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Cost-effectiveness of ticagrelor and generic clopidogrel in patients with acute coronary syndrome in Switzerland

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Summary

QUESTION UNDER STUDY: The aim of this study was to evaluate the cost-effectiveness of ticagrelor and generic clopidogrel as add-on therapy to acetylsalicylic acid (ASA) in patients with acute coronary syndrome (ACS), from a Swiss perspective.

METHODS: Based on the PLATelet inhibition and patient Outcomes (PLATO) trial, one-year mean healthcare costs per patient treated with ticagrelor or generic clopidogrel were analysed from a payer perspective in 2011. A two-part decision-analytic model estimated treatment costs, quality-adjusted life years (QALYs), life years and the cost-effectiveness of ticagrelor and generic clopidogrel in patients with ACS up to a lifetime at a discount of 2.5% per annum. Sensitivity analyses were performed.

RESULTS: Over a patient's lifetime, treatment with ticagrelor generates an additional 0.1694 QALYs and 0.1999 life years at a cost of CHF 260 compared with generic clopidogrel. This results in an Incremental Cost Effectiveness Ratio (ICER) of CHF 1,536 per QALY and CHF 1,301 per life year gained. Ticagrelor dominated generic clopidogrel over the five-year and one-year periods with treatment generating cost savings of CHF 224 and 372 while gaining 0.0461 and 0.0051 QALYs and moreover 0.0517 and 0.0062 life years, respectively. Univariate sensitivity analyses confirmed the dominant position of ticagrelor in the first five years and probabilistic sensitivity analyses showed a high probability of cost-effectiveness over a lifetime.

CONCLUSION: During the first five years after ACS, treatment with ticagrelor dominates generic clopidogrel in Switzerland. Over a patient's lifetime, ticagrelor is highly cost-effective compared with generic clopidogrel, proven by ICERs significantly below commonly accepted willingness-to-pay thresholds.

Key words: *ticagrelor; generic clopidogrel; PLATO; cost-effectiveness; QALY; life years; Markov Model; Switzerland*

Introduction

Acute coronary syndrome (ACS), used as an umbrella term for non-ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI) and unstable angina (UA), is known to be a significant health problem within cardiovascular diseases. ACS is associated with high death rates, myocardial infarction (MI), and subsequent diagnostics and treatment. In 2008 almost 15,000 patients in Switzerland suffered at least one ACS event; 18% of these patients died as a consequence of an ACS event. ACS caused more than 19,000 hospital stays in 2008, with an average length of stay of 9.1 days [1]. Wieser et al. estimated the direct costs of ACS to be 1.17% of the total health expenditure in Switzerland in 2008 [1].

In the past, clinical practice guidelines for patients with ACS recommended dual anti-platelet therapy with clopidogrel and acetylsalicylic acid (ASA) [2–5]. A multicentre, randomised, double-blind trial, the PLATelet inhibition and patient Outcomes (PLATO) study (NCT00391872), compared two anti-platelet agents, ticagrelor 90 mg twice daily and clopidogrel 75 mg daily add-on to ASA, for the prevention of cardiovascular events in patients with ACS. Ticagrelor versus clopidogrel showed highly significant reductions in the primary endpoint which was a composite of death from vascular causes, MI, or stroke (9.8% vs. 11.7%) as well in the secondary endpoints in death rates from any cause, MI, or stroke (10.2% vs. 12.3%), in rates of MI (5.8% vs. 6.9%) and in rates of death from vascular causes (4.0% vs. 5.1%). The improved effectiveness profile was not associated with an increase in the overall rate of major bleedings [6]. The current European Society of Cardiology (ESC) Guidelines 2011 recommend ticagrelor as first-line therapy in patients with non-ST elevation ACS and in the 2012 guidelines as first-line therapy in patients with ST elevation acute myocardial infarction [4, 7].

Ticagrelor, co-administered with ASA, is indicated for the prevention of atherothrombotic events in adult patients with ACS. This includes patients who are managed medically, and those who are managed through percutaneous coronary intervention (PCI) or coronary artery by-pass

grafting (CABG). The main aim of the present study was to evaluate the cost-effectiveness of ticagrelor compared with the current standard of care, clopidogrel, for patients in Switzerland with ACS over a short- and long-term time period. As ticagrelor enters into a newly generic clopidogrel market it is interesting to evaluate if the clinical efficacy overcompensates the higher drug costs compared to clopidogrel.

Table 1: Hospital day costs.

Cost element	Costs in CHF
Hospital day – general ward	1,250
Hospital day – cardiology ward	2,117
Hospital day – coronary care unit	2,117
Hospital day – thoracic intensive care unit	7,539
Hospital day – intensive care unit	7,529
Source: Reference [9]	

Table 2: Costs of investigations.

