect size assumed in the sensitivity analyses for the combination of aspirin, B-blocker, ACE-inhibitors and statin. The shaded cells apply to the reference model.

	Relative risk by aspirin	Hypothetical relative risk by a 4-drug combination (110% aspirin effect)	Hypothetical relative risk by a 4-drug combination (115% aspirin effect)	Hypothetical relative risk by a 4-drug combination (120% aspirin effect)	Hypothetical relative risk by a 4-drug combination (125% aspirin effect)
30-day nonfatal re-MI	0.49 (0.37-0.64)	0.44 (0.34-0.58)	0.42 (0.32-0.56)	0.39 (0.3-0.52)	0.37 (0.28-0.48)
30-day nonfatal CHF	0.97 (0.93-1.0)	not applicable	not applicable	not applicable	not applicable
30-day nonfatal cardiac arrest	0.90 (0.75-1.06)	0.81 (0.68-0.96)	0.76 (0.64-0.91)	0.72 (0.6-0.85)	0.67 (0.57-0.80)
30-day nonfatal stroke	0.53 (0.32-0.86)	0.48 (0.29-0.78)	0.45 (0.27-0.74)	0.42 (0.26-0.7)	0.40 (0.24-0.65)
30-day nonfatal bleeding	1.25 (1.02-1.54)	not applicable	not applicable	not applicable	not applicable
30-day all-cause death	0.79 (0.72-0.86)	0.71 (0.65-0.78)	0.67 (0.61-0.73)	0.63 (0.58-0.69)	0.60 (0.54-0.65)
1-year all-cause mortality	0.9 (0.82-0.99)	0.81 (0.74-0.89)	0.77 (0.7-0.84)	0.72 (0.66-0.79)	0.68 (0.61-0.74)

():95% confidence interval; CHF: congestive heart failure; MI: myocardial infarction

Table 5. Costs and health consequences of PMI screening with 4 postoperative Troponin T measurements and of standard care in patients undergoing noncardiac surgery

	Troponin T screening	Standard care	Incremental	Incremental costs to avoid missing an event (CAD$)	30-day mortality (%) (95%CI)
Cost (CAD$)	$ 110.98	$ 11.53	$ 99.45		
Detected PMI (n)	0.03057	0.01139	0.01918	$ 5,183.74	12.9% (10.1-16.4)
Detected isolated Troponin T elevations (n)	0.03334	0	0.03334	$ 2,983.25	7.7% (5.7-10.3)

PMI: perioperative myocardial infarction

Table 6. Impact of varying scenarios of resource utilisation and of false positive rates in the standard care alternative on the cost-effectiveness estimates (deterministic sensitivity analysis).

	Incremental cost (CAD$) per patient undergoing noncardiac surgery	Incremental costs to avoid missing a PMI
Reference case, deterministic analysis	$ 95.25	$ 4,964
25% increase in resource utilisation in the screening and 25% reduction in resource utilisation in the standard care alternative (worst case)	$ 106.80	$ 5,565
25% reduction in resource utilisation in the screening and 25% increase in resource utilisation in the standard care alternative (best case)	$ 83.70	$ 4,362
0% false positive in standard care	$ 96.96	$ 5,053
10% false positive in standard care	$ 90.13	$ 4,697

PMI: perioperative myocardial infarction

Table 7. Cost-effectiveness ratio, budget impact and incremental detected events in populations at various risk

	Incremental Cost/detected PMI (CAD$)	Incremental Cost/ detected isolated Troponin T (CAD$)	Annual volume (n)	Budget impact (million CAD$)	Incremental detected PMI (n)	Incremental detected isolated Troponin elevations (n)
All noncardiac surgery ≥ 45 years	$5'184	$2'983	100,000	9.94	1,918	3,334
≥ 65 years	$3'597	$2'572	49,600	5.56	1,545	2,161
≥ 75 years	$2'900	$2'154	23,600	3.01	1,037	1,397
RCRI ≥ 1	$3'452	$2'161	35,700	4.21	1,220	1,949
RCRI ≥ 2	$2'489	$1'590	10,100	1.57	629	986
RCRI ≥ 3	$2'236	$1'259	2,600	0.51	228	405
Urgent or emergent surgery	$2'680	$2'445	10,300	1.31	490	537
History of CAD	$2'706	$2'288	16,900	2.19	809	957
History of CHF	$2'504	$1'465	3,300	0.52	207	354
History of diabetes	$3'721	$2'251	18,600	2.12	571	943
History of PVD	$2'711	$1'516	4,900	0.72	264	473
Major orthopedic surgery	$3'795	$3'244	27,500	2.89	762	891
Major general surgery	$4,800	$2,518	15,300	1.61	335	639

CAD: coronary artery disease; PMI: perioperative myocardial infarction; PVD: peripheral vascular disease; RCRI: Revised Cardiac Risk Index
Major general surgery included complex visceral resection, partial or total colectomy or stomach surgery, other intra-abdominal surgery, and major head and neck resection for tumor. Major Orthopedic Surgery included major hip or pelvis surgery (hemi or total hip arthroplasty, internal fixation of hip, pelvic arthroplasty. Revised Cardiac Risk Index ≥ 1, ≥ 2, and ≥ 3 included at least 1, 2, and 3 of the following: history of coronary artery disease, of congestive heart failure, of cerebrovascular accident, diabetes mellitus requiring insulin-treatment, preoperative creatinine concentrations > 2 mg/dL.

Table 8. Probability of the health states by the various screening alternatives.

	4 Troponin T measurements	1 Troponin T measurement (6 to 12 hours after surgery)	2 Troponin T measurements (6 to 12 hours after surgery and POD 1	3 Troponin T measurements (6 to 12 hours after surgery and POD 1 & 2)
No PMI (TN)	5746 (93.4%)	5746 (93.4%)	5746 (93.4%)	5746 (93.4%)
PMI				
Symptomatic	70 (1.1%)	20 (0.3%)	38 (0.6%)	56 (0.9%)
Asymptomatic*	118 (1.9%)	45 (0.7%)	70 (1.1%)	101 (1.6%)
Isolated Troponin elevation**	205 (3.3%)	75 (1.2%)	131 (2.1%)	185 (3.0%)
FN Troponin screening	10 (0.2%)	263 (4.3%)	164 (2.7%)	61 (1%)

*part of true positive for Troponin T screening, false negative for symptom-triggered approach; ** false negative for for symptom-triggered approach; FN: false negative; PMI: perioperative myocardial ifnarction; POD: postoperative day; TN: true negative; TP: true positive

Table 9. Cost-effectiveness ratio, budget impact and incremental detected events by various PMI screening alternatives

Number and timing of measurements	Incremental cost per detected PMI (CAD$)	Incremental cost per detected Troponin T elevations (CAD$)	Budget impact (million CAD$)	Incremental detected PMI (n)	Incremental detected isolated Troponin T elevations (n)
4 Troponin T measurements	$ 5,183.74	$ 2,983.25	9.94	1,918	3,334
1 Troponin T measurement	$ 7,304.29	$ 4,369.46	5.34	731	1,222
2 Troponin T measurements	$ 5,978.10	$ 3,197.85	6.81	1,139	2,128
3 Troponin T measurements	$ 5,141.90	$ 2,802.23	8.43	1,640	3,009

PMI: perioperative myocardial infarction.
Budget impact and incremental numbers of detected events assume an annual surgical volume of 100,000 noncardiac procedures.

Table 10. Incremental cost per patient undergoing noncardiac surgery and cost per averted death at 1 year after surgery (reference case).

	Troponin T screening	Standard care	Incremental	Incremental costs to avert one death (CAD$)
Intervention-related cost (CAD$)	$ 262.18	$ 85.91	$ 176.27	
Events-related cost (CAD$)	$ 917.26	$ 925.34	$ -8.08	
Total cost (CAD$)	$ 1,179.44	$ 1,011.25	$ 168.19	
Death at 1 year after surgery (n)	0.06090	0.06265	-0.0017	$ 96,314.79

Table 11. Incremental cost per patient undergoing noncardiac surgery and cost per averted death at 1 year after surgery under various assumptions (sensitivity analyses).

