ORIGINAL RESEARCH

Cost-effectiveness Analysis of Rivaroxaban in the Secondary Prevention of Acute Coronary Syndromes in Sweden

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ABSTRACT

Background: Worldwide, coronary heart disease accounts for 7 million deaths each year. In Sweden, acute coronary syndrome (ACS) is a leading cause of hospitalization and is responsible for 1 in 4 deaths.

Objective: The aim of this analysis was to assess the cost-effectiveness of rivaroxaban 2.5 mg twice daily (BID) in combination with standard antiplatelet therapy (ST-APT) versus ST-APT alone, for the secondary prevention of ACS in adult patients with elevated cardiac biomarkers without a prior history of stroke/transient ischemic attack (TIA), from a Swedish societal perspective, based on clinical data from the global ATLAS ACS 2-TIMI 51 trial, literature-based quality of life data and costs sourced from Swedish national databases.

Methods: A Markov model was developed to capture rates of single and multiple myocardial infarction (MI), ischemic and hemorrhagic stroke, thrombolysis in myocardial infarction (TIMI) major, minor, and "requiring medical attention" bleeds, revascularization events, and associated costs and utilities in patients who were stabilized after an initial ACS event. Efficacy and safety data for the first 2 years came from the ATLAS ACS 2-TIMI 51 trial. Long-term probabilities were extrapolated using safety and effectiveness of acetylsalicylic acid data, which was estimated from published literature, assuming constant rates in time. Future cost and effects were discounted at 3.0%. Univariate and probabilistic sensitivity analyses were conducted.

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Results: In the base case, the use of rivaroxaban 2.5 mg BID was associated with improvements in survival and quality-adjusted life years (QALYs), yielding an incremental cost per QALY of 71,246 Swedish Krona (SEK) (€8045). The outcomes were robust to changes in inputs. The probabilistic sensitivity analysis demonstrated rivaroxaban 2.5 mg BID to be cost-effective in >99.9% of cases, assuming a willingness-to-pay threshold of SEK 500,000 (€56,458).

Conclusion: Compared with ST-APT alone, the use of rivaroxaban 2.5 mg BID in combination with ST-APT can be considered a cost-effective treatment option for ACS patients with elevated cardiac biomarkers without a prior history of stroke/TIA in Sweden.

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INTRODUCTION

Coronary heart disease (CHD) is a major public health concern; it is the leading cause of mortality worldwide, accounting for more than 7 million deaths each year [1]. The majority of CHD-related deaths are due to acute coronary syndrome (ACS) or resulting complications [2, 3]. In Sweden, 1 in 4 deaths are estimated to be due to ACS [4]. ACS is based on the underlying pathophysiology of thrombosis, which is induced by the rupture or erosion of vulnerable coronary plaque. Such a rupture will cause the formation of a blood clot, which subsequently blocks the artery, leading to a sudden or substantial reduction in the coronary blood flow. Manifestations of ACS typically fall into three categories: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). All three are associated with a (very) high, moderate and (very) low degree of obstruction to myocardial perfusion and severity of myocardial ischemia, respectively. Electrocardiograms (ECGs) and cardiac biomarkers (e.g., troponin) can be used to differentiate between the types of ACS (i.e., between [N]STEMI and UA) and these play a crucial role in risk stratification because biomarker elevation can help to identify myocardial cellular damage and potentially predict short-term outcomes of subsequent myocardial infarction (MI) and death [5, 6].

Current European guidelines recommend dual antiplatelet therapy of acetylsalicylic acid (ASA) plus a $P2Y_{12}$ inhibitor (i.e., ticagrelor, prasugrel, ticlopidine or clopidogrel) to reduce the risk of thrombus formation in ACS patients [7, 8]. Dual antiplatelet therapy has proven efficacy in reducing the likelihood of secondary cardiovascular (CV) events, with an increase in the rate of major bleeding [8]. Despite such 'dual antiplatelet' prophylaxis, 20% of patients die within 5 years of an ACS event. The vast majority of these deaths occur after discharge from hospital for the initial ACS event (the index event) [5, 9]. To further reduce this burden, several novel oral anticoagulants (apixaban, dabigatran and rivaroxaban) have been investigated for the prevention of secondary events in the ACS indication [8, 10, 11].

The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2-Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2-TIMI 51) trial (Clinicaltrials.gov identifier: NCT00809965) was a global multicenter, randomized, double-blind, placebo-controlled, event-driven study.

The design and clinical results have been reported elsewhere [11]. The trial randomized 15,526 patients with a recent ACS event to receive twice-daily (BID) doses of 2.5 mg or 5 mg rivaroxaban in combination with standard antiplatelet therapy (ST-APT), defined as acetylsalicylic acid (ASA) alone or ASA in combination with clopidogrel or ticlopidine, versus ST-APT alone. Rivaroxaban 2.5 mg BID in combination with ST-APT was shown to reduce the risk of the composite endpoint of death from CV causes, MI or stroke (hazard ratio [HR] = 0.84; 95% confidence interval [CI] 0.72–0.97); the risk reduction in all-cause mortality (HR = 0.68; 95% CI 0.53–0.87) was achieved without an increase in the risk of fatal bleeding (HR = 0.67; 95% CI 0.24–1.89) [11].

Rivaroxaban 2.5 mg BID has marketing approval in Europe for an adult post-ACS patient population with elevated cardiac biomarkers and without a prior history of stroke or transient ischemic attack (TIA). The aim of this research was to estimate the cost-effectiveness of rivaroxaban 2.5 mg BID when used as secondary prevention versus ST-APT alone in such patients, from a Swedish societal perspective.

METHODS

The current study consists of a cost-effectiveness analysis (CEA) of secondary prevention in adult ACS patients with elevated cardiac biomarkers without a prior history of stroke or TIA. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Patients enter the model following stabilization of their ACS event which is defined according to the ATLAS ACS-TIMI 51 study as the time, up to 7 calendar days after the subject has been hospitalized for the index ACS event, when the initial inpatient treatment (including revascularization procedures and parenteral anticoagulant therapy) would have been discontinued. To inform the design of the model and specify model inputs, formal systematic literature reviews of economic evaluations, clinical data from epidemiological studies and clinical trials, quality of life data, and costs and resource use were performed according to published guidelines [12, 13]. The searches encompassed, among other sources, electronic medical databases commonly prescribed by HTA authorities (Medline, Medline in-process, Embase, EconLit, National Health Service Economic Evaluation Database, Health Technology Assessment Database, and Cochrane Library [CENTRAL and database of systematic reviews]), and conference proceedings of most important cardiovascular and health economic conferences (American Heart Association [AHA], European Society of Cardiology [ESC], American College of Cardiology [ACC], American College of Chest Physicians [ACCP] and International Society for Pharmacoeconomics and Outcomes Research [ISPOR]). The full details of the literature review are provided in the online appendix to this article on the publisher's website.

