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Cost-effectiveness of ticagrelor plus aspirin versus aspirin in acute ischaemic stroke or transient ischaemic attack: an economic evaluation of the THALES trial

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ABSTRACT

Objective THALES demonstrated that ticagrelor plus aspirin reduced the risk of stroke or death but increased bleeding versus aspirin during the 30 days following a mild-to-moderate acute non-cardioembolic ischaemic stroke (AIS) or high-risk transient ischaemic attack (TIA). There are no cost-effectiveness analyses supporting this combination in Europe. To address this, a cost-effectiveness analysis was performed.

Methods Cost-effectiveness was evaluated using a decision tree and Markov model with a short-term and long-term (30-year) horizon. Stroke, mortality, bleeding and EuroQol-5 Dimension (EQ-5D) data from THALES were used to estimate short-term outcomes. Model transitions were based on stroke severity (disabling stroke was defined as modified Rankin Scale >2). Healthcare resource utilisation and EQ-5D data beyond 30 days were based on SOCRATES, another trial in AIS/TIA that compared ticagrelor with aspirin. Long-term costs, survival and disutilities were based on published literature. Unit costs were derived from national databases and discounted at 3% annually from a Swedish healthcare perspective.

Results One-month treatment with ticagrelor plus aspirin resulted in 12 fewer strokes, 4 additional major bleeds and cost savings of €95 000 per 1000 patients versus aspirin from a Swedish healthcare perspective. This translated into increased quality-adjusted life-years (0.04) and reduced societal costs (–€1358) per patient over a lifetime horizon. Key drivers of cost-effectiveness were number of patients experiencing subsequent disabling stroke and degree of disability. Findings were robust over a range of input assumptions.

Conclusion One month of treatment with ticagrelor plus aspirin is likely to improve outcomes and reduce costs versus aspirin in mild-to-moderate AIS or high-risk TIA.

Trial registration number NCT03354429.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The total cost of stroke in Europe is high; this burden is predicted to dramatically increase over the next few years. Improving stroke care at all stages of the pathway, including prevention of subsequent strokes, would not only improve patient-reported outcomes, but also reduce this burden. Based on this growing need, this analysis examined the cost-effectiveness of ticagrelor plus aspirin versus aspirin in subsequent stroke prevention.

WHAT THIS STUDY ADDS

⇒ This cost-effectiveness model was based on data from THALES, which showed that ticagrelor plus aspirin significantly reduced stroke or death but increased major bleeding risk within 30 days versus aspirin in patients following a mild-to-moderate acute ischaemic stroke or transient ischaemic attack. Ticagrelor plus aspirin improved outcomes and reduced healthcare costs in this population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This is the first paper to examine cost-effectiveness of ticagrelor plus aspirin in subsequent stroke prevention. Despite higher medication cost and increased bleeding, treatment with ticagrelor plus aspirin for 1 month enabled cost savings of €95 000 per 1000 patients because of fewer subsequent strokes. Treatment with ticagrelor plus aspirin is likely to reduce events and costs over a patient's lifetime, from a healthcare and societal perspective.

INTRODUCTION

Stroke is a leading cause of morbidity and mortality worldwide. In 2016, there were 948 896 deaths and 2 466 197 new cases in Europe alone.[1] Individuals who have experienced an ischaemic stroke or transient ischaemic attack (TIA) are also at increased risk for subsequent stroke; this risk ranges from 4% to 17% in the first 3 months alone.[2 3] The total cost of stroke in Europe (32 countries) was estimated to be €60 billion in 2017, which included €27 billion for healthcare,

€5 billion for social care (including nursing or residential care), €16 billion for informal caregiver time and €12 billion attributed to lost productivity.[4] The total burden is forecast to increase to €86 billion by 2040 (+44%).[4] These findings clearly highlight an urgent need for cost-effective treatment strategies to reduce disability and care costs and prevent the premature mortality associated with stroke.[5]