Cost element	Costs in CHF
Stress test	188
Echocardiography	368
Myocardial scintigraphy	249
Electrophysiology study	1,068
Holter study	234
Ventilation/perfusion scan	90
Pulmonary angiography	321
Coronary angiography	1,715
Computer tomography head/brain	255
Computer tomography spinal	339
Computer tomography chest	315
Computer tomography helical	339
Computer tomography abdomen	312
Computer tomography extremity	264
Magnetic resonance imaging head/brain	443
Magnetic resonance imaging spinal	574
Magnetic resonance imaging chest	514
Magnetic resonance imaging abdomen	554
Magnetic resonance imaging extremity	553
Source: Reference [11]	

Table 3: Costs of interventions.

Cost element	Costs in CHF
Pacemaker	10,077
Implantable cardiac defibrillator	38,204
Intra-aortic balloon pump	7,057
Left ventricular assist device	175,000
Percutaneous coronary intervention without stent	1,676
Percutaneous coronary intervention with stent (excl. stent cost)	2,362
Bare metal stent	1,235
Drug eluting stent	2,726
Coronary artery bypass grafting without valve replacement	3,425
Coronary artery bypass grafting with valve replacement	8,935
Source: References [1, 15, 36]	

Methods

Cost study

The mean healthcare costs per patient were estimated based on the resource use observed in the PLATO trial for the treatment of ticagrelor versus clopidogrel. For each health state, detailed resource use was recorded in the PLATO trial for each cost item. This included length of hospitalisation, investigations (e.g. stress test, myocardial scintigraphy, computed tomography, etc.), interventions (e.g. pacemaker, percutaneous coronary intervention, etc.), as well as the number of reoperations due to bleeding as an adverse event after anti-platelet therapy. The population regarded in the model consisted of the patients eligible for 12 months follow-up in the PLATO trial. This reflects the Intention to treat population. The base year of the analysis was 2011.

The detailed resource use of the PLATO trial is published elsewhere [8]. The unit costs for resource use were derived from official prices and tariffs or if not applicable from specified published cost assessments. Only direct medical costs were considered in the model from a payer perspective. Costs were expressed in Swiss Francs (CHF) at 2011 prices. Costs were converted to 2011 price levels using the statutory health insurance rate index, if required [9]. The mean healthcare costs per patient were calculated by multiplying the resource use with the respective unit costs. These costs vary between both medications and depending on the event occurred due to the different resource use observed in the PLATO trial.

The daily drug costs of ticagrelor (CHF 3.40, as reimbursed in Switzerland in December 2011) and generic clopidogrel (CHF 1.12, lowest available price in Switzerland in December 2011) were applied [10]. The daily drug costs were multiplied by the number of days patients were on the study drug.

The cost of hospital days due to hospitalisation was represented by hospital day costs, which includes costs for hotel-type services and basic nursing care (table 1). Hospital day costs were calculated based on the tariff regulations for public hospitals of the Canton of Basel City. For hospital day costs in the general ward, the basic tariff was applied. For hospital day costs in the cardiology ward and the coronary care unit, a monitoring ward supplement was added to the basic tariff. For hospital day costs in the intensive care unit and thoracic intensive care unit, an intensive ward supplement was added to the basic tariff [9]. In Switzerland, hospital costs are reimbursed partly by the Swiss social health insurance and partly by the respective cantons. To show the total hospital day costs, the costs reimbursed by the canton (in this case the Canton of Basel City) as well as the supplements considered were added to the basic tariff [9].

Unit costs for investigations were priced according to the Swiss official tariff schedule (TARMED) for fee-for-service based physician remuneration (table 2). TARMED defines a code for each medical procedure reimbursed in the outpatient setting. A specific number of points are assigned to each code according to the medical and technical effort of the respective procedure [11]. The resource use for ACS patients mainly occurs in an inpatient setting. While

DRGs – applicable since 2012 – only allow cost allocation related to diagnosis, TARMED was the most representative approach in Switzerland to distinguish the costs of investigations at the same level of detail as gathered in the PLATO trial. To obtain the monetary value of each cost item the number of points corresponding to each TARMED code was multiplied with the value of one TARMED point [12]. The average value of one TARMED point for hospitals in 2011 was CHF 0.90 [13].

For unit costs for interventions (table 3), the TARMED costs were combined with a cost survey conducted in 5 representative Swiss hospitals on ACS from the Winterthur Institute of Health Economics. TARMED was used to price the direct cost of the interventions, whereas the cost survey was used to gather the cost for medical devices used in the interventions (e.g. pacemaker) [14]. The cost for implanting a left ventricular assist device was taken from Carrel (2010), considering the average cost of the presented cost range [15]. The interventions are also mainly used for hospitalised patients. As with the investigations, TARMED is the best available approach to compare these costs at this level of detail. In both, investigations and interventions, costs based on TARMED might be underestimated for the hospital setting.