	Incremental cost per patient undergoing noncardiac surgery (CAD$)	Incremental cost per averted death
Treatment effect size		
Hypothetical relative risk by a 4-drug combination (115% aspirin effect)-reference case	$ 168.19	$ 96,315
Hypothetical relative risk by aspirin only	$ 172.48	$ 196,566
Hypothetical relative risk by a 4-drug combination (110% aspirin effect)	$ 164.93	$ 117,927
Hypothetical relative risk by a 4-drug combination (115% aspirin effect)	$ 153.45	$ 75,087
Hypothetical relative risk by a 4-drug combination (120% aspirin effect)	$ 148.20	$ 62,728
Adherence		
75% adherence of treatment triggered by Troponin screening -reference case	$ 168.19	$ 96,315
50% adherence of treatment triggered by Troponin screening -worst case	$ 169.85	$ 154,195
90% adherence of treatment triggered by Troponin screening -best case	$ 170.07	$ 82,310
Natural course		
VISION incidences are untreated incidences -reference case	$ 168.19	$ 96,315
VISION incidences are treated incidences	$ 135.30	$ 59,213
Treatment approach		
Clopidogrel only in patients undergoing PCI (bare-metal stent)-reference case	$ 168.19	$ 96,315
Clopidogrel in all patients with PMI or isolated Troponin elevation	$ 181.57	$ 102,493
Drug-eluting stent in all patients undergoing PCI	$ 176.17	$ 99,519

Table 12. Cost-effectiveness ratio, budget impact and incremental averted death at 1 year in populations at various risk levels

	Incremental Cost/averted death (CAD$)	Annual volume (n)	Budget impact (million CAD$)	Incremental averted death(n)
All noncardiac surgery >= 45 years	96,315	100,000	16.82	175
>= 65 years	78,129	49,600	9.13	117
>=75 years	59,159	23,600	4.60	78
Urgent/emergent surgery	58,612	35,700	6.97	119
Major general surgery				
Orthopedic surgery				
RCRI ≥ 1	65,407	10,100	1.87	29
RCRI ≥ 2	40,494	2,600	0.04	1
RCRI ≥ 3	31,800	10,300	2.59	82

RCRI: Revised Cardiac Risk Index:

Major general surgery included complex visceral resection, partial or total colectomy or stomach surgery, other intra-abdominal surgery, and major head and neck resection for tumor. Major Orthopedic Surgery included major hip or pelvis surgery (hemi or total hip arthroplasty, internal fixation of hip, pelvic arthroplasty. Revised Cardiac Risk Index ≥ 1, ≥ 2, and ≥ 3 included at least 1, 2, and 3 of the following: history of coronary artery disease, of congestive heart failure, of cerebrovascular accident, diabetes mellitus requiring insulin-treatment, preoperative creatinine concentrations > 2 mg/dL.

8. FIGURES

Figure 1. Flow chart of study population

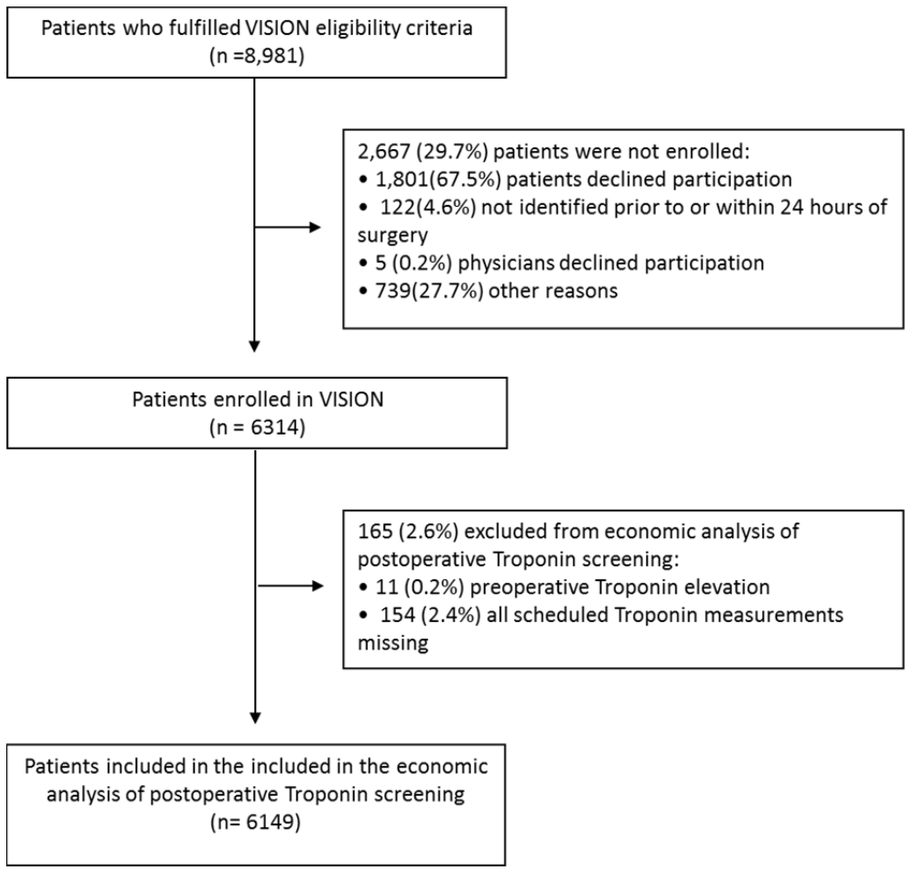


Figure 2. Decision tree representing the alternatives and the health states at the end of the screening period

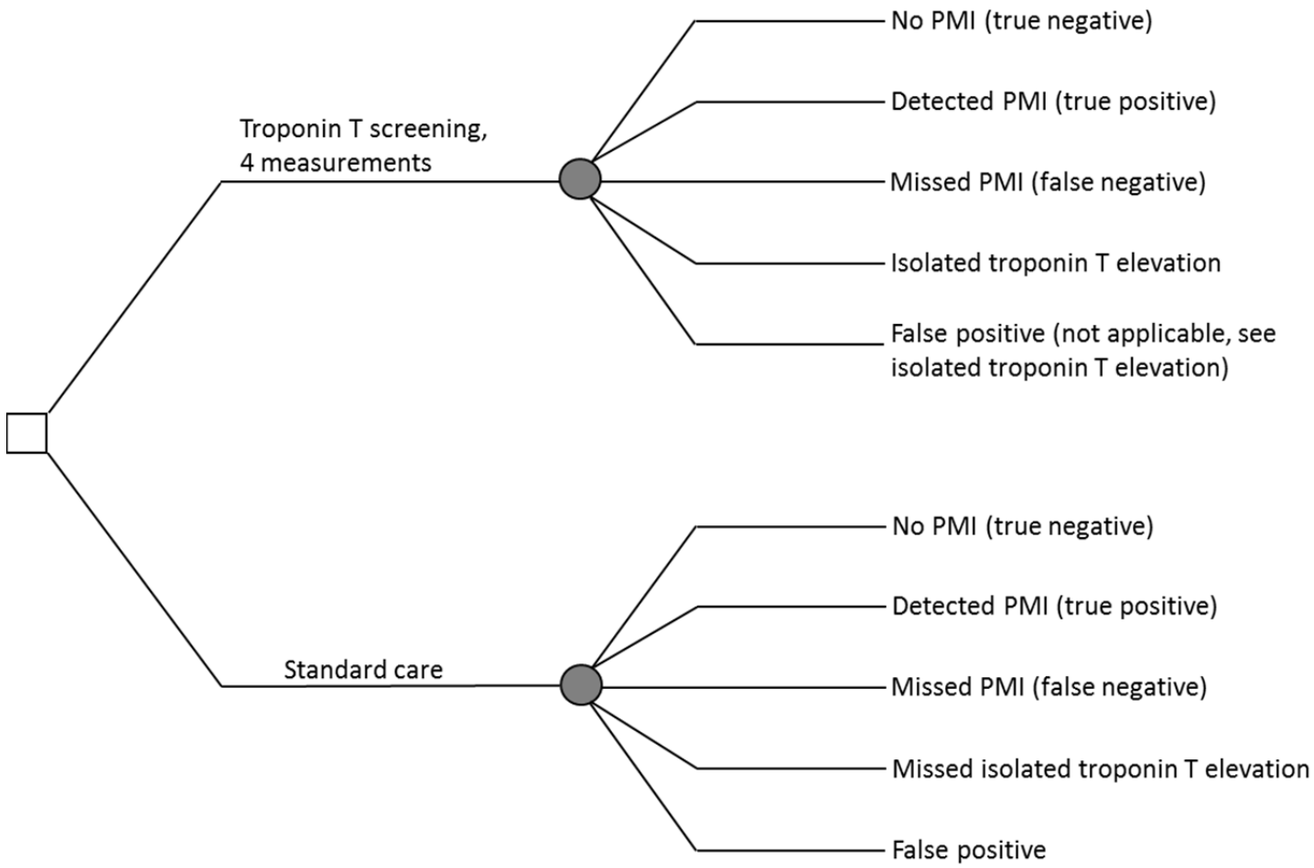


Figure 3. Decision tree representing the alternatives and the health states at the end of 1 year after noncardiac surgery.