Aspirin has been the mainstay of treatment for secondary prevention of stroke.[6–8] However, there is growing interest in the role of antiplatelet drugs, including ticagrelor based on findings from the SOCRATES and THALES trials. SOCRATES (NCT01994720) included 13 199 patients with high-risk TIA ($ABCD^2$ score ≥4 and/or ipsilateral stenosis) or acute ischaemic stroke (AIS; National Institutes of Health Stroke Scale (NIHSS) ≤5); most patients had NIHSS ≤3 (67.4%) and mean age was 65.9 years. In this trial, occurrence of the primary composite endpoint of stroke, myocardial infarction or death within 90 days was lower with ticagrelor versus aspirin (6.7% vs 7.5%; HR 0.89; 95% CI 0.78 to 1.01; p=0.07), as was major bleeding (HR 0.83; 95% CI 0.52 to 1.34; p=0.45).[9] THALES (NCT03354429) subsequently evaluated ticagrelor plus aspirin versus aspirin for the prevention of the composite of stroke or death within 30 days (primary endpoint) in 11 016 patients with high-risk TIA ($ABCD^2$ score ≥6 and/or ipsilateral stenosis) or AIS (NIHSS ≤5); most patients also had NIHSS ≤3 (60.6%) and mean age was 65.2 years.[10] Compared with aspirin, ticagrelor plus aspirin significantly reduced the risk of the composite of stroke and death (6.6% vs 5.5%; HR 0.83; 95% CI 0.71 to 0.96; p=0.02) but increased the risk of major bleeding (0.5% vs 0.1%; HR 3.99; 95% CI 1.74 to 9.14; p=0.001). A subanalysis of 3312 patients from THALES with moderate AIS (NIHSS 4–5) showed that ticagrelor plus aspirin also non-significantly reduced stroke or death versus aspirin in this high-risk group (7.7% vs 9.1%; HR 0.84; 95% CI 0.66 to 1.06; p=0.14).[11]

After a priority review based on these data, the US Food and Drug Administration approved dual antiplatelet therapy (DAPT) with ticagrelor plus aspirin for the reduction of stroke in patients with AIS (NIHSS ≤5) or high-risk TIA in November 2020.[12] The most recent (2021) American Heart Association/American Stroke Association, European Stroke Organisation and European Society of Cardiology guidelines now recommend DAPT with ticagrelor and aspirin for the treatment of non-cardioembolic ischaemic stroke (ischaemic stroke NIHSS ≤5 or TIA and ipsilateral stenosis).[6–8]

DAPT with ticagrelor and aspirin reduces subsequent stroke risk, but it is essential to determine the cost-effectiveness of any new approach for all decision makers involved in treatment appraisals. It is cost prohibitive and extremely uncommon to measure the lifelong impact of new treatments in clinical trials, so modelling approaches are necessary. Stroke outcome models are well established.[13 14] Based on the published literature, models specific to stroke should be constructed to address two phases: (1) immediate treatment of the index stroke and (2) long-term prognosis following treatment using natural history data as a comparison where available.[14] It is recommended that results are reported as incremental cost-effectiveness ratios, which capture the benefits of treatment comparisons in terms of cost versus quality-adjusted life-years (QALYs) based on short-term outcomes from clinical trial data extrapolated over a patient's lifetime.[13 14] Any decision-maker can, therefore, consider both short-term implications of new stroke treatments and the potential long-term benefits.

The aim of this analysis was to evaluate the cost-effectiveness of ticagrelor plus aspirin versus aspirin in the prevention of subsequent stroke. The model was constructed in accordance with the published recommendations described above[13 14] using short-term and long-term outcomes in a European (Swedish healthcare) setting.

METHODS

Overview

A de novo economic model was developed to estimate the cost-effectiveness of ticagrelor plus aspirin compared with aspirin after AIS or TIA, based on an established approach.[13 14] The base-case model consisted of a 1-month decision tree that reflected the THALES trial duration followed by a long-term Markov model with monthly cycles to allow for a lifetime extrapolation over a 30-year period. The Markov model included four health states: no subsequent stroke, non-disabling stroke(s) (NDS), disabling stroke(s) (DS) and death (figure 1). The base-case analysis was conducted using a Swedish societal perspective. A 3% discount rate was applied to costs and outcomes annually in accordance with the Professional Society for Health Economics and Outcomes Research (known as ISPOR) guidance.[15]

Population and interventions

The model population corresponded to the inclusion criteria of THALES. Patients with acute onset of cerebral ischemia due to either an AIS with NIHSS ≤5 or high-risk TIA with $ABCD^2$ ≥6 were included.[10] The baseline age used in the model was 65 years, which reflected the mean baseline age in THALES.

Interventions were based on the ticagrelor plus aspirin or aspirin regimens in THALES. Patients received either a loading dose of ticagrelor 180 mg plus aspirin 300–325 mg on day 1 followed by ticagrelor 90 mg two times per day plus aspirin 75–100 mg once daily for 30 days, or they received a loading dose of aspirin 300–325 mg on day 1 plus placebo followed by aspirin 75–100 mg once daily plus placebo for 30 days.