The costs of reoperation due to bleeding were also calculated according to TARMED (table 4). The cost of blood products was taken from the price list of the Blood Transfusion Service Zurich [16].

Cost-effectiveness model

A two-part decision-analytic model, comprising of a one-year decision tree and a long-term Markov model, was constructed to estimate lifetime costs and quality-adjusted life years (QALYs) of treating ACS patients for one year with ticagrelor plus acetylsalicylic acid (ASA) compared with clopidogrel plus ASA. A detailed model description has been published elsewhere [17].

In brief, the first year was analysed by a decision-tree model. The average patient entered the model diagnosed with ACS. During the first year, the average patient could suffer a non-fatal myocardial infarction (MI), a non-fatal stroke or a fatal event or the patient could stay free of events during the first year. To estimate the long-term cost-effectiveness, the decision tree was extended to a Markov state transition model. The Markov model divided the disease into discrete health states in which the average patient stayed during a cycle. The patient entered the Markov model depending on the event that occurred in the one-year decision tree (See the detailed structure of the cost-effectiveness-model in MI, published by Nikolic et al. 2013 [17]).

Patients who did not suffer from a major cardiovascular event in the decision tree entered the long-term Markov model in the "no event" state. During each cycle, these patients were at risk of a non-fatal MI or a non-fatal stroke. In the case of a non-fatal event during a Markov cycle, patients moved to the "non-fatal MI" or "non-fatal stroke" states. These Markov states account for increased mortality, costs, and decreased quality of life for patients one year after an event. "Non-fatal MI" and "non-fatal stroke" are tunnel states, in which patients remain for one cycle only. Patients who survive a non-fatal event for one year move to the "post MI" or "post stroke" states, respectively. These states represent the prognosis in terms of decreased mortality, costs and unchanged quality of life for patients in the second and subsequent years after a non-fatal event since entering the model. Patients who suffered a non-fatal stroke or non-fatal MI in the first year (during the decision-tree model) entered the Markov model as either "post MI" or "post stroke".

Patients with a fatal event during the first year entered the Markov model as "dead", as well as patients who died from the "no event" state. Patients who die in a non-fatal event state or post event state pass to the dead post event state.

Using individual patient data from PLATO, the event rates, resource use, and QALYs were estimated for the first year. For the second year onwards, external data sources and assumptions were applied to extrapolate quality-adjusted survival, conditional on whether a non-fatal MI, a non-fatal stroke or no event occurred during the first year [18–20].

Costs

The costs for the one-year decision-tree model are the same costs as applied to the cost study. They are based on resource use from the PLATO study. Drug costs for the one-year decision-tree model were entered as a separate parameter and applied as long as patients remained alive during the 12 months of therapy. Patients eligible for 12 months of follow-up were also regarded in this analysis. Further details of the 12 months cohort are published by Nikolic et al. 2013 [17]. The aim was not to underestimate healthcare costs (including drug costs) in the one-year decision-tree model.

The costs for the long-term Markov model were determined in a specific cost survey from the Winterthur Institute of Health Economics on ACS. The survey used different sources (e.g. literature analysis, interviews with stakeholders from health care provider and health insurances as well as specific patient data base) to estimate a comprehensive picture for the direct cost picture of the ACS related events: Myocardial infarction (e.g. NSTEMI and STEMI) and stroke (e.g. ischaemic stroke and intracranial haemorrhage) were assessed due to a prevalence approach of the year 2008 comprising of all follow-up costs of an event in the first year and in each subsequent year, respectively. The follow-up costs include inpatient and outpatient costs for acute care and rehabilitation [1]. The costs were converted to 2011 price levels using the statutory health insurance rate index [21]. The costs for stroke were higher than costs for MI. Second year costs of MI decreased more than for stroke (table 5). The costs for the one-year decision-tree model were also regarded in the Markov model as costs according to the entry state.

Transition probabilities and quality-of-life data

For the decision-tree model, transition probabilities for the different health states as well as the utilities were applied as observed in the PLATO study.

In order to populate the transition probabilities for the Markov model, data beyond the duration of the PLATO trial were required. Transition probabilities for non-fatal MI and non-fatal stroke were estimated based on information from the observed PLATO data using the Weibull model

[22, 23]. One key assumption therefore is that no treatment effect is incorporated in the Markov model as patients are no longer on the study medications. This assumption yields identical transition probabilities for both treatments.

The annual mortality risk without cardiovascular events was calculated according to data of 2008 from the Federal Office of Statistics [24, 25]. The increased mortality risk for stroke for year one and two, as well as for subsequent years, was reported in Hankey et al. [19]. The increased mortality for ACS patients without further major cardiovascular events, as well as the increased mortality for MI, were estimated.

The QALY estimates for the Markov model were based on the PLATO trial. For the "No event" state the mean estimate of ticagrelor and clopidogrel patients from the decision tree-model was applied. For older patients a decrement due to age was applied. For the non-fatal MI and stroke states, the decrements as reported in the PLATO study were applied.

