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ORIGINAL ARTICLE
Coronary artery disease

Cost–effectiveness of ticagrelor in patients with type 2 diabetes and coronary artery disease: a European economic evaluation of the THEMIS trial

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Aims

To conduct a health economic evaluation of ticagrelor in patients with type 2 diabetes and coronary artery disease (CAD) from a multinational payer perspective. Cost–effectiveness and cost–utility of ticagrelor were evaluated in the overall effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) trial population and in the predefined patient group with prior percutaneous coronary intervention.

Methods and results

A Markov model was developed to extrapolate patient outcomes over a lifetime horizon. The primary outcome was incremental cost–effectiveness ratios (ICERs), which were compared with conventional willingness-to-pay thresholds [€47 000/quality-adjusted life-year (QALY) in Sweden and €30 000/QALY in other countries].

Treatment with ticagrelor resulted in QALY gains of up to 0.045 in the overall population and 0.099 in patients with percutaneous coronary intervention (PCI). Increased costs and benefits translated to ICERs ranged between €27 894 and €42 252/QALY across Sweden, Germany, Italy, and Spain in the overall population. In patients with prior PCI, estimated ICERs improved to €18 449, €20 632, €20 233, and €13 228/QALY in Sweden, Germany, Italy, and Spain, respectively, driven by higher event rates and treatment benefit.

Conclusion

Based on THEMIS results, ticagrelor plus aspirin compared with aspirin alone may be cost–effective in some European countries in patients with T2DM and CAD and no prior myocardial infarction (MI) or stroke. Additionally, ticagrelor is likely to be cost–effective across European countries in patients with a history of PCI.

Keywords

Coronary artery disease • Cost–effectiveness • Percutaneous coronary intervention • Ticagrelor • Type 2 diabetes

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Introduction

Type 2 diabetes mellitus (T2DM) had an estimated global prevalence of ~500 million in 2019.[1] T2DM is associated with an increased risk of vascular disease, with around one third of patients diagnosed with cardiovascular disease (CVD) and a two- to four-fold increased risk of developing events such as cardiovascular (CV) death, myocardial infarction (MI), stroke, and amputation.[2–4] Patients with coronary artery disease (CAD) and T2DM represent a group at particularly high risk of atherothrombotic events.[5–7] Even in patients without a prior ischemic event, the combination of CAD and T2DM substantially increases the risk of suffering CV events,[8] with some estimates placing the risk of patients with T2DM and CAD but without prior MI in the range of patients without T2DM and with prior MI.[9] Furthermore, classic CV risk factors such as hypertension and elevated cholesterol are common and often not at goal in patients with atherothrombosis, further increasing the risk of CV events in this population.[10]

Current standard antithrombotic preventive therapy in patients with established CAD and T2DM is low-dose aspirin. Ticagrelor is currently indicated to reduce the rate of CV death, MI, and stroke in patients with acute coronary syndrome or a history of MI by the North American and European regulatory agencies,[11,12] and in patients with CAD and T2DM who have a history of percutaneous coronary intervention (PCI) by Health Canada.[13] The clinical benefits of adding ticagrelor to background preventive therapy with aspirin were investigated in patients with CAD and T2DM but without prior MI or stroke in the effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS; NCT01991795).[14–20] This multinational, randomized, double-blind, placebo-controlled trial evaluated the effect of 90 mg ticagrelor (lowered to 60 mg partway through the trial in line with product labelling) twice daily on the incidence of CV death, MI, or stroke in 19 220 patients with T2DM.[14,21] In THEMIS, adding ticagrelor to aspirin reduced the number of events of the composite endpoint of CV death, MI, and stroke, although with an increase in major bleeding compared with aspirin alone.[14–20] Net clinical benefit was assessed using a prespecified irreversible harm composite endpoint of all-cause death, MI, stroke, fatal bleed, or intracranial haemorrhage. While there was no net clinical benefit in patients without a history of PCI, net clinical benefit was favourable in patients with a history of PCI[14–20] with a 15% relative reduction (*P*-value for interaction = 0.012).