Model structure and assumptions

Clinical outcomes (rate of NDS, DS and death) in THALES were used to determine the proportion of

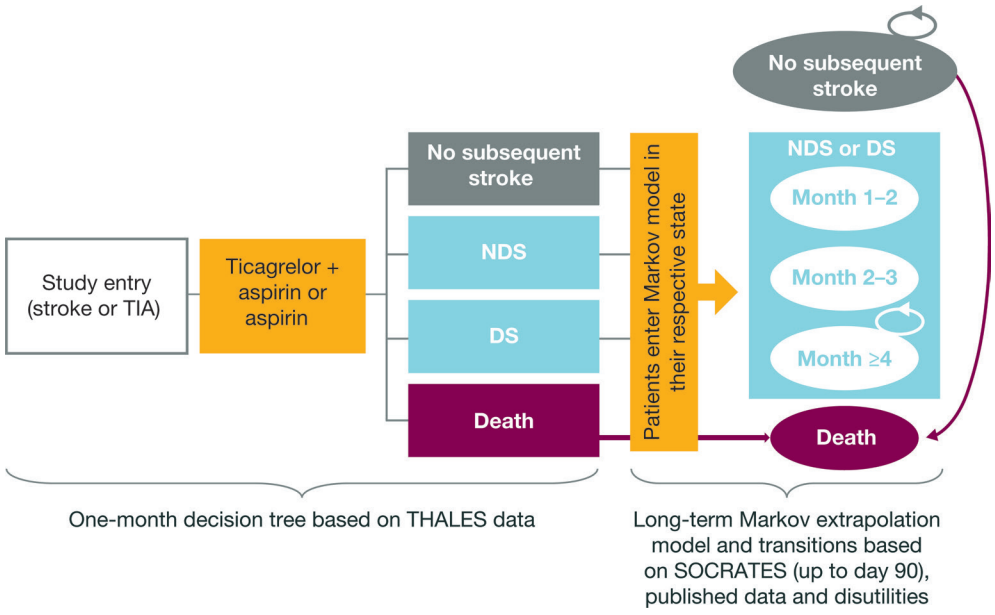

Figure 1 Decision tree structure for the first month and Markov model structure with monthly cycles. DS, disabling stroke; NDS, non-disabling stroke; TIA, transient ischaemic attack.

patients transitioning to one of the four health states in the decision tree following treatment with either ticagrelor plus aspirin or aspirin. Transitions to NDS and DS in the decision tree were made using the modified Rankin Scale (mRS). The threshold for DS in the base-case analysis was mRS >2; this threshold was used as it was associated with greater mortality risk, utility loss and costs than mRS 0–2.[10 16 17]

At the end of 1 month, patients entered the respective health states in the Markov model (figure 1). Time-dependent transition probabilities were then facilitated using tunnel states (months 0–1, 1–2, 2–3, 3–4 and 4+) for the NDS and DS health states, that is, when a patient enters either the NDS or DS health state, they move along these tunnel health states over time. In the early time points of the tunnel states (ie, months 0–1), patients have greater risk of another stroke, lower utilities and higher costs.[18] Patients in the NDS state could move to the DS state or remain in the NDS state, but once a patient was in the DS state, they remained in that state, irrespective of whether the subsequent stroke was an NDS or DS (see online supplemental table 1).

Bleeding events experienced during THALES (shown in online supplemental table 2)[10] were also included in the model and were assigned long-term cost and utility losses. These included intracranial haemorrhage (ICH; disabling and non-disabling), fatal bleed and other Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) bleeds (moderate and severe). Dyspnoea, a known side effect of ticagrelor, was seen as a cause of treatment discontinuation in THALES for both the treatment and comparator (1.03% and 0.18%, respectively) and would be expected to result in a general practitioner (GP) visit; therefore, treatment-specific discontinuation probabilities and GP visit costs were applied to the first cycle after discontinuation in the Markov model.

Data sources

Transition probabilities for NDS and DS

Base-case transitions for NDS and DS during months 1 and 2 were based on the 30 day duration of THALES (shown in online supplemental table 3A).[10] Transition from the no subsequent stroke state from month 2 onward was derived from published data.[19] Transition probabilities were calculated with the assumption that the ratio of NDS to DS were the same as that observed for the first subsequent stroke event in THALES. No other transitions were introduced since, in SOCRATES, the only other randomised controlled trial of ticagrelor versus aspirin in patients who had a stroke, 6199 (94%) patients in the ticagrelor group and 6160 (93%) patients in the aspirin group did not have a subsequent stroke over a longer 90-day duration.