Clinical event risks, safety and treatment discontinuation rates from the ATLAS ACS 2-TIMI 51 trial, combined with real-world evidence to estimate event rates beyond the trial period, were used to evaluate the long-term cost-effectiveness of treating patients with rivaroxaban 2.5 mg BID in combination with ST-APT. The clinical data, used to inform the first 2 years of the model, were estimated from the intent-to-treat (ITT) trial population, comprising adult patients with elevated cardiac

biomarkers without a prior history of stroke or TIA, which represents the European label for rivaroxaban. A maximum treatment duration of 2 years was assumed for rivaroxaban 2.5 mg BID in the analysis. To comply with current clinical guidelines for ACS, the maximum treatment duration for clopidogrel or ticlopidine in both arms of the analysis was 1 year [7, 8].

Model Structure

With consideration of ESC guidelines [8], a Markov model was constructed to assess the cost-effectiveness of rivaroxaban 2.5 mg BID in combination with ST-APT versus ST-APT alone. The underlying model structure applied was similar in design to previously published

economic evaluations in ACS and wider CV disease [14–17].

The Markov model was constructed in Microsoft Excel 2010 with a 40-year (i.e., lifetime) horizon to simulate the costs and benefits of rivaroxaban 2.5 mg BID treatment in combination with ST-APT. The model considered a patient cohort with an average age of 62 years, to replicate the average age of patients with elevated biomarkers without a prior history of stroke or TIA in the ATLAS ACS 2-TIMI 51 trial.

The model consisted of 16 health states which represent the occurrence of single and multiple cardiovascular events over time (Fig. 1). Health states separately describing MI, ischemic stroke (IS), hemorrhagic stroke/
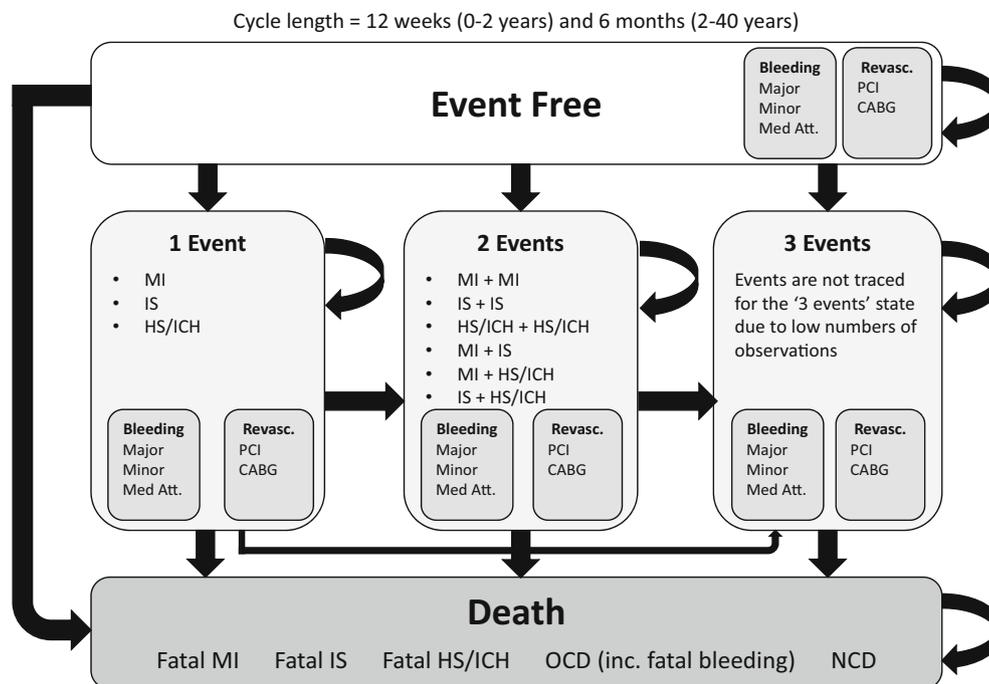
Fig. 1 Markov model structure showing 16 health states; bleedings and revascularizations were considered as transient health states with a one-off cost and short-term disutility impact. *CABG* coronary artery bypass graft, *HS* hemorrhagic stroke, *ICH* intracranial hemorrhage, *Incl.* including, *IS* ischemic stroke, *MI* myocardial infarction, *Med Att.* medical attention, *NCD* non-cardiovascular death, *OCD* other cardiovascular death, *PCI* percutaneous coronary intervention

intracranial hemorrhage (HS/ICH), and death define the model framework. These are key events that a patient might experience after an ACS. Within each of the non-fatal event states there are tunnel states representing the time since the event. These allow for variable transition probabilities, costs and utility decrements following a cardiovascular event [11, 18, 19]. Fatal events in the model, although grouped together in the final outcome, consider fatal MI, fatal IS, fatal HS/ICH, other CV death and non-CV death as distinct events in terms of event probabilities and costs. Fatal bleeding events are considered within the 'other CV death' health state and ICHs are captured in the 'HS/ICH' health state. Other non-fatal bleeds, including thrombolysis in myocardial infarction (TIMI) major, TIMI minor and TIMI requiring medical attention bleeding events, are associated with a one-off cost and short-term disutility, and were thus considered transient health states. Percutaneous coronary interventions (PCI) and coronary artery bypass grafts (CABG) were also included as transient health states. All short-term clinical data were taken from the European label population subgroup of ATLAS ACS 2-TIMI 51 trial, that is, patients with elevated biomarkers without a prior history of stroke/TIA. Clinical results for this population have been published elsewhere [20]. A full and detailed description of each health state, and how patients may transition between these, is provided in Table 1.

The model considered 12 weekly cycles in the first 2 years (observation period) in line with study visits in ATLAS ACS 2-TIMI 51, and 6 monthly cycles thereafter (extrapolation period), to allow for variable transition probabilities, costs and utilities as patients recover from the initial event and their risk of secondary events decreases [21]. A half-cycle correction was applied to reflect the continuous nature of the occurrence of transitions during each cycle by assuming that, on average, all transitions occur halfway through any particular cycle. At the end of each model cycle, patients remained in their current health state, experienced a subsequent CV event or died. After an event, patients accrued additional costs and utility decrements in subsequent cycles until they transitioned to a new health state. The model distinguished between three phases within each non-fatal health state: a period comprising the first 6 months after the event, a period comprising the second 6 months after the event, and subsequent 6-month periods (post 12 months). Therefore, the first two phases were incorporated as tunnel states in which patients can remain for one (6-month) cycle only.

Model Assumptions

The model assumed there was no treatment effect associated with rivaroxaban or clopidogrel or ticlopidine after treatment discontinuation. In line with treatment guidelines, ASA monotherapy was assumed to be continued after discontinuation of all other treatment(s) for the remainder of the model. Rivaroxaban was assumed to be prescribed for a maximum of 2 years. Clopidogrel and ticlopidine were assumed to be discontinued in both treatment arms after 1 year. As ticlopidine is not available in Sweden for the treatment of ACS patients, it was assumed that all patients who received ticlopidine in the ATLAS ACS 2-TIMI 51 clinical trial (<1% of patients) were subsequently treated with clopidogrel, without affecting the overall clinical outcomes.