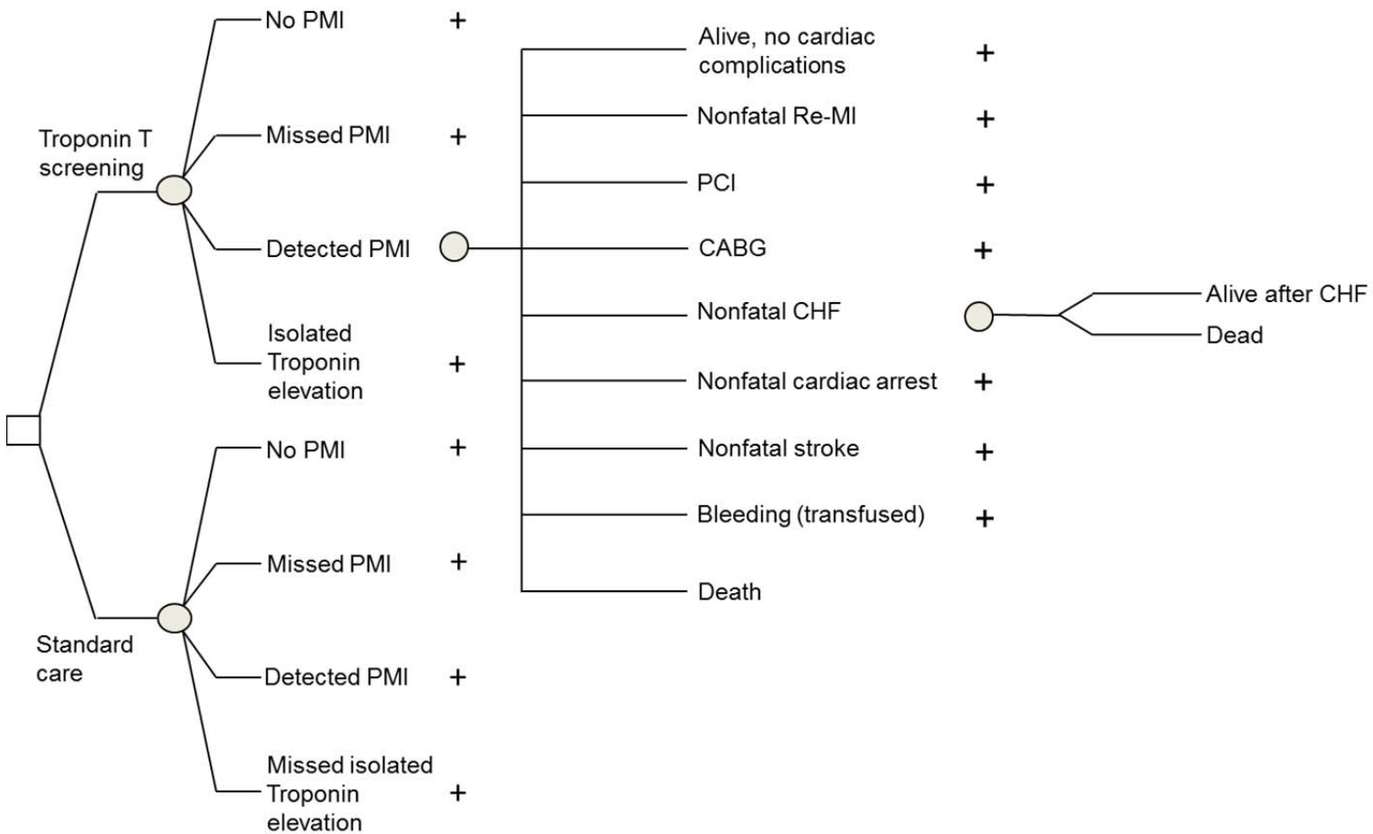


Figure 4a. Distribution of the Monte-Carlo simulations of the reference case in the incremental cost-effectiveness plan.

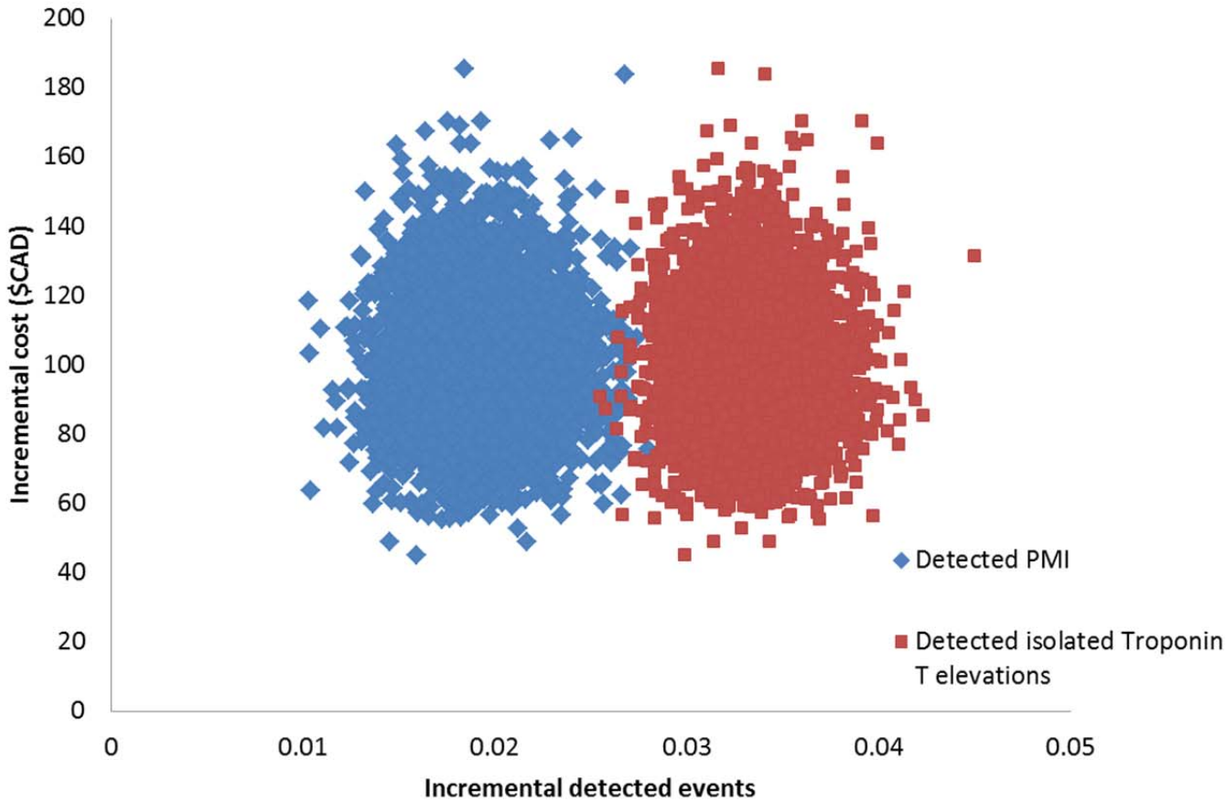


Figure 4b. Cost-effectiveness acceptability curve for the detection of PMI and of isolated Troponin T elevations in the reference case.

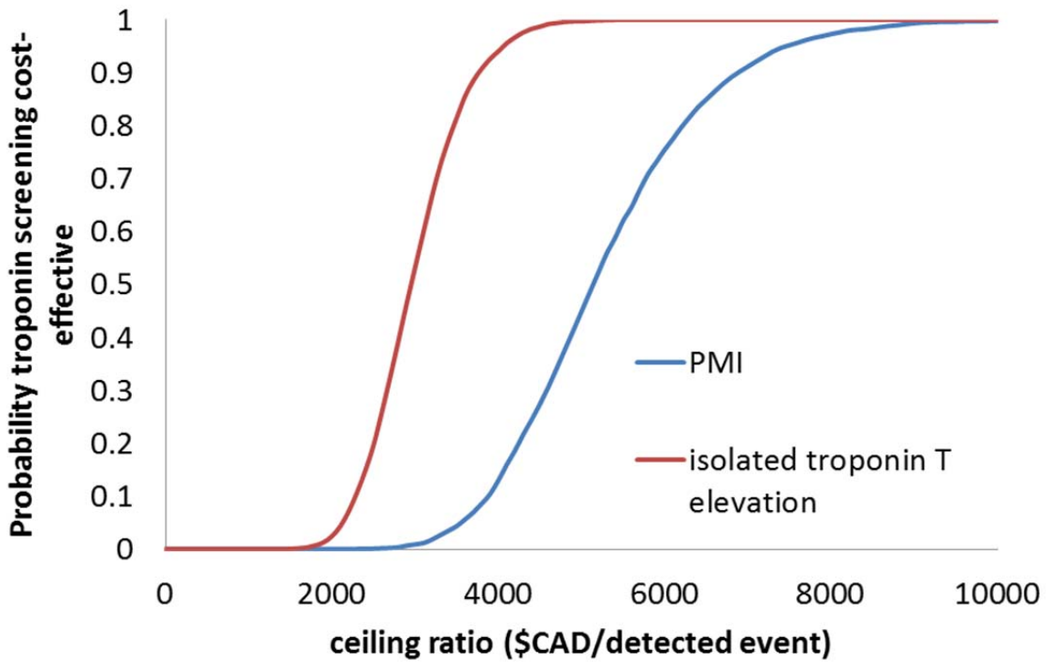


Figure 5. Probability of the cost-effectiveness of the postoperative Troponin T screening was in patients' subgroups defined by preoperative characteristics.