Transition probabilities for mortality rates

Transition probabilities for mortality rates were chosen as close to both trials as possible, based on the month of occurrence; when not possible, published HRs were used. Following these principles, mortality rates were derived from THALES for months 1 and 2,[10] and from SOCRATES[9] for transitions from the no subsequent stroke state from month 2 onward; mortality following a subsequent initial stroke from month 2 onward was adjusted for NDS and DS using published HRs.[17] Base-case mortality rates are listed in online supplemental table 3B).[9 10 17 19]

Utilities

Utilities used in the model are summarised in online supplemental table 4.[9 10 20 21] EuroQol- 5 Dimension

Table 1 Results of (A) trial duration (30 days) costs and (B) lifetime costs and QALYs for ticagrelor plus aspirin versus aspirin

(A) Trial duration costs (per patient)	Aspirin	Ticagrelor+aspirin	Incremental
Total costs for strokes	**€839**	**€650**	**–€189**
Non-disabling strokes	€221	€183	–€38
Disabling strokes	€618	€467	–€151
Total costs for bleeding	**€14**	**€40**	**+€26**
ICH bleed: non-disabling	€0	€6	+€6
ICH bleed: disabling	€9	€14	+€5
Fatal bleed	€3	€14	+€11
Other GUSTO moderate and severe	€2	€6	+€4
Medication costs	**€2**	**€70**	**+€68**
Total costs	**€855**	**€760**	**–€95**
(B) Lifetime costs and QALYs (per patient)	**Aspirin**	**Ticagrelor+aspirin**	**Incremental**
Total costs	**€57 009**	**€55 651**	**–€1358**
Stroke related	€37 941	€37 390	–€551
Caregiver related	€19 045	€18 142	–€903
Bleeding related	€20	€48	+€28
Drug related	€3	€71	+€68
Total QALYs	**7.55**	**7.59**	**+0.04**
Stroke related	7.59	7.64	+0.05
Bleeding related	–0.04	–0.05	–0.01
Costs per QALY			**Dominant**

GUSTO, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; ICH, intracranial haemorrhage; QALY, quality-adjusted life-year.

(EQ-5D) data collected in THALES[10] and SOCRATES[9] were used to generate utility values by applying the UK EQ-5D tariff published by Dolan.[21] This approach was used to calculate utility values at months 0, 1 and 3. The utility at month 2 was obtained by linear interpolation. The health state utilities for each month in the long-term model were set equal to the 3-month health state utilities. Age-related utility decrements were based on the relationship between age and utility values observed in the general population using the following relationship from Ara and Brazier[22] :

$$General\ population\ EQ-5D = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

Bleeding event disutilities were applied for ICH and GUSTO moderate and severe bleeds, using the values for 'other ICH' and 'clinically relevant non-major bleed' from Lanitis *et al*,[20] respectively, for the first cycle in the NDS state and for the long-term in the DS state. These events were modelled separately from the transition matrices. In the societal perspective, a caregiver disutility of 0.065 was applied in the DS state only. This was based on the work of Persson *et al*,[23] who reported a statistically significant disutility of 0.065 for caregivers (spouses) of stroke survivors with mRS 3–5.

Resource use and cost data

Unit costs for drug acquisition were calculated from published sources,[24] and dosing was aligned with THALES.[10] All costs were valued in 2021 Euros. The cost per month for ticagrelor and aspirin was €67.57 and €2.13, respectively.[24]

The mean length of stay for each complication was derived from SOCRATES. Medical resource costs (hospitalisations and outpatient costs for stroke) were based on published DRG codes.[25] The mean cost per hospitalisation for an NDS and DS event was calculated to be €6623 and €12 502, respectively, using costs from the Swedish National Board of Health and Welfare (Socialstyrelsen) (online supplemental table 5).[9 10 24–26] Outpatient care costs in the first 3 months were also based on published DRG codes, with the resource use for each health state being based on SOCRATES.[9] From month 3 onwards, outpatient costs were calculated after applying a percentage reduction on the acute monthly costs, ie, for months 1–3. This reduction was determined using published sources,[26] adjusted as per proportion with different mRS scores based on THALES (in the 'no event' state, the mRS distribution at visit 3 from the THALES trial is assumed; in the NDS and DS states, the mRS distribution at visit 3 following the subsequent event is used to inform the ratio of mRS scores within the relevant state).

Table 2 Results of trial duration (30 days) costs and lifetime costs and QALYs for ticagrelor plus aspirin versus aspirin in patients following acute ischaemic stroke (NIHSS 4–5)

Trial duration costs (per patient)	Aspirin	Ticagrelor+aspirin	Incremental
Total costs for strokes	**€1265**	**€1024**	**–€241**
Non-disabling strokes	€236	€237	+€1
Disabling strokes	€1029	€787	–€242
Total costs for bleeding	**€36**	**€77**	**+€13**
ICH bleed: non-disabling	€0	€0	€0
ICH bleed: disabling	€15	€7	–€8
Fatal bleed	€4	€22	+€18
Other GUSTO moderate and severe	€3	€6	+€3
Medication costs	**€2**	**€70**	**+€68**
Total costs	**€1289**	**€1129**	**–€160**
Lifetime costs and QALYs (per patient)	**Aspirin**	**Ticagrelor+aspirin**	**Incremental**
Total costs	**€61 001**	**€59 096**	**–€1905**
Stroke related	€39 379	€38 719	–€660
Caregiver related	€21 585	€20 256	–€1329
Bleeding related	€34	€51	+€17
Drug related	€2	€70	+€68
Total QALYs	**7.34**	**7.46**	**+0.12**
Stroke related	7.40	7.50	+0.10
Bleeding related	–0.06	–0.04	+0.02
Costs per QALY			**Dominant**

GUSTO, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; ICH, intracranial haemorrhage; NIHSS, National Institutes of Health Stroke Scale; QALY, quality-adjusted life-year.