In the absence of health utility data specific to the Swiss setting, utilities from the PLATO study were applied [8].

Discounting, time horizon and perspective

The costs and outcomes of the model were discounted by 2.5 per cent per annum in line with current recommendations [26]. The model had a cycle length of one year and a life-time horizon. The results were evaluated for three different time periods: one year, five years and life-time. Costs were accounted for from the perspective of a third-party payer, the Swiss social health insurance.

Cost-effectiveness

The Incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs of ticagrelor versus clopidogrel through the incremental effects. The ICER was calculated for both effects, life years expected and QALYs gained.

Sensitivity analyses

Probabilistic, univariate, and multivariate sensitivity analyses were performed to analyse the impact of variations in key parameters on the results. The probabilistic sensitivity analysis, where all input parameters are considered as random quantities, was performed for 5,000 iterations.

Drug costs were varied according to expected future price variations. For ticagrelor, drug prices were varied by 25% to examine the impact of possible changes in the price of ticagrelor. Further sensitivity analyses were conducted varying different cost items by 25%. This includes all cost items of investigations and all cost items for interventions to evaluate the influence of a possible underestimation of unit costs by the TARMED approach. These sensitivity analyses were also conducted for hospital day costs and the respective cost items of investigations and interventions with the highest resource use. These were coronary angiography and percutaneous coronary intervention with stents for investigations and interventions, respectively. As these unit costs were applied to the one-year decision tree, the results of the sensitivity analyses of these cost items are presented for the one-year time horizon (table 8).

In the Markov model the discount rates were both varied at 0% and 5%. The Markov state costs were varied by 25%. The sensitivity analyses of the Markov model are presented for the five-year and lifetime horizon (table 9).

Results

Results of the cost study

The results of the cost study showed three times higher drug costs for ticagrelor compared to generic clopidogrel (table 6). The other cost categories showed lower costs for ticagrelor due to reduced resource use. In total, ticagrelor showed mean healthcare costs per patient at 12 months of CHF 456 lower than generic clopidogrel. The 95% confidence interval (CI) ranged from –653 to 1,564, and the *p*-value was 0.421.

Results of the cost-effectiveness model

The results of the one-year decision tree showed slightly higher effects regarding life years gained of 0.0062 and QALYs gained 0.0051 and lower costs for ticagrelor compared to generic clopidogrel of CHF 372 (table 7). This

Table 4: Costs of re-operation due to bleeding.

Cost element	Costs in CHF
Re-operation due to bleedings	1,376
Units of packed red blood cells	218
Units of whole blood	276
Units of fresh frozen plasma	150
Units of platelets	1,368

Source: References [16, 36]

Table 5: Markov state costs.

Cost element	Costs in CHF
Cost non-fatal MI first year	16,923
Cost MI second and subsequent years	1,734
Cost non-fatal stroke first year	19,828
Cost post stroke second and subsequent years	11,967
Cost no event state	1,734

MI = myocardial infarction

Table 6: Mean healthcare costs per patient at 12 months.

Health-care costs and cost categories (CHF)	Generic Clopidogrel (N = 5,339)	Ticagrelor (N = 5,347)	Difference (95% CI)	*p*-value
Hospital days	25,405	24,507	898.7 (–125.4 to 1921.7)	0.085
Investigations	2,279	2,256	23.1 (–26.4 to 73.7)	0.354
Interventions	4,591	4,444	147.4 (–62.7 to 358.6)	0.170
Bleeding related	257	251	6.6 (–80.3 to 92.4)	0.884
Study drug	312	933	–620.4 (–633.6 to –607.2)	<0.001
Total costs	**32,845**	**32,390**	**455.4 (–653.4 to 1564.2)**	**0.421**

CI = confidence interval

means that generic clopidogrel was numerically dominated by ticagrelor.

The five-year results showed slightly higher effects, both in terms of life years gained of 0.0517 and QALYs gained of 0.0461, and lower costs for ticagrelor compared to generic clopidogrel of CHF 224 (table 7). Therefore generic clopidogrel was still dominated by ticagrelor.

For the life-time horizon, ticagrelor showed a QALY gain of 0.1694 and 0.1999 life years saved per patient combined with slightly higher costs of CHF 260. This resulted in an Incremental cost-effectiveness ratio (ICER) of CHF 1,536 per QALY gained and CHF 1,301 per life year saved (table 7).

Sensitivity analyses

The probabilistic sensitivity analysis showed robust model results for plausible changes in the input parameters for the lifetime horizon. 5,000 iterations were performed. The results of the probabilistic analysis were plotted on the cost-effectiveness plane to show the uncertainty of the cost-effectiveness results (fig. 1). The results showed that the treatment of ACS with ticagrelor results in a gain in QALYs together with incremental costs in the majority of simulations.