Different assumptions regarding post-event treatment discontinuation rates were applied to

the first 12 months and subsequent 12 months of the modeled time period.

- Discontinuations of rivaroxaban and/or clopidogrel or ticlopidine for the first year were reflective of the discontinuation rates observed in the clinical trial.

- Based on expert opinion, rivaroxaban discontinuation in the second year of treatment is predicted to be higher in real-life practice than observed in the clinical study.

  - During the second year of treatment, an overall discontinuation rate of 81% was assumed. Efficacy and treatment costs for rivaroxaban in the second year of the model were adjusted accordingly. This assumption is conservative and reflective of the informed decision about therapy physicians make in the second year of treatment.

Revascularization and non-ICH bleeding events were assumed to only occur during the observation period (in accordance with the specified length of treatment in each arm) as the rates would be considered equal after rivaroxaban and ST-APT discontinuation, and their impact on the incremental outcomes negligible after the observation period. The disutility associated with these events does not exceed one model cycle length (12 weeks) and were therefore not modeled as separate health states.

Model Setting

The CEA was performed from a Swedish societal perspective. The model was run for 40 years after which less than 1% of patients were still alive (lifetime horizon). All future costs and health outcomes were discounted at a rate of 3.0% per year, as recommended by the Swedish guidelines for economic evaluations [22]. Costs were expressed in Swedish Krona (SEK) at 2013 prices using the Consumer Price Index (CPI) to inflate costs where relevant [23]. Direct costs were captured in the form of direct medical costs related to antithrombotic treatment and secondary events. Indirect costs were captured in the form of productivity losses and costs of additional life years, constituting a conservative approach given the age of patients in the model [24–27]. All costs were also expressed in Euros (€1 = SEK 8.8561, exchange rate taken on January 3, 2014) using foreign exchange rates taken from the European Central Bank (ECB) [28].

Transition Probabilities

Clinical data from the ATLAS ACS 2-TIMI 51 trial in adults with elevated cardiac biomarkers without a prior history of stroke/TIA show a statistically significant reduction in the combined primary endpoint of CV death, MI or stroke, with rivaroxaban 2.5 mg twice daily versus placebo (HR = 0.80, 95% CI = 0.68–0.94). These data have been reported elsewhere [20]. Patient-level data considering each event type separately were used to estimate transition probabilities for the model. In doing so, both clinical benefits (such as are seen in the case of MIs) and increased risks of events (such as with HS/ICH events) are appropriately modeled. The data were interpolated using a parametric, Weibull-based survival analysis to generate consistent cycle-dependent transition probabilities, adjusting for potentially distorting patient drop-out as observed in the trial (i.e., survival progression after an event within the later trial observations was not considered truly reflective of real-world survival due to low patient numbers comprising those later trial observations, thereby resulting in inconsistent estimates for

Table 1 Description of model health states

Health state	Description	Transitions possible from this health state
Free of secondary events following index ACS event ("event-free")	Patients in this health state have not experienced a secondary cardiovascular event. During each cycle patients in this health state are at a risk of a non-fatal or fatal event, or a combination of events	Patients may transition to any other health state from here
Non-fatal MI	Patients enter this health state if their first secondary event (i.e., their first event following their index ACS event) is a non-fatal MI. Within this health state are tunnel states depending on the time since the non-fatal MI occurred. When patients enter the non-fatal MI health state they enter the first tunnel state and they remain here until the next model cycle. If the patient experiences no further event in the following cycle they are still within the non-fatal MI state, but they move to the second tunnel state, with risks of further events, costs and utilities associated with the event changing to represent the improvement in patient's health as the time since the event increases. This pattern continues until the patient reaches the third, and last state associated with the event they have experienced. Patients will remain here until they experience another non-fatal or fatal event which would cause them to move health states	Patients may transition to any of the following health states from the non-fatal MI state, regardless of the time since the MI: two MIs, MI + IS, MI + HS/ICH, 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death
Non-fatal IS	Patients enter this health state if their first secondary event is a non-fatal IS. As with the non-fatal MI state described in the above paragraph, there are tunnel states depending on the time since the non-fatal IS occurred	Patients may transition to any of the following health states from the non-fatal IS state, regardless of the time since the event: two ISs, MI + IS, IS + HS/ICH, 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death
Non-fatal HS/ICH	Patients enter this health state if their first secondary event is a non-fatal HS/ICH. Within this health state are tunnel states depending on the time since the non-fatal HS/ICH occurred	Patients may transition to any of the following health states from the non-fatal HS/ICH state, regardless of the time since the event: two HS/ICHs, MI + HS/ICH, IS + HS/ICH, 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death
Non-fatal MI + non-fatal MI	This health state contains patients who have experienced two non-fatal MIs since their index event. Within this health state are tunnel states depending on the time since the second non-fatal MI occurred, as described above for the single event states	Patients may transition to any of the following health states from the MI + MI health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death
Non-fatal IS + non-fatal IS	This health state contains patients who have experienced two non-fatal ISs since their index event. As with the MI + MI state described in the above paragraph, there are tunnel states depending on the time since the second event causing a patient to be in the IS + IS health state occurred	Patients may transition to any of the following health states from the IS + IS health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death
Non-fatal HS/ICH + non-fatal HS/ICH	This health state contains patients who have experienced two non-fatal HS/ICHs since their index event. As with the MI + MI and IS + IS states, within this health state are tunnel states depending on the time since the second non-fatal HS/ICH occurred	Patients may transition to any of the following health states from the non-fatal HS/ICH + non-fatal HS/ICH health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death

Table 1 continued

Health state	Description	Transitions possible from this health state
Non-fatal MI + non-fatal IS	This health state contains patients who have experienced the combination of a non-fatal MI and a non-fatal IS since their index event. As with the health states described above where patients have experienced two secondary events, there are tunnel states depending on the time since the second event causing a patient to be in the MI + IS health state occurred. The second event may be either the non-fatal MI or the non-fatal IS, the sequence of events is not explicitly modeled	Patients may transition to any of the following health states from the non-fatal MI + non-fatal IS health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death
Non-fatal MI + non-fatal HS/ICH	This health state contains patients who have experienced a non-fatal MI and a non-fatal HS/ICH since their index event. As with the health states described above where patients have experienced two secondary events, there are tunnel states depending on the time since the second event causing a patient to be in the MI + HS/ICH health state occurred. The second event may be either the non-fatal MI or the non-fatal HS/ICH, the sequence of events is not explicitly modeled	Patients may transition to any of the following health states from the non-fatal MI + non-fatal HS/ICH health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death
Non-fatal IS + non-fatal HS/ICH	This health state contains patients who have experienced the combination of a non-fatal IS and a non-fatal HS/ICH since their index event. As with the health states described above where patients have experienced two secondary events, there are tunnel states depending on the time since the second event causing a patient to be in the IS + HS/ICH health state occurred. The second event may be either the non-fatal IS or the non-fatal HS/ICH, the sequence of events is not explicitly modeled	Patients may transition to any of the following health states from the non-fatal IS + non-fatal HS/ICH health state: 3 events, fatal MI, fatal IS, fatal HS/ICH, other CV death, or non-CV death
Three events	Patients in this health state have experienced three non-fatal events since the index ACS event. The three events may be any combination of MIs, ISs and HS/ICHs. Due to the small numbers of patients who experience three separate non-fatal events the distinction between the event types is not made in this health state. However, the distinction of time periods within this health state as described for all other non-fatal event health states above is still considered	Patients may only transition to fatal health states from the three events state
Fatal events	Five fatal event health states (fatal MI, fatal IS, fatal HS/ICH, other CV death, non-CV death) are absorbing states. Once a patient enters one of these 5 states they remain there until the end of the model	No transitions possible