Given these findings, it is important to determine the long-term cost–effectiveness of ticagrelor in these populations. As such, the objective of this study is to conduct a health economic evaluation of ticagrelor added to standard therapy, including aspirin, vs. standard therapy alone from a multinational payer perspective. The analysis was conducted in the overall trial population, in patients with prior PCI, and, given that 'modern' PCI typically involves placement of a stent, in patients with prior PCI and stenting. Given the heterogeneity of costs and willingness-to-pay thresholds in Europe, we conducted the analysis in four major European countries.

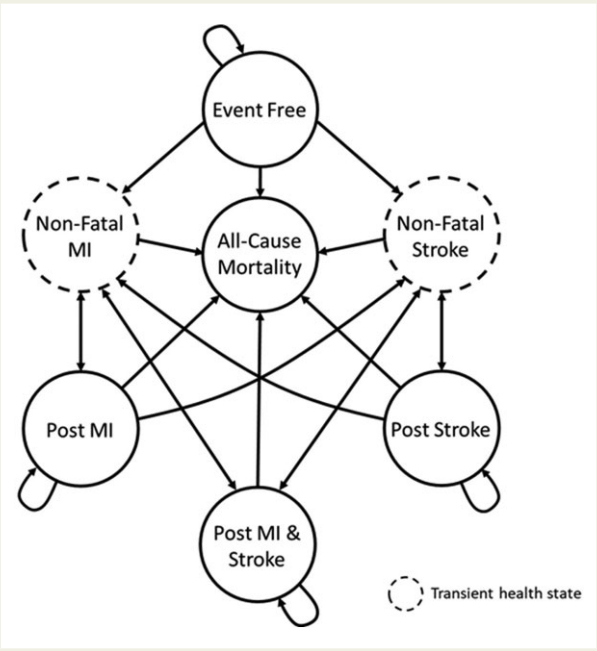

Figure 1 Cost–effectiveness model schematic.

Methods

Decision problem and model

A *de novo* Markov state-transition model was developed to model the health economic outcomes associated with the use of ticagrelor for the prevention of CV outcomes in CAD patients with T2DM. The health states consisted of event-free (patients not experiencing a MI or stroke event), non-fatal MI event, non-fatal stroke event, and all-cause mortality in addition to health states capturing the long-term impacts of the incidence of MI and/or stroke. In addition to efficacy outcomes, safety outcomes, including Thrombolysis In Myocardial Infarction (TIMI) Major bleeding, TIMI Minor bleeding, or bleeding requiring medical attention and dyspnoea, were also included in the model, and assumed to have a transient impact on cost and quality of life.[22] In addition, the incidence of major amputation was also modelled. The model employed a lifetime perspective to accommodate the chronic nature of CAD, with a six-monthly cycle length and a half-cycle correction. The primary model outcome was the incremental cost–effectiveness ratio (ICER), expressed as the cost per quality-adjusted life-year (QALY) gained. Analysis was conducted from German, Italian, Spanish and Swedish healthcare payer perspectives, chosen as large European countries that frequently require cost–effectiveness evaluations for reimbursement. Explicit willingness-to-pay (WTP) thresholds are not established in Germany, Italy, Spain, or Sweden.[23] The ICERs for each setting were compared with WTP thresholds commonly used in published literature [an assumption of €30 000/QALY for Germany, Italy, and Spain[24] and €47 000/QALY (500 000 kr/QALY) for Sweden].[25] For Sweden, an exchange rate of €1 = 10.57 kr was used. Differences in WTP thresholds between countries are a result of differences in costs associated with treatment and event management, and different economic valuations of

Table 1 Baseline profiles for the overall population and the history of PCI, and the history of PCI with stent subgroups data are presented as mean ± standard deviation or *n* (%)