The probability of ticagrelor being a cost-effective treatment for ACS for different willingness to pay, or threshold values, of a QALY compared to generic clopidogrel is presented in figure 2. Considering conventional threshold values for a QALY, the probabilistic sensitivity analysis shows a high probability for ticagrelor being cost effective.

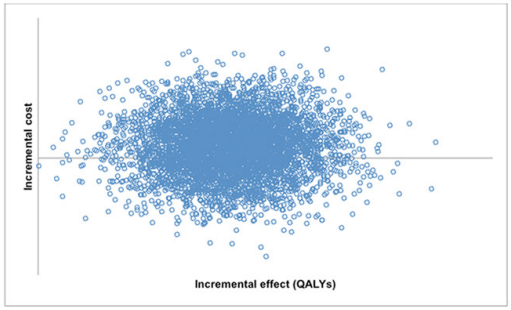

Figure 1

Results of the probabilistic sensitivity analysis.
Incremental costs and effects are calculated as ticagrelor minus generic clopidogrel.

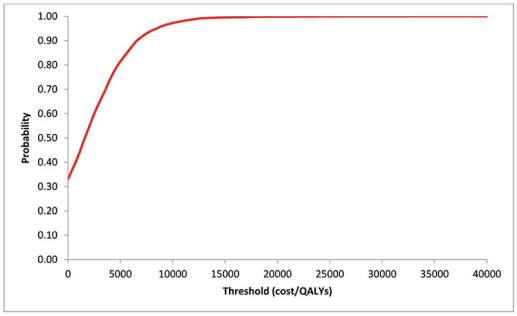

Figure 2

Cost-effectiveness acceptability curve for ticagrelor.
Incremental costs and effects are calculated as ticagrelor minus generic clopidogrel.

Univariate sensitivity analyses were conducted. The highest impact of cost variations on total costs was observed for hospital day costs. The application of 25% higher hospital day costs showed higher treatment costs for the one-year perspective of 19% for both ticagrelor and clopidogrel. The application of 25% lower hospital day costs led to 19% lower costs for the one-year perspective for both ticagrelor and generic clopidogrel.

The variation of investigation costs, intervention costs, costs for coronary angiography, costs for percutaneous coronary intervention with stent and stent costs as well as drug costs for ticagrelor, each by 25%, had an impact of less than 5% on the total costs in the one-year perspective and even less than 1% for the variation of drug costs for ticagrelor by 25% (table 8).

The application of a discount rate of 0% showed increased costs of 1% for the five-year perspective and 18% for the lifetime perspective for both ticagrelor and generic clopidogrel. The application of a discount rate of 5% showed decreased costs of 1% for the five-year time horizon and 11% for the lifetime horizon for both ticagrelor and generic clopidogrel. The application of 25% higher Markov state costs showed increased costs of 4.7% for ticagrelor and 4.6% for generic clopidogrel for the five-year time horizon and about 12.6% for ticagrelor and 12.4% for generic clopidogrel for the lifetime horizon. The application of 25% lower Markov state costs showed lower costs at the same extent for both ticagrelor and generic clopidogrel (table 9).

In the sensitivity analyses the model results were robust. The positive variation of cost data showed a slightly higher impact on the model results in the generic clopidogrel vs. ticagrelor arm. Furthermore, increased input cost data led to better cost-effectiveness for ticagrelor, whereas a reduction was associated with a better result for generic clopidogrel. Hospital day costs showed the highest impact on total costs in the sensitivity analyses of the one-year decision tree model. The other unit costs showed a low impact on total costs. However, during all changes in the input costs of the one-year decision tree model ticagrelor still dominated clopidogrel in QALYs and life years gained. At the changes in the Markov model ticagrelor also still dominated generic clopidogrel for the five-year time horizon in QALYs and life years gained.

Discussion

This paper presents the first health economic analysis of ticagrelor in the Swiss setting. Ticagrelor was compared to generic clopidogrel for the treatment of patients with ACS. For both effectiveness outcomes, life-years and QALYs, a one-year therapy for ACS patients with ticagrelor yielded higher effects for all model time horizons (i.e. one year, five years, or life-time). Furthermore, total costs under ticagrelor were slightly lower for the one year and five year time horizon and therefore ticagrelor numerically dominated generic clopidogrel. A main result was the lower amount of hospital days, which could be identified as an important cost driver for the treatment cost. For the thoracic intensive care unit, 12% of hospital days could be

avoided. For the intensive care unit, hospital days could even be reduced by 28%. As hospital day costs are the main cost driver due to the reduction of hospital days and the high costs per hospital day, the cost savings of ticagrelor are supposed to be made in the inpatient setting.