ACS acute coronary syndrome, *CV* cardiovascular, *HS* hemorrhagic stroke, *ICH* intracranial hemorrhage, *IS* ischemic stroke, *MI* myocardial infarction

transition probabilities for the first 2 years of the model). The decision to continue treatment with clopidogrel or ticlopidine in the second year of the ATLAS ACS 2-TIMI 51 trial was at the physician's discretion (reflective of real-life setting). To comply with European Society of

Cardiology (ESC) guidelines, and accommodate the recommended discontinuation of clopidogrel or ticlopidine after the first year, transition probabilities were adjusted by a factor of 1/0.8. This adjustment factor was based on the relative risk reduction (RRR) for clopidogrel versus ASA demonstrated in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial [29].

To capture long-term survival rates, transition probabilities on the effectiveness and safety of ASA were extrapolated assuming constant rates in time. The Weibull distribution, chosen to reflect the fact that patient risk decreases over time following a qualifying event, is time dependent and was used to estimate transition probabilities for each 12-week cycle within the observation period. Therefore, an average estimate over multiple cycles in which to base the extrapolation period was not required. The last observation from the control arm of the observation period is used to estimate transition probabilities applied in the extrapolation period, with the RRR calculated from CURE used to model transition probabilities based on ASA monotherapy use in the long term.

Furthermore, event rates applied in the extrapolation period were based on, and corrected for, the increased risk of events due to aging, initial case fatalities and the reduction in relative risk of experiencing subsequent events over time. Swedish life tables provided probabilities of non-CV death for patients aged 62 years (using an elimination method) [30, 31].

In an aging population, patients with ACS are at an increased risk of experiencing subsequent CV events or developing comorbidities that may contribute to the onset of future events [6, 32]. The annual age-specific risks of experiencing fatal and non-fatal events were taken from Swedish sources (Table 2). Patients who have experienced an ACS event are at an elevated risk of experiencing a subsequent event, typically within the first 6 months following an event, although this risk diminishes over time [33]. The risk of suffering a second subsequent event after the first is assumed to be 1.5 times the risk of suffering a first subsequent event after the index event [33]. Initial case fatalities (proportion of fatal events typically within 28–30 days of onset) taken from the ATLAS ACS 2-TIMI 51

Table 2 Annual age-specific increased risk of non-fatal and fatal event estimates used to validate the model within the extrapolation period

Event	% annual age-specific increase	Confidence interval (%)	References
Non-fatal MI	5.00	2.50–7.50	[30]
Non-fatal IS	9.10	4.55–13.65	[30]
Non-fatal HS/ICH	5.90	2.95–8.85	[30]
Fatal MI	4.50	2.25–6.75	[30]
Fatal IS	3.10	1.55–4.65	[30]
Fatal HS/ICH	3.10	1.55–4.65	(Assumption based on IS)
OCD	6.80	3.40–10.20	[30]
NCD	5.60	2.80–8.40	[34]

HS hemorrhagic stroke, *ICH* intracranial hemorrhage, *IS* ischemic stroke, *MI* myocardial infarction, *NCD* non-cardiovascular death, *OCD* other cardiovascular death

clinical trial (MI) and published literature (IS and HS/ICH) were used to define the probability that a patient's first modeled event would result in a fatality [34].

The Sweden MONitoring of trends and determinants In CArdiovascular disease (MONICA) study reported a weighted estimate of median survival after a first MI (based on gender distribution) of 15.82 years [35]. The model was calibrated so that the predicted life expectancy of patients on ST-APT alone after the first MI event was 15.82 years.

Resource Use and Costs

The cost of non-fatal MI events is estimated based on the mean cost per patient taken from a paper which estimates costs from a Swedish register, accounting for administrative costs, hospitalizations, diagnostic work-ups, interventions and rehabilitation [36]. The proportion of costs allocated to the first 6 months, second 6 months and post 12 month periods following an event were based on those reported by Heeg et al. [21]. Based on Heeg et al.'s findings, 43% of the total costs of MI are accrued in the first 3 months following the event, 19% are accrued in the second 3 months, and 38% are accrued in the remainder of the first year following the event. The cost of non-fatal IS was calculated based on the gender-weighted average costs incurred during an inpatient stay, during outpatient healthcare, and municipal care after a stroke event within the first year [37]. Cost estimates using this information were then applied to the second year after a stroke event. In the absence of specific, separate costs for IS and HS/ICH, the costs were assumed to be the same for the stroke types. Costs for non-fatal/non-ICH bleeding, revascularization and all fatal events (except

non-CV death) were taken from the Socialstyrelsen database [38]. Cost calculations for the transient health states of bleeding and revascularizations were estimated by multiplying the proportion of patients experiencing the event with the unit cost of each procedure/treatment. In the absence of suitable costs for non-CV death, a cost of SEK 0 (€0) was assumed. The daily costs for generic clopidogrel, ASA and rivaroxaban, taken from the TLV database, were SEK 1.47 (€0.17), SEK 0.61 (€0.07) and SEK 20.91 (€2.36), respectively; the lowest available prices in February 2013 were used for generic medications [39]. The daily drug price is multiplied by the number of days per model cycle and applied to each living patient within the specified treatment duration (Table 3).