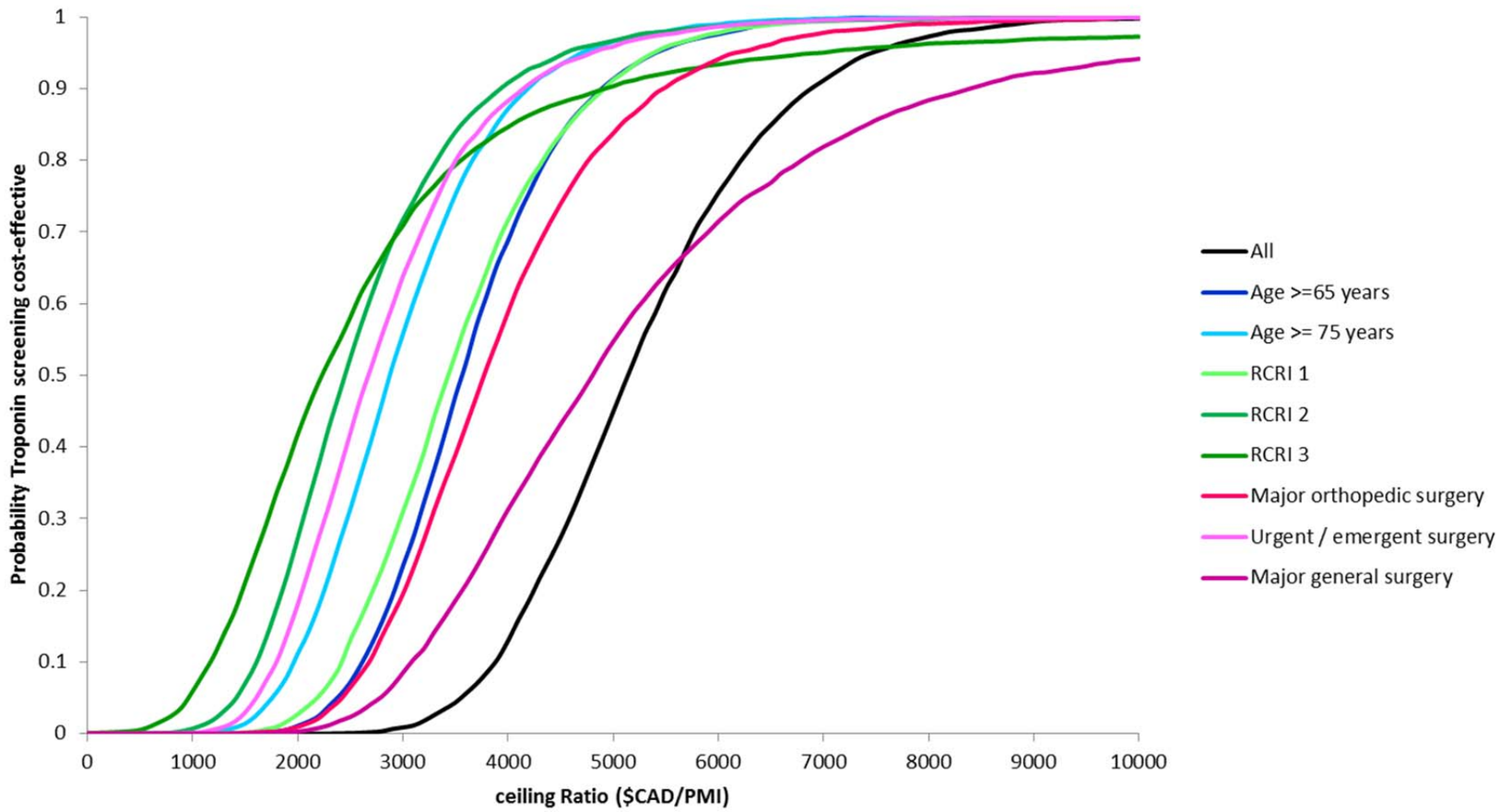


Figure 6a. Distribution of the Monte-Carlo simulations of the reference case in the incremental cost-effectiveness plan.

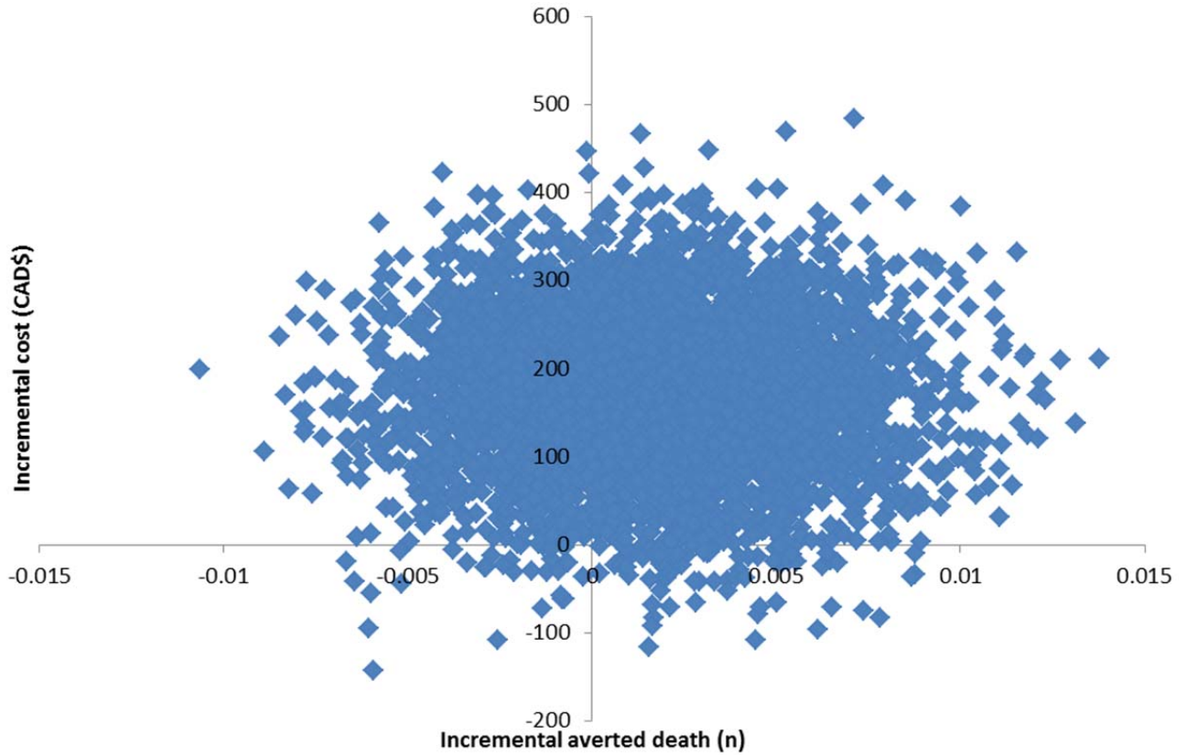


Figure 6b. Cost-effectiveness acceptability curve of a postoperative Troponin T screening for 1-year survival.

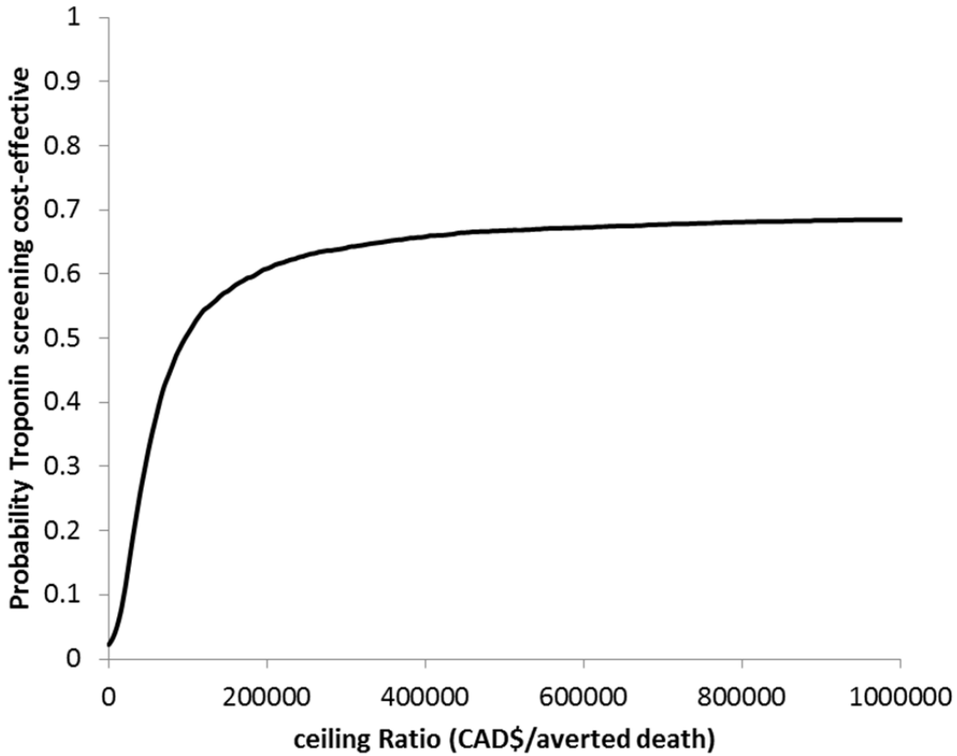


Figure 7. Cost-effectiveness acceptability curve of a postoperative Troponin T screening for 1-year survival under assumption of various treatment effect sizes.