Bleeding event–related costs for fatal bleed (€7274), ICH (non-disabling, without complications; €6623), ICH (disabling, with complications; €12 502) and other GUSTO bleeding (€2499, assuming an average of 'gastrointestinal bleed, inpatient' and 'gastrointestinal bleed, outpatient') were derived from published sources that calculated them using a microcosting approach.[25] These were applied as one-off events. As dyspnoea was a common cause of discontinuation in THALES and was associated with a GP visit, treatment discontinuation cost was applied as a cost per GP visit of €191. Monthly caregiver costs of €90 and €2289 to account for informal support by caregivers of independent (mRS 0–2) and dependent (mRS 3–5) stroke survivors were applied based on published sources inflated to 2021.[27] Costs associated with independent stroke survivors were applied to the NDS state and costs associated with dependent stroke survivors were applied to the DS state; no caregiver costs were applied to the 'no event' state.

Sensitivity and scenario analyses

To assess the impact of uncertainty in the model parameters, deterministic one-way sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA), and scenario analyses were performed. Patient characteristics were based on THALES, and the following parameters were included in the DSA and PSA: transition probabilities, adverse event rates and utilities, and the impact of changes to the time horizon, discount rates, stroke definition and mortality rates. Payer perspective was included as an alternative scenario, which tested the results after excluding caregiver costs and disutility.

In the DSA, the parameter variation was determined using either the 95% CI or a standard error (SE) ±20% variation when no other information was available. The most influential parameters identified are presented in the RESULTS section. In the PSA, distributions assigned to appropriate parameters were based on the quantity and quality of evidence as well as type of variable (online supplemental table 6). Distributions for transitions in the decision tree were estimated through 95% CIs for both ticagrelor plus aspirin and aspirin from THALES. A 10% variation was considered to calculate SE for the rest of the transition probabilities.

Subgroup analyses

Cost-effectiveness was evaluated in patients with moderate AIS (NIHSS score 4–5) and in those with ipsilateral atherosclerotic stenosis ≥30%. Ticagrelor plus aspirin was shown to be effective in these high-risk groups in THALES. All statistical analyses were programmed and analysed using

Table 3 Results of trial duration (30 days) costs and lifetime costs and QALYs for ticagrelor plus aspirin versus aspirin in patients with ipsilateral stenosis ≥30%

Trial duration costs (per patient)	Aspirin	Ticagrelor+aspirin	Incremental
Total costs for strokes	**€1426**	**€1103**	**–€323**
Non-disabling strokes	€306	€238	–€68
Disabling strokes	€1120	€865	–€255
Total costs for bleeding	**€37**	**€70**	**+€33**
ICH bleed: non-disabling	€0	€0	€0
ICH bleed: disabling	€25	€50	+€25
Fatal bleed	€7	€7	€0
Other GUSTO moderate and severe	€5	€12	+€7
Medication costs	**€2**	**€70**	**+€68**
Total costs	**€1465**	**€1243**	**–€222**
Lifetime costs and QALYs (per patient)	**Aspirin**	**Ticagrelor+aspirin**	**Incremental**
Total costs	**€63 177**	**€59 879**	**–€3298**
Stroke related	€40 260	€38 973	–€1287
Caregiver related	€22 858	€20 742	–€2116
Bleeding related	€56	€94	+€38
Drug related	€2	€70	+€68
Total QALYs	**7.20**	**7.26**	**+0.06**
Stroke related	7.31	7.43	+0.13
Bleeding related	–0.11	–0.18	–0.07
Costs per QALY			**Dominant**

GUSTO, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; ICH, intracranial haemorrhage; QALY, quality-adjusted life-year.

Microsoft Excel version Office 365 (Microsoft, Redmond, Washington, DC, USA).

RESULTS

Base-case analysis

Treatment with ticagrelor plus aspirin for 30 days resulted in 12 fewer strokes and four major additional bleeds per 1000 patients versus aspirin. The reduction in strokes enabled a cost savings of €189 000 per 1000 patients (€189 per patient), which offset the incremental medication costs with ticagrelor plus aspirin (€68 per patient) and the incremental cost of treating additional bleeds (€26 per patient) over the first cycle, respectively (table 1A). This resulted in an overall cost saving of €95 000 per 1000 patients (€95 per patient) for treatment with ticagrelor plus aspirin.