Indirect costs included productivity losses due to the events, calculated using the human capital method (HCM) as prescribed by the Swedish authority [22], and the cost of survival from added life years. The HCM assumes that all productivity loss due to disease can be accounted for as indirect costs and reflects the fact that short-term absence from work due to medical visits as well as due to events of ACS patients lead to (indirect) costs for society. This method is applicable to all patients under the national age of retirement (65 years in Sweden) [40]. The cost of daily productivity loss is given by $\left(\frac{\alpha \times 12}{365}\right) \cdot (1 + \beta_1 + \beta_2)$, where α is the average monthly salary (SEK 29,000) [22], β_1 is the employer benefit (31.42%) [26] and β_2 is the union benefit (10%) [26]. The resulting daily cost of SEK 1388 (€152) is then multiplied by the number of days of productivity loss assumed per event (Table 4). The cost of added life years takes into account the difference between consumption and production for patients of each modeled age category (Table 5). The costs

Table 3 Direct and indirect costs (SEK, 2013 values and €, 2014 conversion) applied in the model

Variable	Base-case value	Confidence interval	Definition	References
Daily cost of rivaroxaban (2.5 mg BID)	SEK 20.91 (€2.36)	–	–	–
Daily cost of ASA 75 mg/day	SEK 0.61 (€0.07)	–	–	[39]
Daily cost of clopidogrel 75 mg/day	SEK 1.47 (€0.17)	–	–	[39]
Cost of MI (first 3 months, acute treatment)	SEK 76,812 (€8789)	SEK 57,609–SEK 96,015 (€6579–€10,986)	Costs per patient for administration, hospitalization, diagnostic work-up, intervention and rehabilitation for each diagnosis on a national level	[21, 30]
Cost of MI (second 3 months, follow-on care)	SEK 33,940 (€3883)	SEK 25,455–SEK 42,425 (€2913–€4854)	Costs per patient for administration, hospitalization, diagnostic work-up, intervention and rehabilitation for each diagnosis on a national level	[21, 36]
Cost of MI (second 6 months, follow-on care)	SEK 67,881 (€7767)	SEK 50,911–SEK 84,851 (€5825–€9709)	Costs per patient for administration, hospitalization, diagnostic work-up, intervention and rehabilitation for each diagnosis on a national level	[21, 25]
Cost of MI (second 12 months, follow-on care)	SEK 47,602 (€5445)	SEK 35,702–SEK 59,503 (€4085–€6808)	Costs per patient for administration, hospitalization, diagnostic work-up, intervention and rehabilitation for each diagnosis on a national level	[21, 36]
Cost of IS (first 3 months, acute treatment)	SEK 109,392 (€12,517)	SEK 82,044–SEK 136,740 (€9387–€15,646)	Average costs for men and women during inpatient stay, after inpatient, outpatient healthcare and municipal care	[37]
Cost of IS (second 3 months, follow-on care)	SEK 22,099 (€2529)	SEK 16,574–SEK 27,624 (€1896–€3161)	Average costs for men and women during inpatient stay, after inpatient, outpatient healthcare and municipal care	[37]

Table 3 continued

Variable	Base-case value	Confidence interval	Definition	References
Cost of IS (second 6 months, follow-on care)	SEK 44,868 (€5138)	SEK 33,651–SEK 56,085 (€3850–€6417)	Average costs for men and women during inpatient stay, after inpatient, outpatient healthcare and municipal care	[37]
Cost of IS (second 12 months, follow-on care)	SEK 50,823 (€5815)	SEK 38,117–SEK 63,529 (€4361–€7269)	Average costs for men and women during inpatient stay, after inpatient, outpatient healthcare and municipal care	[37]
Cost of HS/ICH (first 3 months, acute treatment)	SEK 109,392 (€12,517)	SEK 82,044–SEK 136,740 (€9387–€15,646)	Assumed same as IS in absence of specific data	–
Cost of HS/ICH (second 3 months, follow-on care)	SEK 22,099 (€2529)	SEK 16,574–SEK 27,624 (€1896–€3161)	Assumed same as IS in absence of specific data	–
Cost of HS/ICH (second 6 months, follow-on care)	SEK 44,868 (€5138)	SEK 33,651–SEK 56,085 (€3850–€6417)	Assumed same as IS in absence of specific data	–
Cost of HS/ICH (second 12 months, follow-on care)	SEK 50,823 (€5815)	SEK 38,117–SEK 63,529 (€4361–€7269)	Assumed same as IS in absence of specific data	–
Cost of fatal events (excluding NCD)	SEK 15,853 (€1790)	SEK 11,890–SEK 19,816 (€1360–€2267)	Fatal MI, dead within 3 days (DRG E42N)	[38]
Cost of NCD	SEK 0 (€0)	–	Conservative assumption	–
Cost of PCI	SEK 61,626 (€6959)	SEK 46,220–SEK 77,033 (€5288–€8814)	Weighted average cost for PCI (DRG 112E and 112F)	[38]
Cost of CABG	SEK 199,119 (€22,484)	SEK 149,380–SEK 248,899 (€17,087–€28,479)	Weighted average cost for CABG (DRG E07E, E06N, and E07A)	[38]
Cost of TIMI major bleeding	SEK 35,811 (€4044)	SEK 26,858–SEK 44,763 (€3073–€5122)	Weighted average cost for GI bleeding events (DRG F40A, F40C and F40E)	[38]

Table 3 continued

Variable	Base-case value	Confidence interval	Definition	References
Cost of TIMI minor bleeding	SEK 2983 (€337)	SEK 2237–SEK 3729 (€256–€427)	Physician visit at cardiology clinic	[38]
Cost of TIMI bleeding requiring medical attention	SEK 1359 (€153)	SEK 1019–SEK 1699 (€117–€194)	Outpatient GP visit	[38]
Cost of daily loss productivity	SEK 1388 (€152)	SEK 1011–SEK 1685 (€116–€193)	Calculated as described in text	–

ASA acetylsalicylic acid, *BID* twice daily, *CABG* coronary artery bypass graft, *DRG* diagnosis related group, *GI* gastrointestinal, *GP* general practitioner, *HCM* human capital method, *HS* hemorrhagic stroke, *ICH* intracranial hemorrhage, *IS* ischemic stroke, *MI* myocardial infarction, *NCD* non-cardiovascular death, *OCD* other cardiovascular death, *PCI* percutaneous coronary intervention, *SEK* Swedish Krona, *TIMI* thrombolysis in myocardial infarction

for consumption include health care, social services, education, general public consumption and private consumption [24]. The proportion of patients in each age category is representative of the ATLAS ACS 2-TIMI 51 trial.

Utilities

The ATLAS ACS 2-TIMI 51 trial was not optimally designed to measure utilities per health state, thus data from literature was considered more appropriate. The utility values for the non-fatal events of MI, IS and HS/ICH were taken from the Platelet inhibition and patient Outcomes (PLATO) trial [14]. This source was selected because it represents a recent source of utility estimates elicited from a large number of ACS patients. In addition, these utility values have been applied in many recent health technology appraisal submissions of treatment for ACS, and have been accepted as a robust source in those submissions. Utility values for stroke over time were not reported for the PLATO study. Hence, the best alternative source identified through the systemic literature review was used to estimate values for the second 6 months and later periods [41].

The lengths of disutility associated with bleeding and revascularization events were based on literature and expert opinion, and were assumed to be 30 days for TIMI major bleeding and PCI, 2 days for TIMI minor bleeding and TIMI bleeding requiring medical attention, and 84 days for CABG [15–17]. The proportion of patients suffering an event, multiplied by the respective disutility corrected for event-specific duration of quality of life impact, was deducted from the overall quality of life model outcomes. The utility values applied in the model are provided in Table 6.