The life-time horizon analysis resulted in an ICER of CHF 1,536 per QALY gained and CHF 1,301 per life year saved for ticagrelor versus generic clopidogrel. This result was robust in the probabilistic sensitivity analysis. The federal court judgment on myozyme from 26th November 2011 decided that a cost benefit threshold of 100,000 CHF per life year saved was still acceptable. The ICER of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitor in the treatment of non-ST-segment elevation acute coronary syndromes was estimated to be £9,906 per QALY gained over lifetime in UK [27].

The cost per QALY gained of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting turned out to be more than CHF 50,000 [28].

While a cost per QALY gained threshold is missing in Switzerland, in UK the NICE has appointed a cost effectiveness threshold to £ 20,000–£ 30,000 for a treatment or a medical device [29]. Therefore from all perspectives mentioned – the judged cost threshold per life year gained

Table 7: Cost-effectiveness of ticagrelor vs. generic clopidogrel for the five-year time and lifetime horizon.

	Ticagrelor	Generic Clopidogrel	Difference	ICER (CHF)
One-year time horizon				
Costs (CHF)	32,658	33,029	–372	
Life years	0.9769	0.9707	0.0062	Dominated
QALYs	0.8399	0.8348	0.0051	Dominated
Five-year time horizon				
Costs (CHF)	40,181	40,404	–224	
Life years	4.4753	4.4236	0.0517	Dominated
QALYs	3.8737	3.8276	0.0461	Dominated
Lifetime horizon				
Costs (CHF)	65,886	65,626	260	
Life years	15.0615	14.8616	0.1999	1,301
QALYs	12.4890	12.3196	0.1694	1,536

ICER = Incremental cost effectiveness ratio, QALYs = quality adjusted life year

Table 8: Uni- and multivariate sensitivity analyses for the one-year decision tree model.

Input data changed	Change	Total costs (change to base case in %)		ICER (Life-years)	ICER (QALY)
		Ticagrelor	Clopidogrel		
Base case	–	32,658	33,029	Dominated	Dominated
Drug costs (ticagrelor)	+25%	32,961 (+0.9%)	33,029 (+0%)	Dominated	Dominated
	–25%	32,354 (–0.9%)	33,029 (+0%)	Dominated	Dominated
Investigations	+25%	33,222 (+1.7%)	33,600 (+1.7%)	Dominated	Dominated
	–25%	32,094 (–1.7%)	32,458 (–1.7%)	Dominated	Dominated
Interventions	+25%	33,832 (+3.6%)	34,244 (+3.7%)	Dominated	Dominated
	–25%	31,484 (–3.6%)	31,816 (–3.7%)	Dominated	Dominated
Coronary angiography	+25%	38,781 (+1.4%)	39,402 (+1.4%)	Dominated	Dominated
	–25%	26,538 (–1.4%)	26,660 (–1.4%)	Dominated	Dominated
Percutaneous coronary intervention with stent and stent costs	+25%	33,107 (+2.6%)	33,486 (+2.7%)	Dominated	Dominated
	–25%	32,208 (–2.6%)	32,572 (–2.7%)	Dominated	Dominated
Hospital day costs	+25%	33,520 (+18.8%)	33,924 (+19.3%)	Dominated	Dominated
	–25%	31,796 (–18.7%)	32,135 (–19.3%)	Dominated	Dominated

ICER = Incremental cost effectiveness ratio, QALYs = quality adjusted life year

Table 9: Sensitivity analyses for the Markov model.

Input data changed	Change	Time horizon	Total costs (change to basecase in%)		ICER (Life-years)	ICER (QALY)
			Ticagrelor	Clopidogrel		
Base case		5 years	40,181	40,404	Dominated	Dominated
		lifetime	65,886	65,626	1,301	1,536
Discount rate	0%	5 years	40.653 (+1.2%)	40.884 (+1.2%)	Dominated	Dominated
		Lifetime	77.832 (+18.1%)	77.355 (+18.1%)	1,769	2.114
	5%	5 years	39.737 (-1.1%)	39.984 (-1.0%)	Dominated	Dominated
		Lifetime	58.314 (-11.5%)	58.215 (-11.5%)	635	742
Markov state costs	+25%	5 years	42.053 (+4.7%)	42.260 (+4.6%)	Dominated	Dominated
		lifetime	74.190 (+12.6%)	73.792 (+12.4%)	1,991	2.350
	–25%	5 years	38.295 (–4.7%)	38.568 (–4.5%)	Dominated	Dominated
		lifetime	57.579 (-12.6%)	57.489 (-12.4%)	450	532

ICER = Incremental cost effectiveness ratio, QALYs = quality adjusted life year

in Switzerland, the extensively used NICE guidelines regarding the cost per QALY gained threshold, and by comparison with ICERs of indication relevant treatments – ticagrelor might be considered highly cost-effective compared to generic clopidogrel in Switzerland.