Across a lifetime horizon (30 years) and from a societal perspective, the benefits of early subsequent stroke prevention translated into QALY gains of 0.04 (95% CI 0.043 to 0.044) and cost savings of €1358 (95% CI –€1371 to –€1351) per patient, indicating that the intervention dominates the comparator. Reduction in stroke risk and disability with ticagrelor plus aspirin also resulted in lower lifetime caregiver costs versus aspirin (table 1B).

Subgroup analysis

Treatment with ticagrelor plus aspirin for 30 days resulted in 13 fewer strokes and three additional bleeds per 1000 patients in patients with moderate stroke severity NIHSS 4–5, and 28 fewer strokes and five additional bleeds in patients with ipsilateral stenosis ≥30% compared with aspirin.

Treatment with ticagrelor plus aspirin enabled total lifetime cost savings of €1905 for patients with stroke severity NIHSS 4–5 and total lifetime cost savings of €3298 for patients with ipsilateral stenosis ≥30% compared with aspirin. These savings were due to fewer subsequent strokes in these groups, which offset the incremental medication and bleeding costs (tables 2 and 3).

Sensitivity and scenario analyses

The base-case analysis was robust to changes in parameters. Based on 5000 simulations, PSA indicated that ticagrelor plus aspirin remained dominant and was associated with QALY gains at reduced incremental cost (including medication, health state, adverse event and caregiver costs) in 93.0% of simulations using a willingness-to-pay threshold of €50 000 (figure 2). DSA showed that key drivers of cost-effectiveness were transition probabilities of DS or no subsequent stroke during treatment with