Clinical characteristics	Full THEMIS population (*N* = 19 220)	History of PCI subgroup (*N* = 11 154)	History of PCI with stent subgroup (*N* = 10 295)
Baseline demographics			
Age (years)	66.31 ± 7.76	66.36 ± 7.76	66.3 ± 7.77
Aged 65 ≤ 75	8247 (42.9%)	4799 (43.0%)	4414 (42.9%)
Aged ≥ 75	3039 (15.8%)	1762 (15.8%)	1616 (15.7%)
Male	13 189 (68.6%)	7718 (69.2%)	7147 (69.4%)
BMI > 30 kg/m^2	8206 (42.7%)	4587 (41.1%)	4203 (40.8%)
Current smoker	2094 (10.9%)	1334 (12.0%)	1237 (12.0%)
Central and South America	2178 (11.3%)	1166 (10.5%)	1061 (10.3%)
Europe and South Africa	9759 (50.8%)	5427 (48.7%)	5007 (48.6%)
North America	2995 (15.6%)	1667 (15.0%)	1491 (14.5%)
Asia and Australia	4288 (22.3%)	2894 (26.0%)	2736 (26.6%)
T2DM ≤ 10 years	9702 (50.5%)	5595 (50.2%)	5176 (50.3%)
HbA1c ≤ 7%	9108 (47.4%)	5315 (47.7%)	4915 (47.7%)
eGFR < 60 mL/min/1.73 m^2	4549 (23.7%)	2589 (23.2%)	2363 (23.0%)
T2DM complications	4910 (25.5%)	2734 (24.5%)	2493 (24.2%)
Prior medical history			
CABG	5537 (28.8%)	1346 (12.1%)	1106 (10.7%)
Proportion with coronary arterial revascularization	15 345 (79.8%)	11 154 (100.0%)	10 295 (100.0%)
Multivessel CAD	11 935 (62.1%)	6310 (56.6%)	5808 (56.4%)
Polyvascular disease	2579 (13.4%)	1339 (12.0%)	1201 (11.7%)
PAD	1687 (8.8%)	905 (8.1%)	810 (7.9%)
PCI (any)	11 154 (58.0%)	11 154 (100.0%)	10 295 (100.0%)
PCI with stent	10 295 (53.6%)	10 295 (92.3%)	10 295 (100.0%)
Angina	10 801 (56.2%)	6606 (59.2%)	6087 (59.1%)
Insulin use	5508 (28.7%)	3036 (27.2%)	2800 (27.2%)
PPI use	4901 (25.5%)	2986 (26.8%)	2779 (27.0%)
Statin use	17 266 (89.8%)	10 107 (90.6%)	9341 (90.7%)

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary arterial disease; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PPI, proton-pump inhibitor; T2DM, type 2 diabetes mellitus.

health benefits. Future costs and benefits were discounted at a rate of 3.0% per annum.[26] An overview of the model structure is presented in *Figure 1*.

Analysis

The base case analysis reflected the enrolled patient population of THEMIS. In addition, the analysis was repeated in prespecified subgroups of patients with a history of PCI, and patients with a history of PCI and stent, representing >90% of the patients enrolled in THEMIS with a history of PCI. *Table 1* shows baseline profiles for the THEMIS trial patient population as well as patients with a history of PCI and those who were stented. One-way deterministic sensitivity analysis was used to explore the impact of varying input parameters over specified ranges on model outcomes. Probabilistic sensitivity analysis characterized overall parameter uncertainty using Monte Carlo simulation, with 1000 iterations, on modelled outcomes.

Mortality and cardiovascular events

The incidence of MI, stroke and mortality are described by covariate-adjusted survival equations derived from the analysis of individual patient level data from the THEMIS trial. This allows the model to capture changing hazards over time due to changes in risk factors such as age or the impact of different patient characteristics on modelled outcomes. In order to estimate the probability of an event occurring in each model cycle, the relative decrease in survival was estimated as a function of the probability of survival in the previous cycle. The benefits of ticagrelor in terms of prevention of CV events and mortality are captured through the application of hazard ratios to a survival equation describing the control arm of the trial; this approach was taken to ensure plausible differences in outcomes when extrapolating beyond the end of trial-follow up. Equation covariates for all-cause mortality and non-fatal MI and stroke are available in the Supplemental Material. Hazard ratios for each endpoint and for each of the trial subgroups are presented in *Table 2*. The impact of CV events on the incidence of mortality is also captured through the application of hazard ratios, where patients having