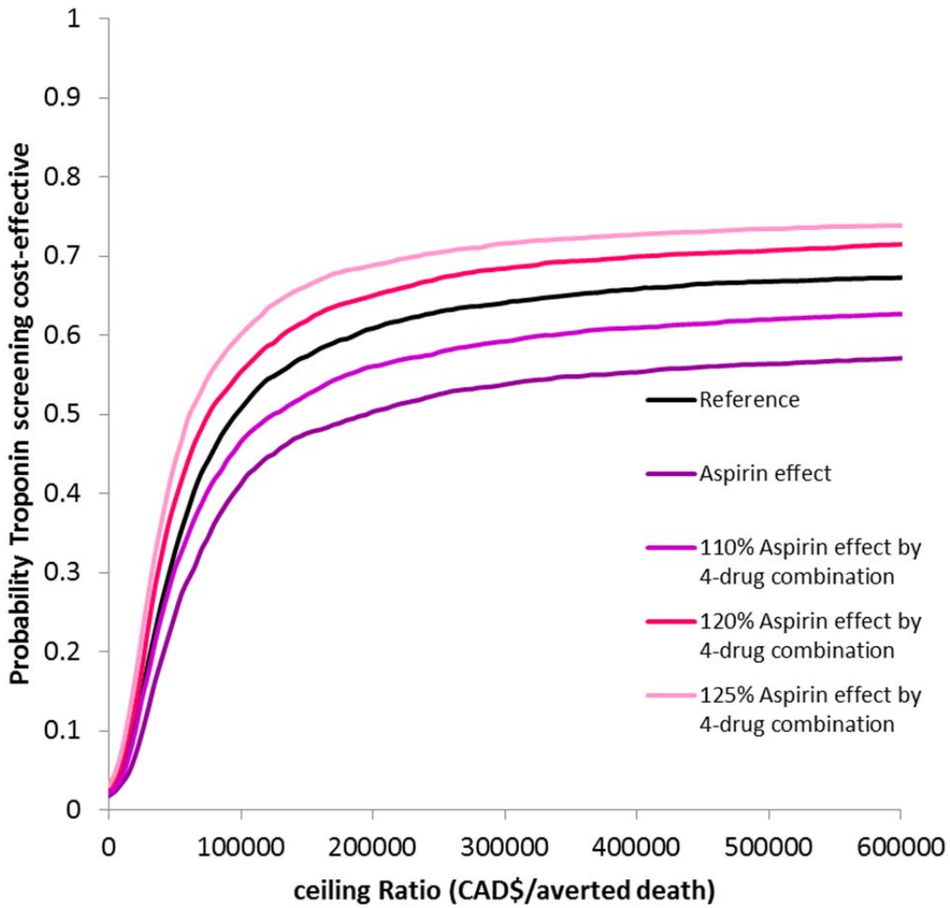


Figure 8. Cost-effectiveness acceptability curve of a postoperative Troponin T screening for 1-year survival under assumption of high and low treatment adherence.

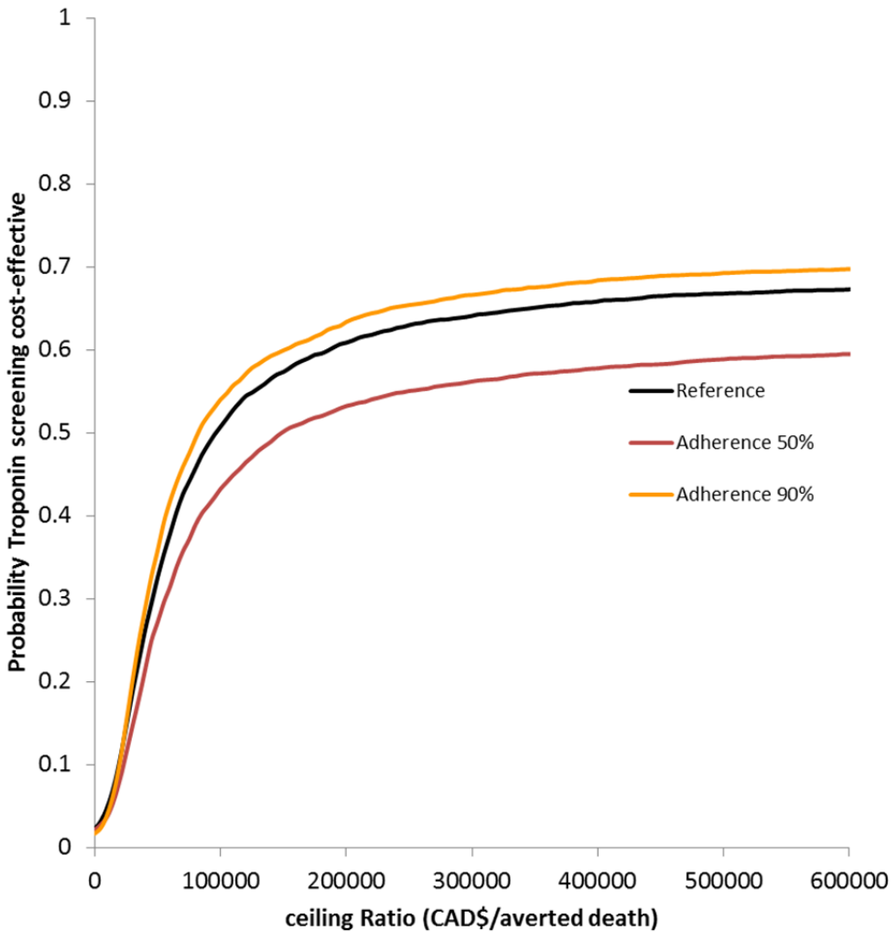


Figure 9. Cost-effectiveness acceptability curve of a postoperative Troponin T screening for 1-year survival under assumption that the VISION incidence of cardiovascular events represented the treated course rather than the natural course after PMI or isolated Troponin T elevation.

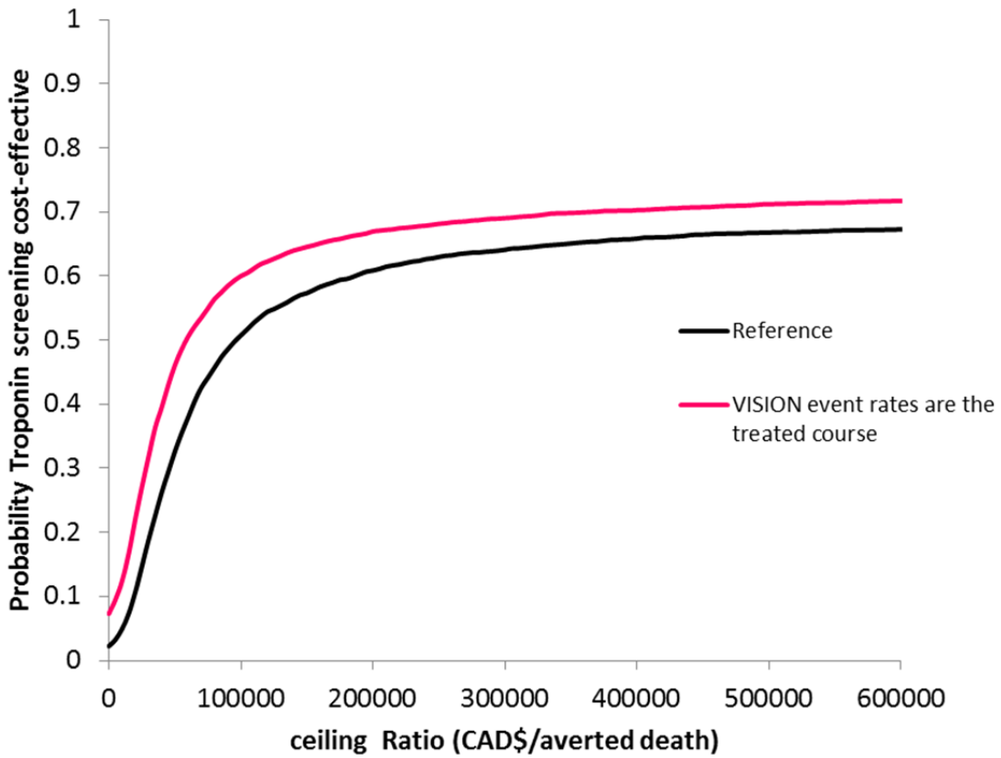


Figure 10. Cost-effectiveness acceptability curve of a postoperative Troponin T screening for 1-year survival in populations defined by age.

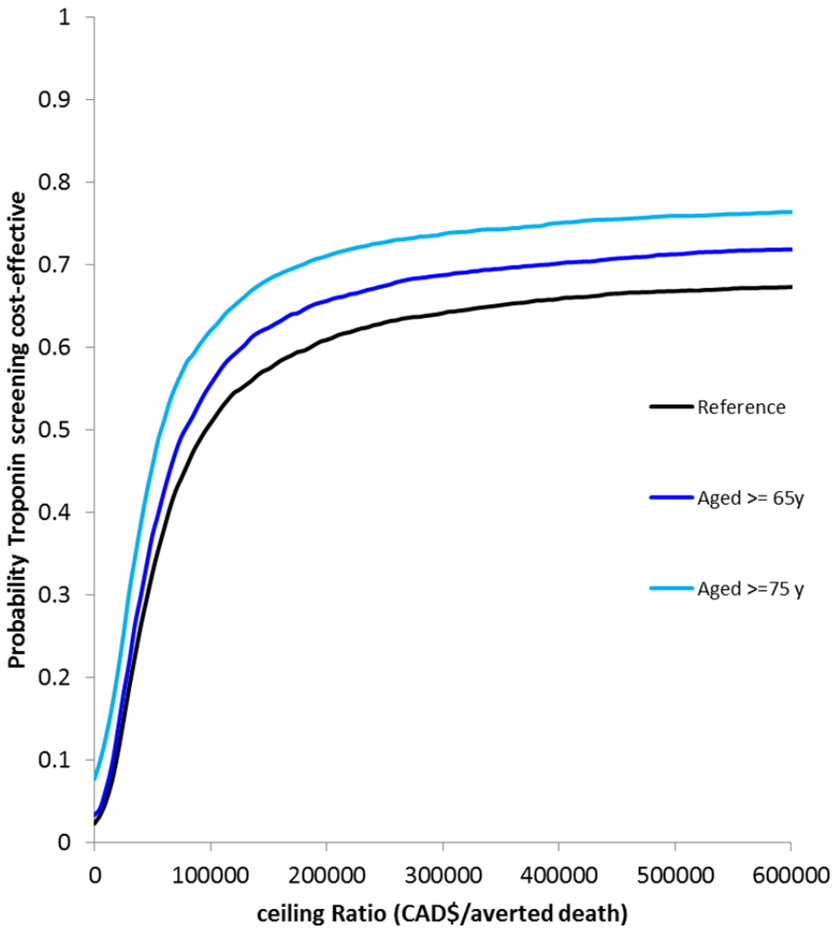


Figure 11. Cost-effectiveness acceptability curve of a postoperative Troponin T screening for 1-year survival in patients undergoing various types of surgery