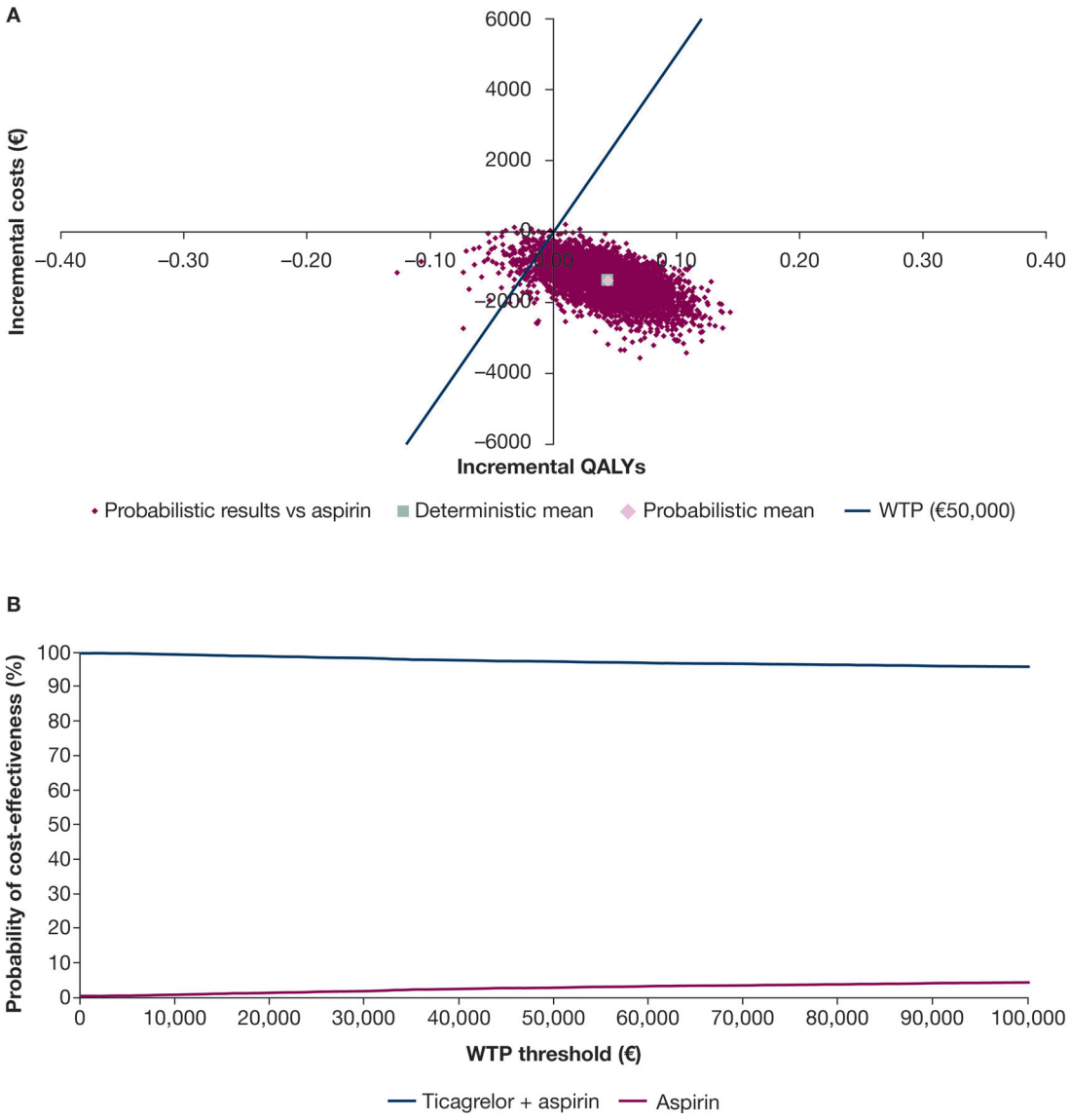

Figure 2 (A) Cost-effectiveness plane and (B) cost-effectiveness acceptability curve for ticagrelor plus aspirin versus aspirin. QALY, quality-adjusted life-year; WTP, willingness to pay.

ticagrelor plus aspirin or aspirin, that is, key drivers for the cost offset associated with ticagrelor plus aspirin were the number of patients experiencing subsequent stroke and the degree of disability (figure 3). Ticagrelor plus aspirin was dominant in the majority of scenario analyses tested (online supplemental table 7).[18 19 26 28] Ticagrelor plus aspirin remained dominant over 1-year and 10-year time frames, at variable discount rates, and from a payer perspective.

DISCUSSION

Effective interventions and policies are required to mitigate the costs associated with stroke, while also maximising the health outcomes and quality of life for stroke survivors.[4 29] Improving stroke care at all stages of the pathway would not only improve health, but also reduce the overall economic burden of stroke.[4]

The focus of our analysis was to examine the cost-effectiveness of ticagrelor plus aspirin in the prevention of subsequent AIS based on data from THALES. Effective prevention in this setting could have a positive impact on quality of life and reduce costs over a long term. Recent analyses have shown that patients with AIS/TIA and a subsequent stroke were more often disabled at 3 months and associated with substantially higher healthcare costs compared with those without a subsequent stroke.[30] Costs associated with hospital readmissions within the 12 months following a stroke can be extremely high. One retrospective claims analysis showed that mean all-cause costs for Medicare patients (N=31 037) were US$44 929 per patient in the 12 months following a stroke, with 45%–50% of these costs occurring within the first month; this indirectly supports the inclusion of the 1-month decision tree in stroke models.[31] Most of these initial costs are related to hospitalisations (66.5%). Twenty-eight

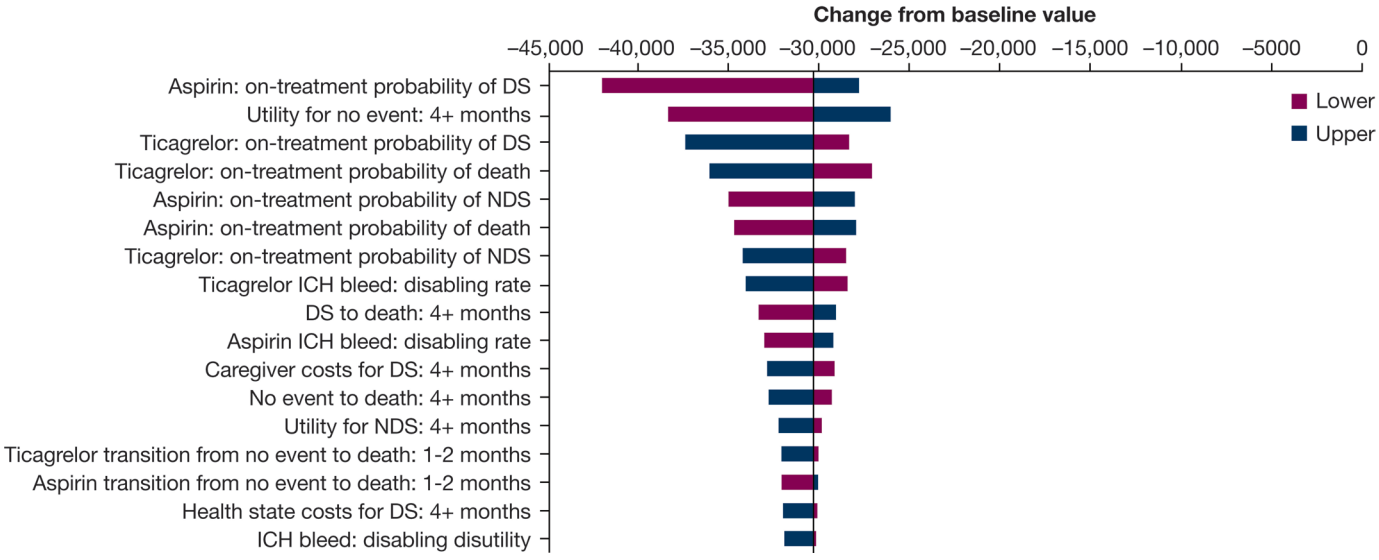

Figure 3 Tornado plots of one-way deterministic sensitivity analyses for ticagrelor plus aspirin versus aspirin. DS, disabling stroke; ICH, intracranial haemorrhage; NDS, non-disabling stroke.