Cost-effectiveness analyses of ticagrelor versus clopidogrel in patients with ACS were conducted in several additional country-specific settings. These analyses showed numerical differences in the published cost-effectiveness results, but the ICER per QALY gained was also below conventional thresholds for cost-effectiveness [17, 30, 31]. As the resource use, event rates, transition probabilities for the different health states and utilities were adapted from the PLATO trial in all models, the main difference between the models regarding input data was the use of different costs applied to the one-year decision tree model, Markov state costs, discount rates and country-specific mortality risk without cardiovascular events. The Swedish [17] and the German [31] results show lower total costs and lower results for life years gained and QALYs. The main reason for lower costs in the Swedish setting are the differences in drug prices and hospital day costs. Drug costs for both ticagrelor and generic clopidogrel are comparable for Germany and Switzerland but higher compared with Sweden. On the other side, the relative proportion of daily drug costs for generic clopidogrel compared to daily drug costs for ticagrelor are much higher in Germany and Switzerland than in Sweden, respectively 25% and 33% versus 3%. In contrast, the hospital day costs are substantially higher in Switzerland than in Germany and Sweden. Compared with an ICER of CHF 1,536 per QALY for a lifetime horizon in the Swiss setting, Nikolic et al. in 2013 reported an ICER of EUR 2,753 per QALY for a lifetime horizon for the Swedish setting, Theidel et al. in 2013 reported an ICER of EUR 2,728 per QALY for a lifetime horizon for the German setting. In summary, both parameters, hospital day costs and drug costs, lead to lower ICERs in Switzerland than in the Swedish setting. The difference in life years gained and QALYs can be explained by the lower discount factors and country-specific mortality risk without cardiovascular events applied in the Swiss setting [17, 31].

Crespin et al. in 2011 compared the cost-effectiveness of ticagrelor to a genotype-driven treatment with anti-platelet agents in the US setting. The model was developed with an ACS population of Medicare beneficiaries. Crespin et al. reported an ICER of USD 10,059 per QALY for a five-year time horizon. The difference to the results for the Swiss setting, where ticagrelor dominates clopidogrel for a five-year time horizon, is mainly based in the high difference of drug costs between ticagrelor and clopidogrel and the different study populations [32].

Lacking Swiss specific databases forced different assumptions and external data sources to estimate the long-term cost-effectiveness. The unit costs of investigations and interventions are supposed to be underestimated being priced with TARMED. The calculation of inpatient services using an outpatient tariff does not reach the real inpatient costs. DRGs were introduced in Switzerland in 2012 whereas the unit costs are based on data of 2011. As DRGs only allow cost allocation related to diagnosis, the calculation of detailed resource use and unit costs as observed in the PLATO cannot be represented sufficiently with DRGs. However, the sensitivity analysis showed a small impact due to higher costs for investigations or interventions, whereby ticagrelor still dominated clopidogrel. Additionally, higher inpatient costs would lead to an even better cost-effectiveness for ticagrelor compared to generic clopidogrel.

Furthermore, adverse and subsequent events are not explicitly modelled in the current model structure due to its simplified representation of reality. However, adverse and subsequent events are accounted for as an increase of mortality rates in the non-fatal MI or stroke states as well as the post MI/post stroke states. In that way, reduced utility and reduced life expectancy due to adverse and subsequent events encompass a worse prognosis and are implicitly represented in this model. The impact of adverse and subsequent events on costs is represented by costs of reoperations due to bleeding in the one-year decision tree model and Markov state costs in the Markov model. As adverse and subsequent events are implicitly represented in both costs and effects, it is difficult to estimate the impact on the ICER. A possible treatment discontinuation of patients is not taken into consideration. However, it could be relevant in clinical practice. The model is already published elsewhere including a description of the model structure [17].

The estimated long-term gain in QALYs is mainly driven by the clinical event rates observed in the PLATO trial. The increased long-term quality-adjusted survival at the 12-month treatment point with ticagrelor compared to clopidogrel, as observed in the PLATO trial, is a key parameter for the estimated gain in QALYs in the cost-effectiveness model.

The PLATO study reflects actual guideline recommendations and thus actual clinical practice, by the comparison of ticagrelor to clopidogrel in early administration at the acute phase of the ACS episode. This means that the results may be also applied to a setting where ticagrelor is already implemented in clinical care. The robust results of the sensitivity analyses, as well as comparable results to the Swedish and German setting for the cost-effectiveness model can lead to the hypothesis of comparable results in settings in other European countries [17, 31].

Conclusion

Ticagrelor reduces mortality in patients with ACS compared to clopidogrel, showing comparable costs even when using generic clopidogrel. One-year treatment with ticagrelor represents a cost-effective option for patients with ACS in Switzerland, showing ICERs widely under the commonly accepted willingness-to-pay thresholds for short- and long-term time horizons compared to generic clopidogrel [33–35].