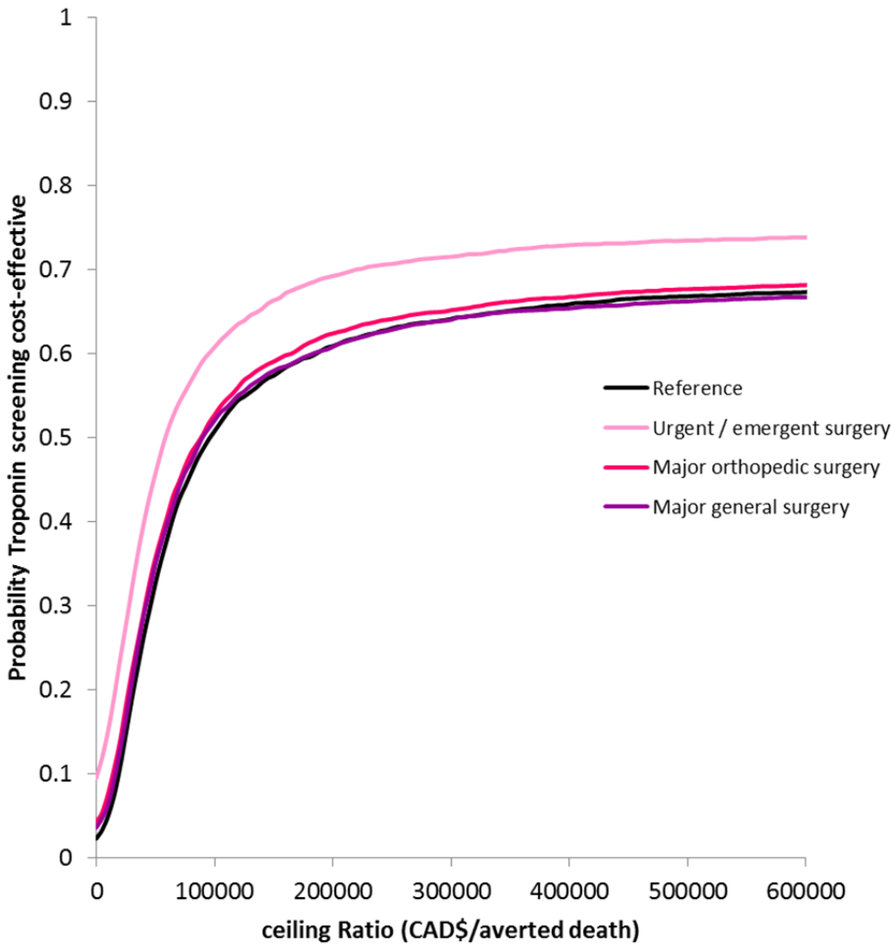
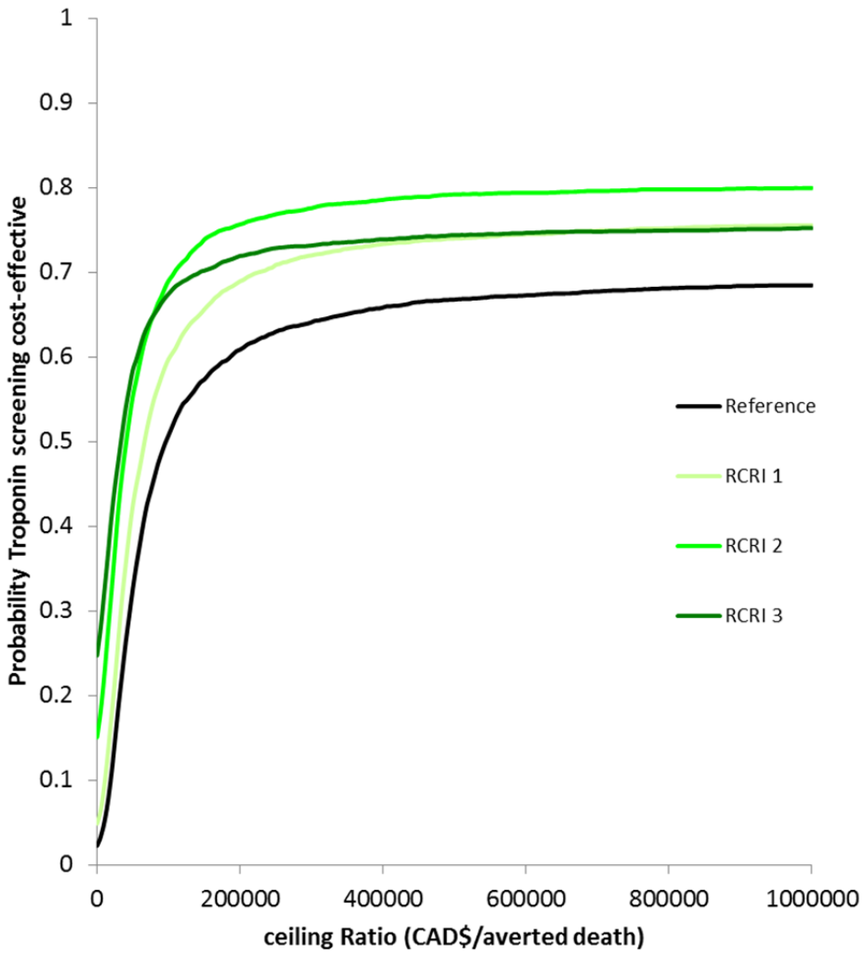


Figure 12. Cost-effectiveness acceptability curve of a postoperative Troponin T screening for 1-year survival in patients with increasing Revised Cardiac Risk Index.



9. APPENDICES.

Appendix 1. Proportion of patients with clinically manifest perioperative myocardial infarction (PMI):

Study	Type of study	Population	Sample size	Event definition	Event (n)	Asymptomatic event	Short-term mortality of asymptomatic events
Devereaux et al, (VISION study, confidential data)	international cohort	aged ≥ 45 years-any noncardiac surgery requiring hospitalisation	14,314	Troponin T elevation and: ischemic symptoms or ECG changes or new wall motion abnormality or coronary revascularisation; or Q-wave development; or autoptic findings of acute MI	944	83.4% (791/944)	9% (71/791)
Devereaux et al, 2011 [35]	cohort study within international RCT	aged ≥ 45 years, with or at risk for CV disease-any noncardiac surgery requiring hospitalisation	8,351	cardiac marker elevation and: ischemic symptoms or ECG changes or new wall motion abnormality or coronary revascularisation; or Q-wave development; or autoptic evidence of acute MI	415	65% (271/415)	12.5% (34/271)
Badner et al, 1998 [37]	cohort study within international RCT	≥ 50 years, CAD, hospitalized for elective noncardiac surgery	323	at least 2 of: CKMB, Troponin elevation, Q-wave development, or scintigrafic evidence	18	39% (7/18)	0% (0/7)
Ashton et al 1993 [36]	cohort study	men >40 year-elective or urgent major noncardiac surgery	512	CKMB elevation and Q-wave development or scintigrafic evidence if ECG or CKMB equivocal	8	20% (3/15)	not reported
Mangano et al, 1990 [38]	cohort study	men with or at high CAD risk-elective surgery with general anesthesia	474	CKMB elevation and Q-wave development, persistent ST-segment changes, or autoptic evidence of acute MI or persistent chest pain >30 min with transient ST-segment changes	15	27% (4/15)	25% (1/4)

CAD: coronary artery disease; CKMB: creatine kinase-MB; CV: cardiovascular; MI myocardial infarction; RCT randomized controlled trial

Appendix 2. Studies reporting on the association between elevated perioperative Troponin concentrations and mortality.