per cent of patients (n=8640/31 037) were readmitted within 1 month due to AIS-related causes, and the average hospital stay was 10.8 days.[31]

In THALES, ticagrelor plus aspirin significantly reduced the composite risk of stroke or death, but the combination increased the risk of major bleeding compared with aspirin in patients following a mild-to-moderate AIS or TIA.[10] The cost-effectiveness model showed that ticagrelor plus aspirin was likely to improve outcomes and reduce healthcare costs versus aspirin in patients with mild-to-moderate AIS or high-risk TIA. These findings were consistent with a cost-effectiveness analysis of ticagrelor plus aspirin in AIS/TIA in a Chinese setting, which used a similar model.[32] Ticagrelor plus aspirin was associated with higher drug acquisition costs and bleeding event-related costs versus aspirin in our model. These costs were more than offset by the reduction in subsequent stroke, making ticagrelor plus aspirin a cost-effective option. Cost savings were observed after 1 month of treatment and persisted over a lifetime horizon. Cost-effectiveness of ticagrelor plus aspirin remained robust across most scenarios tested, including from a payer perspective. This is particularly important for healthcare policy-makers involved in reimbursement decisions. Although the analysis used inputs from the Swedish health system, results are likely applicable in other developed countries given the robustness of the findings.

Efficacy and safety of DAPT for subsequent stroke prevention in patients with moderate-risk AIS (NIHSS 4–5) or those with ipsilateral stenosis ≥30% are lacking, with limited data from THALES.[11] These patients are associated with high absolute risk of subsequent stroke. The model demonstrated large 1 month and lifetime cost savings in these patients as well with ticagrelor plus aspirin.

Limitations

The cost-effectiveness model was found to be robust across most of the sensitivity and scenario analyses tested and was based on a large cohort of approximately 25 000 patients from THALES and SOCRATES. However, there were some assumptions used. It should be noted that total strokes were split into NDS and DS as per the distribution observed in THALES; this proportion might vary in the real world and can change over time. The model assumes that the stroke risk after 2 months was similar between groups (there was no adjustment for sex, age or other baseline covariates that could impact long-term stroke risk). Patients who have more than one NDS or DS can incur high costs, but the same costs were assumed after each subsequent stroke. Mortality rates in the 'no subsequent stroke' group could be high, as this group included patients with all mRS scores (0–5) whereas patients in the NDS group only had mRS scores of 0–2. The model did not adjust for the long-term natural history of stroke; however, 30-year survival curves were estimated using the model outcomes plotted against observational data to visually assess plausibility between datasets (see online supplemental figure 1).

Most of these limitations could be alleviated by further evidence generation, especially regarding long-term stroke risk, and long-term difference between patients with more than one NDS or DS. Despite these limitations, the results of the model are very robust, as tested through sensitivity analyses.

Conclusions

Despite higher medication cost and increased bleeding, treatment with ticagrelor plus aspirin over 1 month enabled cost savings of €95 per patient because of fewer subsequent strokes, particularly strokes that resulted in disability. Lifetime extrapolation of 1-month treatment

with ticagrelor plus aspirin resulted in a QALY gain of 0.04 and cost savings of €1358 per patient versus aspirin, which was also driven by reductions in DSs. Ticagrelor plus aspirin is the only DAPT therapy that has demonstrated a risk reduction in patients with NIHSS 4–5 and in patients with ipsilateral stenosis. The greater absolute risk reduction with ticagrelor plus aspirin compared with aspirin led to a greater 1 month and lifetime cost savings. These data show that for patients presenting with mild-to-moderate AIS or high-risk TIA, treatment with ticagrelor plus aspirin is likely to improve outcomes and reduce costs compared with aspirin. This cost benefit was observed as early as 1 month and remained over a lifetime from a societal perspective. The model also showed lower caregiver costs over a lifetime. These analyses can assist with considerations for policy development and resource management. It would also be helpful to have cost analyses versus other comparators, different treatment strategies, and in wider populations, according to age, ethnicity, comorbidities and with more comprehensive societal costs and impact.

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