Table 4 Days of lost productivity

Event	Number of days of productivity lost	Confidence interval	References
MI	80	60–100	Mean sick leave for an MI [25]
IS	137	103–171	Mean sick leave for a stroke [25]
HS/ICH	137	103–171	Assumed same as IS in absence of specific data
PCI	3	2–4	Weighted average (DRG: E18C and E18E) of inpatient stay after PCI [41]
CABG	8	6–10	Weighted average (DRG: E07E, E06N and E07A) of inpatient care after CABG [41]
TIMI major bleed	28	21–35	Patients are recommended to take 4 weeks sick leave for surgery of perforated peptic ulcer in accordance with the assumption that major bleed is defined by a GI bleed [38]
TIMI minor bleed	0.5	0.4–0.6	Assumption based on absence from work due to a healthcare visit
TIMI bleed requiring medical attention	0.5	0.4–0.6	Assumption based on absence from work due to a healthcare visit

CABG coronary artery bypass graft, *DRG* diagnosis related group, *GI* gastrointestinal, *HS* hemorrhagic stroke, *ICH* intracranial hemorrhage, *IS* ischemic stroke, *MI* myocardial infarction, *NCD* non-cardiovascular death, *OCD* other cardiovascular death, *PCI* percutaneous coronary intervention, *TIMI* thrombolysis in myocardial infarction

Table 5 Inflated (SEK, 2013 values and €, 2014 conversion) cost of added life years adjusted to the ATLAS ACS 2-TIMI 51 trial age distributions [24]

Age (years)	50–64	65–74	75–84	≥85
Consumption–production	SEK −15,382 (€−1737)	SEK 21,969 (€2481)	SEK 69,771 (€7878)	SEK 147,683 (€16,676)

ATLAS ACS 2-TIMI 51 Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2-Thrombolysis in Myocardial Infarction 51 (Clinicaltrials.gov identifier: NCT00809965), *SEK* Swedish Krona

Analyses

Costs and quality-adjusted life years (QALYs) were calculated over a 40-year (i.e., lifetime) horizon and were presented as mean outcome per patient allowing estimation of the incremental cost-effectiveness ratio (ICER). This approach is standard practice in Markov cohort modeling. An ICER below the assumed willingness-to-pay threshold of SEK 500,000 (€56,458) was considered to demonstrate cost-effectiveness.

A probabilistic sensitivity analysis (PSA) evaluated the uncertainty generated in the estimated ICERs by varying all model input parameters simultaneously for 10,000 iterations. Normal distributions were specified around the Weibull parameters in the model, all other parameters were assigned beta distributions. Univariate analyses varied one

Table 6 Utilities applied in model per health state and for transient health states (representing the time since the event)

Event	Utility	Confidence interval	Definition	References
Health states				
No event (event-free)	0.842	0.632–1.000	No event	[14]
MI first 6 months	0.779	0.584–0.974	MI	[14]
MI second 6 months	0.821	0.616–1.000	Post-MI	[14]
MI subsequent 6 month cycles	0.821	0.616–1.000	Post-MI	[14]
IS first 6 months	0.703	0.527–0.879	Stroke	[14]
IS second 6 months	0.748	0.561–0.935	Post-stroke	[14, 42]
IS subsequent 6 month cycles	0.792	0.594–0.990	Post-stroke	[14, 42]
HS/ICH first 6 months	0.703	0.527–0.879	Assumed same as IS in absence of specific data	–
HS/ICH second 6 months	0.748	0.561–0.935	Assumed same as IS in absence of specific data	–
HS/ICH subsequent 6 month cycles	0.792	0.594–0.990	Assumed same as IS in absence of specific data	–
Transient health states				
PCI	0.792	0.594–0.990	PCI (30 days duration)	[17]
CABG	0.742	0.557–0.928	CABG (30 days duration)	[17]
TIMI major bleeding	0.750	0.563–0.938	GI bleeds (14 days duration)	[15]
TIMI minor bleeding	0.800	0.600–1.000	Minor bleeding (2 days duration)	[16]
TIMI bleed requiring medical attention	0.800	0.600–1.000	Minor bleeding (2 days duration)	[16]

CABG coronary artery bypass graft, *GI* gastrointestinal, *HS* hemorrhagic stroke, *ICH* intracranial hemorrhage, *IS* ischemic stroke, *MI* myocardial infarction, *NCD* non-cardiovascular death, *OCD* other cardiovascular death, *PCI* percutaneous coronary intervention, *TIMI* thrombolysis in myocardial infarction

model parameter at a time to investigate the impact of the upper and lower limits. The univariate analyses were categorized into non-efficacy-related and efficacy-related analyses. The non-efficacy-related analyses varied, for example, event costs and utility estimates. The efficacy-related analyses considered the difference in rates of MI, IS, HS/ICH and other CV death events between the rivaroxaban + ST-APT and ST-APT alone arms. An uncertainty

range of ±25% was applied to all model inputs in the sensitivity analyses, with the exception of efficacy data (Fig. 3b), for which a regression analysis based on the results of the PSA was used to determine the upper and lower bounds of risk per event type (i.e., MI, IS, HS/ICH, CV death) when applying a 95% confidence interval. Plus and minus 25% of the deterministic value offers in almost all cases a much wider interval than would be seen if the interval was based on

published standard errors. The wider interval was chosen for the analyses because published standard errors often offer an unrealistic sense of confidence. For example, in a study by Bagust et al., a utility estimate is presented for ACS patients without secondary events of 0.842, with a standard error of 0.002 [14]. While this may reflect the study sample from which the utility was derived, it does not necessarily represent the average quality of life of a patient from any other ACS population especially given dependency of quality of life on age and the size of the infarction, among other factors. Further scenarios assessed the model outcomes for unadjusted probabilities taken directly from the clinical trial (i.e., reflecting the clinical trial without manual adjustments to mimic Swedish clinical practice), assumed a 10-year modeling time horizon to remove uncertainty around assumptions far into the future, and applied zero costs (SEK 0 [€0]) to all treatments considered in the model. This latter scenario is designed to mimic a scenario driven by clinical efficacy and safety only.

RESULTS

Base-Case Analysis

The base-case cost-effectiveness results are summarized in Table 7. Based on the model, rivaroxaban 2.5 mg BID given in combination with ST-APT was associated with a QALY gain of 0.14 and an incremental cost of SEK 10,000 (€1129), yielding a cost per QALY of SEK 71,246 (€8045) when compared with ST-APT alone. The results showed rivaroxaban 2.5 mg BID to be associated with fewer non-fatal and fatal events (incremental costs of SEK −1337 (€−151) and SEK −226 (€−26) per patient, respectively). When analyzing only those patients in stratum 2 of the ATLAS trial (i.e., only including patients treated with clopidogrel or ticlopidine in addition to ASA, with or without

Table 7 Results of the base-case analysis (SEK, 2013 prices and €, 2014 conversion)