Study	Type of study	Population	Sample size	Type of event	Number events	Independent association (95%CI)
Devereaux et al, 2012 [34]	international cohort	aged ≥ 45 years-any noncardiac surgery requiring hospitalisation	15,133	30-day all-cause mortality	282	HR 2.41 (1.34-3.73) for TnT 0.02 µg/L; HR 5.07 (3.85-6.72) for TnT ≥0.03 and <0.3 µg/L; HR 10.18 (6.28-16.01) for TnT ≥0.3 µg/L
Devereaux et al, 2011 [35]	cohort study within international RCT	aged ≥ 45 years, with or at risk for CV disease-any noncardiac surgery requiring hospitalisation	8,351	30-day all-cause mortality	226	OR 2.54 (1.65-3.90)
Levy et al, 2011 [42]	MA of cohort study	noncardiac surgery	1,538	≤ 12-month all-cause mortality	252	OR 6.7 (4.1-10.9), I^2=0%
			1,780	> 12-month all-cause mortality	207	OR 1.8 (1.4-2.3), I^2=0%
Le Manach et al, 2005 [39]	cohort study	infrarenal aortic surgery	1,136	inhospital all-cause mortality	46	OR 8.1 (95%CI 2.9-22.8) for TnI ≥ 1.5 ng/mL; OR 3.9 (1.8-8.4) for TnI >0.5 and<1.5 ng/mL

CI: confidence intervals; HR: hazard ratio; MA: meta-analysis; OR: odds ratio; RCT: randomized controlled trial; TnI: Troponin I; TnT: Troponin T

Appendix 3: VISION Study Outcome Definitions

A) The myocardial infarction definition requires any of the following:
1. A typical rise of Troponin or a typical fall of an elevated Troponin detected at its peak after surgery in a patient without a documented alternative explanation for an elevated Troponin (e.g., pulmonary embolism) AND either:
a. ischemic signs or symptoms (i.e. chest, arm, or jaw discomfort, shortness of breath, pulmonary edema) within 24 hours of Troponin T elevation
b. development of pathologic Q waves present in any two contiguous leads that are > 30 milliseconds
c. ECG changes indicative of ischemia (i.e. ST elevation [≥ 2mm in leads V1, V2, or V3 and ≥ 1mm in the other leads], ST segment depression [≥ 1mm], or symmetric inversion of T waves ≥ 1mm in at least two contiguous leads, or development of LBBB. ST-depression/elevation and LBBB development must occur within 3 days of Troponin T elevation or ischemic symptoms. T-wave inversion must occur within 5 days of Troponin T elevation or ischemic symptoms.
d. coronary artery intervention (i.e. PCI or CABG surgery) within 2 weeks of Troponin T elevation or ischemic symptoms.
e. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging
or
2. Pathologic findings of an acute or healing myocardial infarction
or
3. Development of new pathological Q waves on an ECG if Troponin levels were not obtained or were obtained at times that could have missed the clinical event.

B) Cardiac Arrest

Cardiac arrest is defined as documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation or cardiac defibrillation.

C) Stroke

Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours.

D) Congestive Heart Failure

The definition of congestive heart failure requires both clinical (i.e. any of the following signs: elevated jugular venous pressure, respiratory rales, crepitations, or presence of S3) and radiographic evidence (e.g. vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

E) Cardiac Revascularization Procedures

Cardiac revascularization procedures include percutaneous coronary interventions (PCI) and coronary artery bypass surgery (CABG) surgery.

F) Bleeding

Blood loss requiring the transfusion of at least 1 unit of packed red blood cells.

Appendix 4. Definitions of the states at the end of the screening period.

	Troponin screening	Standard care
No PMI	no Troponin T elevation and: neither Q-waves development nor autopsy findings of acute or healing myocardial infarction	no clinical symptoms and: neither Troponin T elevation nor Q-waves development nor autopsy findings of acute or healing myocardial infarction
Detected PMI	Troponin T elevation and: clinical symptoms or acute ischemic ECG changes or Q-wave development or new or presumed new cardiac wall abnormality detected by echocardiography	clinical symptoms and Troponin T elevation
Missed PMI	no elevated Troponin T and Q-waves development or autopsy findings of acute or healing myocardial infarction; or elevated Troponin T values measured outside the scheduled Troponin screening period and normal Troponin measurements during the scheduled measurement period	no clinical symptoms but patient had an undetected elevated Troponin T measurement and: acute ischemic ECG changes or new or presumed new cardiac wall abnormality detected by echocardiography
Isolated Troponin T elevation	Troponin T elevation and no clinical symptoms, acute ischemic ECG changes, new or presumed new cardiac wall abnormality detected by echocardiography, development of Q-waves, or autopsy findings of acute or healing myocardial infarction	not applicable
Missed isolated Troponin elevation	an elevated Troponin T value measured outside the scheduled Troponin screening period and negative Troponin T measurements during the scheduled screening period	patient had an undetected elevated Troponin T measurement but no clinical symptoms, acute ischemic ECG changes, new or presumed new cardiac wall abnormality detected by echocardiography, Q-waves development, or autopsy findings of acute or healing myocardial infarction
False positive	not applicable	clinical symptoms with exclusion of PMI, e.g. noncardiac chest pain

ECG: electrocardiogram, PMI perioperative myocardial infarction

Appendix 5. Distribution of the health states at the end of the screening period by Canadian centre.

	All Canadian sites n=6149	Site 1 n=629	Site 2 n=1922	Site 3 n=703	Site 4 n=948	Site 5 n=1536	Site 6 n=411
No PMI (TN)	5746 (93.4)	593 (94.3)	1790 (93.1)	646 (91.9)	894 (94.3)	1441 (93.8)	38 (92.9)
symptomatic PMI (TP)	70 (1.1)	7 (1.1)	28 (1.5)	8 (1.1)	8 (0.8)	13 (0.8)	6 (1.5)
asymptomatic PMI (TP/FN)*	118 (1.9)	12 (1.9)	44 (2.3)	16 (2.3)	14 (1.5)	28 (1.8)	4 (1.0)
Isolated Troponin T elevation	205 (3.3)	16 (2.5)	56 (2.9)	32 (4.6)	32 (3.4)	50 (3.3)	19 (4.6)
FN Troponin T screening	10 (0.2)	1 (0.2)	4 (0.2)	1 (0.1)	0	4 (0.3)	0

*TP in the Troponin screening arm, FN in the standard care alternative; PMI: perioperative myocardial infarction; FN: false negative; TN: true negative; TP: true positive

Appendix 5. Resource utilisation for the various heath states according to the diagnostic algorithms.

	Cardiologist consultation	Cardiologist partial assessment	ECG	Echocardiography	Scheduled Troponin	Triggered Troponin	Angiogram
TN Troponin screening	0	0	0	0	4	0	0
TP Troponin screening	1	3	4	1+probability of MI diagnosis based on Troponin and new wall abnormalities	4	1*probability of increased Troponin T concentration in the last measurement	1*probability of coronary angiogram in patients with symptomatic and asymptomatic PMI
FN Troponin screening	1*probability of missed PMI	3*probability of missed PMI	2*probability of missed PMI	1*probability of missed PMI	4	1*probability of missed PMI	1*probability of coronary angiogram in patients with missed PMI
Isolated Troponin Televation	1	1	4	1	4	1*probability of increased Troponin T concentration in the last measurement	1*probability of coronary angiogram in patients with isolated Troponin T elevation
FP Troponin screening	NA	NA	NA	NA	NA	NA	NA
TN symptom screening	0	0	0	0	0	0	0
TP symptoms screening	1	3	4	1	0	2	1*probability of coronary angiogram in patients with symptomatic PMI
FN symptoms screening	0	0	0	0	0	0	0
FP symptoms screening	0	0	2	0	0	2	0

*: multiplication; +: addition; ECG: electrocardiogram; FN: false negative; FP: false positive; PMI: perioperative myocardial infarction; TN true negative; TP: true positive; Missed PMI: no elevated Troponin T and Q-waves development or autopsy findings of acute or healing myocardial infarction; or elevated Troponin T values measured outside the scheduled Troponin screening period and normal Troponin measurements during the scheduled measurement period (Appendix 4).

Table 7.Short-term effect size of cardiovascular drugs reported in RCT by the type of event.

Study	Population	Study type	n=	Endpoint	Drug	Effectsize (95%CI)
ACEI-MI Collaborative Group, 1998 [57]	after MI	individual patient MA of RCT	98,483	30-day mortality	ACE-inhibitors+ ASA in 88%	RR 0.937 (0.896-0.980)
ISIS-2 [52]	MI	RCT	17,187	35-day mortality (all-cause)	ASA	RR 0.79 (0.72-0.86)
ISIS-1 [55]	MI	RCT	16,027	all-cause mortality at 7 d	BBlocker	RR 0.86 (0.74-0.998)
ISIS-1 [55]	MI	RCT	16,027	vascular death at 14 d	BBlocker	RR 0.87 (0.77-0.99)
Freemantle 1999 [62]	MI	MA of RCT	29,260	mortality (short-term)	short-term BBlocker administration	RR 0.96 (0.85-1.08)
Briel 2006 [60]	after ACS	MA of RCT	12,070	all-cause mortality at 1 month	statin	RR 0.77(0.58-1.01)
Briel 2006 [60]	after ACS	MA of RCT	12,070	cardiovascular mortality at 1 month	statin	RR 0.82 (0.61-1.10)
ACEI-MI Collaborative Group, 1998 [57]	after MI	individual patient MA of RCT	98,483	30-day ReMI	ACE-inhibitors+ ASA in 88%	RR 1.049 (0.985-1.118)
ISIS-2 [52]	MI	RCT	17,187	inhospital nonfatal reinfarction	ASA	RR 0.49 (0.37-0.64)
ISIS-1 [55]	MI	RCT	16,027	inhospital nonfatal reinfarction	BBlocker	RR 0.842 (0.63-1.12)
Briel 2006 [60]	after ACS	MA of RCT	12,070	nonfatal MI at 1 month	statin	RR 1.05 (0.87-1.27)
Briel 2006 [60]	after ACS	MA of RCT	12,070	PCI/CABG at 1 month	statin	RR 1.01 (0.68-1.17)
ACEI-MI Collaborative Group, 1998 [57]	post MI	individual patient MA of RCT	98,483	30-day nonfatal HF	ACE-inhibitors+ ASA in 88%	RR 0.965 (0.935-0.996)
ISIS 4 [56]	post MI	RCT	57,061	35-day cardiac arrest	ACE-inhibitors	RR 0.96 (0.9-1.02)
ISIS-2 [52]	MI	RCT	17,187	inhospital cardiac arrest	ASA	RR 0.87 (0.79-0.96)
ISIS-2 [52]	MI	RCT	17,187	inhospital nonfatal cardiac arrest	ASA	RR 0.896 (0.75-1.06)
ISIS-1 [55]	MI	RCT	16,027	inhospital nonfatal cardiac	BBlocker	RR 0.965 (0.76-1.23)