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Figures (large format)

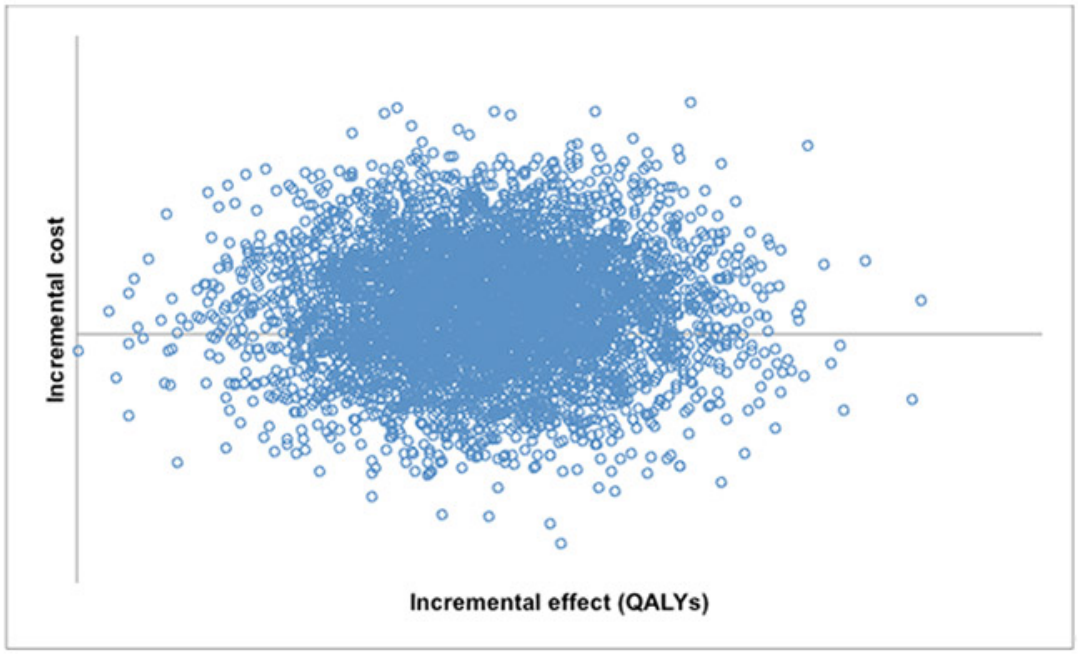

Figure 1

Results of the probabilistic sensitivity analysis.
Incremental costs and effects are calculated as ticagrelor minus generic clopidogrel.

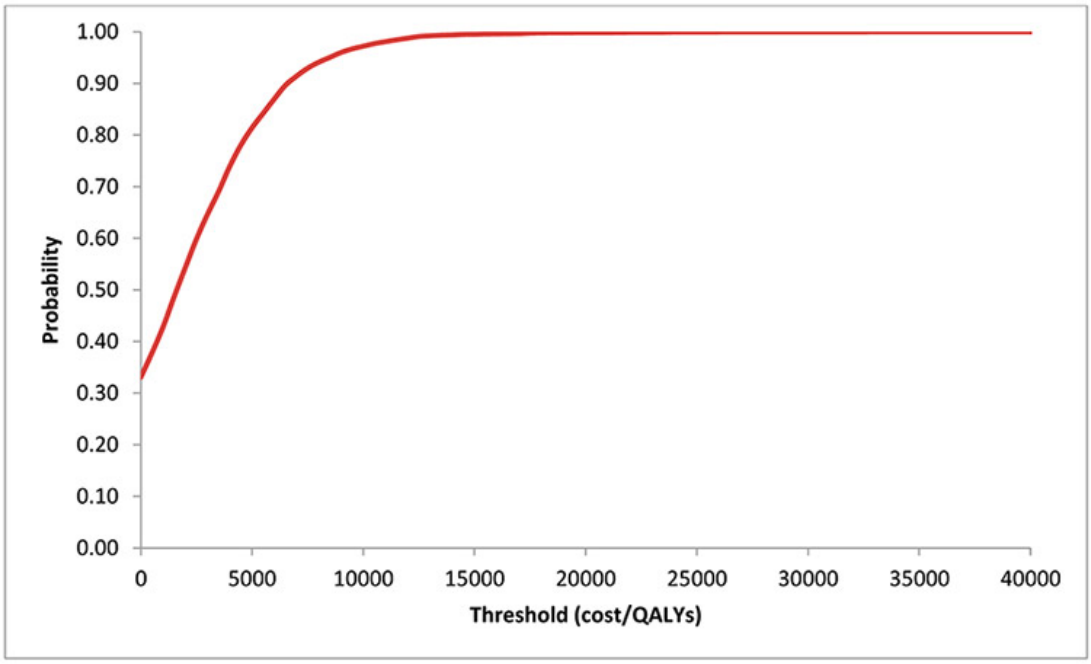

Figure 2

Cost-effectiveness acceptability curve for ticagrelor.
Incremental costs and effects are calculated as ticagrelor minus generic clopidogrel.