	Rivaroxaban + ST-APT	ST-APT alone	Difference (Δ)
Costs[a]			
No event (treatment costs only)	SEK 164,478 (€18,572)	SEK 154,969 (€17,498)	SEK 9509 (€1074)
Non-fatal events	SEK 374,756 (€42,316)	SEK 376,093 (€42,467)	SEK −1337 (€−151)
Fatal events	SEK 7082 (€800)	SEK 7308 (€825)	SEK −226 (€−26)
Bleeding	SEK 1338 (€151)	SEK 494 (€56)	SEK 844 (€95)
Revascularization	SEK 15,257 (€1723)	SEK 14,047 (€1586)	SEK 1210 (€137)
Total	SEK 562,911 (€63,562)	SEK 552, 911 (€64,433)	SEK 10,000 (€1129)
Effects			
QALYs	10.86	10.72	0.14
ICER			
Costs per QALY			SEK 71,246 (€8045)

ICER incremental cost-effectiveness ratio, *SEK* Swedish Krona, *ST-APT* standard antiplatelet therapy, *QALY* quality-adjusted life year

[a] A 3.0% discount rate was applied to all variables [22]

rivaroxaban), the ICER is estimated at SEK 97,059 (€11,105). When considering only those patients not treated with clopidogrel or ticlopidine (stratum 1 of the trial—ASA monotherapy, with or without rivaroxaban), the ICER reduces to SEK 31,149 (€3564). Rivaroxaban is estimated to be a cost-effective option for secondary prevention of cardiovascular events in ACS patients regardless of the standard of care currently being received by the patient (ASA monotherapy or ASA + clopidogrel or ticlopidine).

Sensitivity analyses

Uncertainty around the cost-effectiveness results was demonstrated by plotting simulations from the PSA on a cost-effectiveness plane as presented in Fig. 2a. Almost all of the probabilistic simulations (92.6%) suggest a QALY gain with rivaroxaban, with an associated increase in cost (upper right-hand quadrant of the figure). The probability of rivaroxaban being cost-effective at a willingness-to-pay threshold of SEK 500,000 (€56,458) is estimated to be >99.9% (Fig. 2b).

Univariate sensitivity analyses were performed on all model variables and the results are presented in Fig. 3. The tornado graphs show that the base-case analysis was robust to plausible changes in the input parameters, with a majority of the parameters having minimal impact on the overall ICER (Fig. 3a). In the efficacy-related analysis (Fig. 3b), the results were most sensitive to changes in the difference of other CV death rates between the rivaroxaban 2.5 mg BID + ST-APT and ST-APT alone arms. This is not unexpected as there is a significant CV mortality benefit associated with rivaroxaban [11].
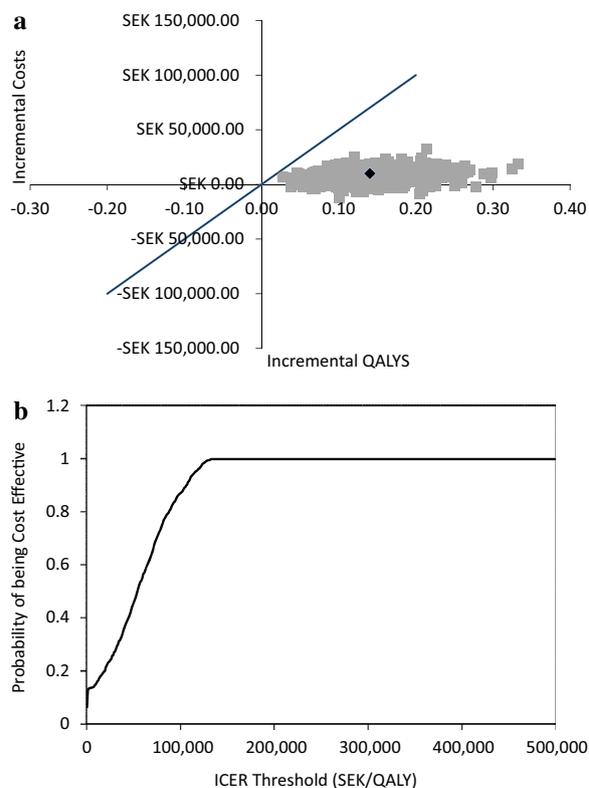
Fig. 2 Probabilistic sensitivity analyses (SEK, 2013 values and €, 2014 conversion): **a** scatterplot, **b** cost-effectiveness acceptability curve. *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year, *SEK* Swedish Krona

Scenario analyses were run to further test the robustness of the model. Applying unadjusted probabilities directly from the clinical trial (not corrected for treatment discontinuations in the second year and not interpolated), resulted in a cost per QALY of SEK 63,855 (€7210).

Applying zero costs to all treatments in the model (rivaroxaban 2.5 mg BID, clopidogrel/ticlopidine and ASA), i.e., results are driven by efficacy alone, provided an ICER of SEK 3500 (€395). Rivaroxaban generated slightly higher costs in this scenario, due to the increased risk of expensive stroke events with this treatment, partially outweighing the savings due to reductions in MIs and deaths. Additionally,
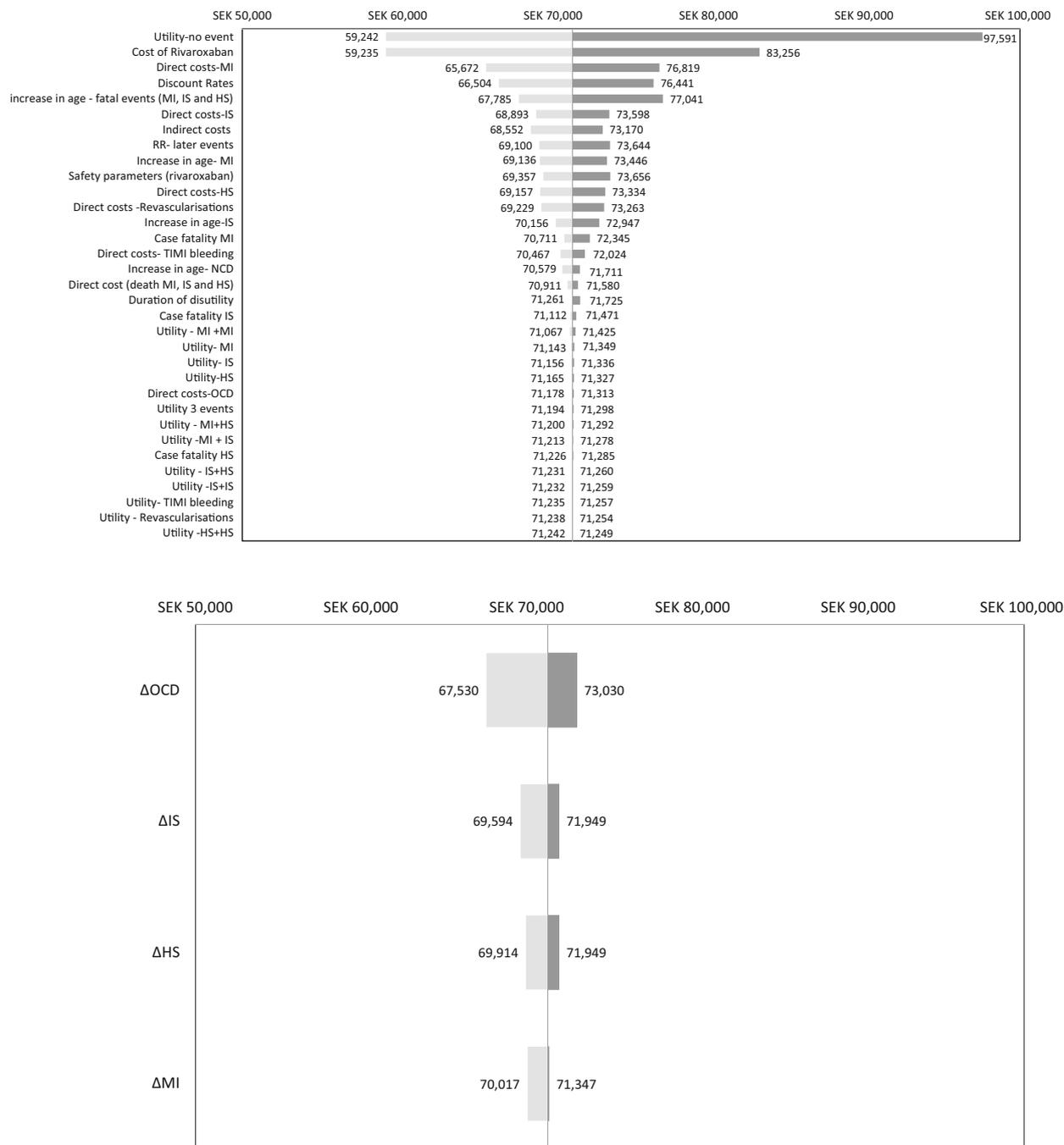
Fig. 3 Univariate sensitivity analyses (SEK, 2013 values and €, 2014 conversion): **a** non-efficacy-related input parameters, **b** efficacy-related input parameters. Costs in SEK are provided above each tornado plot. Equivalent costs in € are provided below each tornado plot. *Δ* difference in,