				arrest		
ACEI-MI Collaborative Group, 1998 [57]	post MI	individual patient MA of RCT	98,483	30-day stroke	ACE-inhibitors+ ASA in 88%	RR 1.078 (0.944-1.231)
ISIS-2[52]	MI	RCT	17,187	inhospital nonfatal stroke	ASA	RR 0.53 (0.32-0.86)
Briel 2006 [60]	after ACS	MA of RCT	12,070	all stroke at 1 month	statin	RR 0.8 (0.48-1.33)
ISIS-2 [52]	MI	RCT	17,187	major bleeding	ASA	RR 0.94 (0.56-1.58)
ISIS-2 [52]	MI	RCT	17,187	any bleeding	ASA	RR 1.26 (1.04-1.52)
PEP [53]	hip fracture surgery or elective TKR or THR	RCT	17,444	any postop bleeding requiring tranfusion	ASA	RR 1.124 (0.94-1.34)

ACE= angiotensin-converting enzyme; ACS= acute coronary syndrome; ASA= aspirin; HF: heart failure; CABG= coronary artery bypass graft; CAD= coronary artery disease; CI=confidence intervals MA= metaanalysis; MI=myocardial infarction; OR= odds ratio; PCI= percutaneous coronary intervention; RR=relative risk; RCT=randomized controlled trial; TIA= transient ischemic attack; TKR= total knee replacement; THR=total hip replacement

Appendix 8. Effect size of cardiovascular drugs reported in RCT for long-term mortality

	Population	Study	n=	Endpoint	Drug	Effectsize (95%CI)
Flather 2000 [61]	HF after MI	individual patient MA of RCT	12,763	1-year mortality	ACE-inhibitors	OR 0.84 (0.73-0.97)
ATT collaboration 2009 [58]	previous MI/stroke/TIA/CAD	MA	43,000 person-years	total mortality long-term	ASA	RR 0.90 (0.82-0.99)
				CAD mortality long-term		RR 0.87 (0.78-0.98)
				vascular mortality long-term		RR 0.91 (0.82-1.00)
				nonfatal MI long-term		RR 0.69 (0.6-0.8)
				any stroke long-term		RR 0.81 (0.71-0.92)
				composite (stroke, MI, vascular death)		RR 0.81 (0.75-0.87)
ISIS-1 [55]	MI	RCT	16,027	vascular death at 1 year	BBlocker	RR 0.89 (0.81-0.97)
				all-cause mortality at 1 year		RR 0.90 (0.93-0.99)
Freemantle 1999 [62]	MI	MA of RCT	24,974	mortality (long-term)	BBlocker (long-term intake)	RR 0.77 (0.69-0.85)
Studer 2005 [64]	secondary prevention	MA of RCT	27,168	all-cause mortality at >6 months	statin	OR 0.78 (0.71-0.86)
Bavry 2007 [59]	early after ACS	MA of RCT	9,553	all-cause mortality at 12 months	intensive statin therapy	OR 0.69 (0.32-1.51)
				all-cause mortality at 24months		OR 0.75 (0.61-0.93)
				cardiovascular mortality at 12 months		OR 0.62 (0.28-1.39)
				cardiovascular mortality at 24 months		OR 0.76 (0.60-0.98)
Hulten 2006 [63]	early after ACS	MA of RCT	17,963	cardiovascular mortality at 12 months	intensive statin therapy	OR 0.64 (0.24-1.72)
				cardiovascular mortality at 24 months		OR 0.74 (0.63-0.86)

ACE: angiotensin-converting enzyme; ACS: acute coronary syndrome; ASA: aspirin; HF: heart failure; CAD: coronary artery disease; CI:confidence intervals; MA: metaanalysis; MI:myocardial infarction; OR: odds ratio; RR:relative risk; RCT:randomized controlled trial; TIA: transient ischemic attack

Appendix 9. Overview of methods and results of the sources of events cost estimates.

Source	Population	Methods of resource utilisation	Methods of unit costing	n=	Year	Location	Time horizon	Estimates include	Cost (2011 CAD$)
OCCI[79]	Hospitalized acute subendocardial MI	Dedicated case costing database	Dedicated case costing database	5,252	2009-2010	Canada (Ontario)	Inhospital	Inhospital cost	9,581 $
OCCI [79]	Hospitalized acute transmural MI	Dedicated case costing database	Dedicated case costing database	2,167	2009-2010	Canada (Ontario)	Inhospital	Inhospital cost	9,164
Frasure-Smith 2000 [80]	Participants in a cohort study and in the control arm of a RCT in hospitalized MI patients that that survived at ≥ 1 year	Administrative data base	Administrative database	848	1991-1995	Cananda (Quebec)	1 year	Initial hospitalization, rehospitalizations, emergency room and outpatients visits, procedures	13,172 $
Wang 2008 [68]	Multivessel CAD-BMS	Model	Model	not applicable	not applicable	Canada	1 year	Initial procedure, drug, hopitalization cost of secondary cardiovascular events	11,050 $
	Multivessel CAD-DES								15,196 $
	Multivessel CAD-off-pump CABG								14,721 $
	Multivessel CAD-on-pump CABG								16,598 $
Lamy 2006 [83]	On-pump CABG	Direct cost assessment inhospital and at 12 months (phone interview)	HHS case costing initiative; OHIP Schedule of Benefit; manufacturers'	2,466	2001-2002	Canada (Ontario)	1 year	Initial procedure, cost of secondary cardiovascular events (literature-based)	16,493 $

	Off-pump CABG		device price; literature for follow-up cost of cardiovascular events						14,070 $
Ontario Case Costing Initiative [79]	Hospitalized congestive heart failure	Dedicated case costing database	Dedicated case costing database	8,185	2009-2010	Canada (Ontario)	Inhospital	Inhospital cost	10,100
Weijsundera 2010 [81]	Adults discharged after heart failure hospitalization	Administrative database	Administrative database	16,443	2005-2008	Cananda (Ontario)	30-day blocks after discharge, stable period, predeath	Hospitalizations, outpatient and emergency department visit, outpatients surgery, medications	12-month cost 22,175 $ (survivors), 52,364 $ (patients that died at 12 months)
Ontario Case Costing Initiative [79]	Hospitalized cardiac arrest with successful rescuscitation	Dedicated case costing database	Dedicated case costing database	158	2009-2010	Canada (Ontario)	Inhospital	Inhospital cost	33,783
Nichol 2009 [70]	Out-of-hospital cardiac arrest, control arm of RCT	Direct cost assessment inhospital and at 3months (phone interview); > 3 months literature-based	Administrative database; literature	28 patients survived until admission, 14 survived after discharge	2000-2003	Canada, USA	not applicable (modelled for long-term)	Inhospital cost (survivors)	73,848 $
								Inhospital cost patients (inhospital death)	39,011 $
								Cost first 3 months after discharge	1,919 $/ month
								Cost >3 months after discharge with ICD	3,926 $ /month
								Cost >3 months after discharge without ICD	3,302 $/month
Ontario Case Costing Initiative [79]	Hospitalized unspecified cerebral infarction	Dedicated case costing database	Dedicated case costing database	1,801	2009-2010	Canada (Ontario)	Inhospital	Inhospital cost	15,295

Caro 2006 [84]	Hospital-survivors of ischemic stroke	Administrative database	OCCI	18,704	1990-2000	Canada	Mean 4.6 years	Vascular and bleed-related rehospitalizations	32,175 $ in the first year
Goereee 2005 [82]	Hospitalizated TIA	Direct cost assessment inhospital and at 3-monthly (phone interview)	OCCI, OHIP Schedule of Benefit, Ontario Drug Benefit Formulary, average industrial wage, average wage for home support workers	365	2001-2002	Canada (Ontario)	1 year	Initial hospitalizsation, rehospitalizations, rehabilitation, long-term care, outpatients visits, prescriptions, test and procedures, assistive devices, lost productivity	20,349 $
	Hospitalizated ischemic stroke								61,351 $
	Hospitalizated hemorrhagic stroke								64,786 $
Stokes 2011 [69]	Inhospital vascular surgery	Administrative database	Administrative database	216,199	2006-2007	USA	Inhospital	Adjusted **incremental** inhospital cost (including blood products, procedures, length of stay)	16,166 $
	Inhospital thoracic surgery			142,562					14,402 $
	Inhospital general surgery			362,512					4,654 $
	Inhospital uro-gynecological surgery			384,132					2,998 $
	Inhospital joint replacement surgery			246,815					3,212 $

BMS: bare metal stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; DES: drug eluting stent; HHS: Hamilton Health Sciences; ICD: implantable cardioverter defibrillator; MA: metaanalysis; MI: myocardial infarction; OCCI: Ontario Case Costing Initiative; OHIP: Ontario Health Insurance; OR: odds ratio; RR: relative risk; RCT: randomized controlled trial; TIA: transient ischemic attack