HS hemorrhagic stroke, *ICH* intracranial hemorrhage; *IS* ischemic stroke, *MI* myocardial infarction, *NCD* non-cardiovascular death, *OCD* other cardiovascular death, *SEK* Swedish Krona, *TIMI* thrombolysis in myocardial infarction

rivaroxaban patients were more likely to experience more subsequent events because they lived longer, and the conservative

estimate of a SEK 0 cost of non-CV death reduces the impact of the cost savings that would be gained with rivaroxaban.

Assuming a 10-year model time horizon resulted in an ICER of SEK 83,111 (€9382). The ICER increased in this scenario because some of the long-term benefits of rivaroxaban therapy were not considered in the analysis.

Allowing the treatment effect to vary, reflecting the clinical trial (without adjustments), removing the cost disadvantage associated with rivaroxaban 2.5 mg BID, and reducing the model time horizon did not alter conclusions of rivaroxaban 2.5 mg BID in combination with ST-APT being considered a cost-effective treatment option.

DISCUSSION

The result from this study demonstrated that, from a Swedish societal perspective, rivaroxaban 2.5 mg BID in combination with ST-APT can be considered a cost-effective treatment option for the secondary prevention of ACS in patients with elevated cardiac biomarkers without a prior history of stroke/TIA. The base-case results are driven by the mortality benefit shown in the clinical data of rivaroxaban 2.5 mg BID. It was observed in the clinical trial that rivaroxaban 2.5 mg BID in combination with ST-APT reduced the occurrence of ACS events; the model demonstrated that the benefits in terms of life expectancy and QALY gain were maintained beyond the trial duration over a 40-year (i.e., lifetime) horizon, confirming the advantages of a dual-pathway strategy in patients with elevated cardiac biomarkers without a prior history of stroke/TIA in the secondary prevention of ACS. Sensitivity analyses were conducted to test the impact of key assumptions. The ICER remained within widely accepted cost-effectiveness thresholds in these analyses.

This is the first published cost-effectiveness analysis of rivaroxaban 2.5 mg BID for secondary prevention of ACS. This model demonstrated several improvements compared to previous ACS models used to estimate the cost-effectiveness of other antithrombotic therapies [14–17]. The model was able to capture both single and multiple ACS events, as well as revascularization procedures. This captured the full picture of secondary event care in ACS patients. In addition, IS and HS/ICH were differentiated, as were fatal and non-fatal events, thus allowing more accurate estimation of costs in the model. The model was developed and calibrated to reflect disease progression in ACS patients as accurately as possible. Calibration to life expectancy after a first MI ensured that the survival following a first MI predicted by the model was reflective of post-MI survival as observed in reality. Increased risks of events due to age and/or the occurrence of earlier events were also explicitly captured in the model structure.

Many of the model inputs were derived from Swedish databases, reflecting the perspective of this study. All of the databases utilized for this research are national databases and are owned by Swedish national authorities. The data held are based on the entire Swedish population and their coverage is generally considered to be high. As such, these databases are considered as strong representations of the population of interest. Furthermore, the databases have existed for decades and the data held within them is widely regarded to be of high quality. To best reflect the current situation in Sweden, the most recent data from each database were used, with at least one data year included to ensure robustness of model inputs.

However, the approach presented here is not without its limitations. The model provides a simplification of what is expected in reality. Long-term outcomes believed to reflect the

consequences of therapy in ACS patients were based on a number of assumptions to capture natural disease progression. Treatment durations of 2 years for rivaroxaban and 1 year for clopidogrel or ticlopidine were assumed to reflect ESC guidelines [7, 8]; a RRR from the CURE trial [29] was applied to both treatment arms to adjust for the removal of clopidogrel or ticlopidine treatment effect after 1 year. Manual adjustments to discontinuation rates in the rivaroxaban arm were required for the second year of treatment to ensure alignment with expectations on the use of rivaroxaban in clinical practice. There is currently no data available on the real-life use of rivaroxaban in this patient population. As such, the discontinuation adjustments applied in the evaluation are based on expert opinion. Further, the model does not consider the long-term impact of non-fatal/non-ICH bleeding events beyond the duration of treatment as this was believed to have marginal impact on the overall model outcomes. In the absence of specific HS/ICH estimates, the costs and utilities applied to patients experiencing IS were also applied to those with HS/ICH.

CONCLUSION

The analysis suggests that rivaroxaban 2.5 mg BID provides a cost-effective treatment strategy in a Swedish societal setting for the secondary prevention of ACS in patients with elevated biomarkers without prior stroke/TIA, mainly driven by a benefit in terms of reduced mortality as demonstrated in the ATLAS ACS 2-TIMI 51 trial. This analysis may help to support the combination of ST-APT and rivaroxaban 2.5 mg BID for the secondary prevention of ACS events, as recommended by the ESC STEMI guidelines in patients with low bleeding risk [8]. The conclusion of cost-effectiveness holds, regardless of the standard of care currently being received by the patient (ASA monotherapy or ASA + clopidogrel or ticlopidine).

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