Table 2 Hazard ratios associated with ticagrelor treatment

Event	Hazard ratio	
	Mean	SE
Full THEMIS population		
Non-fatal MI	0.83	0.0858
Non-fatal stroke	0.81	0.1082
All-cause mortality	0.99	0.0477
Increased risk of mortality in cycle of CV event	1.18	–
Increased risk of mortality in cycles following CV event	2.41	–
THEMIS-PCI population		
Non-fatal MI	0.78	0.106
Non-fatal stroke	0.75	0.1433
All-cause mortality	0.91	0.0649
Increased risk of mortality in cycle of CV event	1.24	–
Increased risk of mortality in cycles following CV event	2.25	–
THEMIS-PCI subpopulation with stent		
Non-fatal MI	0.74	0.1096
Non-fatal stroke	0.75	0.1475
All-cause mortality	0.88	0.0676
Increased risk of mortality in cycle of CV event	1.31	–
Increased risk of mortality in cycles following CV event	2.15	–

CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention; SE, standard error.

experienced a non-fatal MI or stroke in the preceding 6 months (one model cycle) are at an increased risk of mortality; additionally, patients with a history of CV events are also at an increased risk of mortality.

Health-related quality of life

Each of the modelled health states is assigned a utility weight, and the proportion of patients residing within each health state informs the accrual of QALYs over time. Patients in the event-free health state are subject to the utility value specified for people with CAD and T2DM without other complications, which is derived from a mixed-effects regression model fitted to individual patient data from THEMIS and adjusted for population baseline characteristics. Patients in each of the remaining health states are subject to a decrement in utility, relative to the utility associated with CAD and T2DM without complications. Mean utility values in THEMIS were consistent between treatment groups and over time. Using Swedish tariffs, for example, which resulted in the highest utility indices, mean utility values of 0.900 and 0.896 for ticagrelor and placebo, respectively, after 3 years, vs. 0.901 and 0.902 at baseline, were determined. Similar results were seen for Italy, with the lowest utility indices among the four countries, with ticagrelor and placebo means of 0.842 and 0.837 after 3 years and 0.845 and 0.847 at baseline. As such, utility estimates were derived from a pooled analysis of individual patient data from the THEMIS clinical trial. Linear mixed-effects regression models were fitted to predict patient reported utility values derived from EQ-5D-5 L questionnaires, which were collected at randomization and at six monthly intervals throughout the trial. In total, 140 461 EQ-5D-5 L questionnaires were completed, with missing questionnaires assumed to be missing at random. At baseline, 19 219 (99.99% of study participants) EQ-5D-5 L questionnaires were completed, decreasing to 9787 (50.92% of randomized study participants, or 82.19% of the patients with trial follow-up at 3 years) questionnaires at 3 years from baseline.

EQ-5D-5 L responses were converted to utility index scores using the most recently identified mapping algorithms for each of the countries studied. Values for Germany[27] and Spain[28] were derived from published hybrid models consisting of composite time-trade off and discrete choice experiment methods mapped directly to EQ-5D-5 L response data. Values for Sweden[29] were derived from a similar direct mapping of EQ-5D-5 L response data, but using the time trade-off method. For Italy, no such report of direct mapping of EQ-5D-5 L responses to utility weights was identified. In this case, the EQ-5D-5 L data were first mapped to EQ-5D-3 L applying the mapping function developed by van Hout,[30] in line with NICE technology assessment guidelines, and assuming that reported domain scores within individual questionnaires were uncorrelated. The converted Italian EQ-5D-3 L individual response data were then converted to utility weights using the most recent Italian model.[31] Utility estimates were adjusted for patient characteristics, study follow-up, the incidence of MI, stroke, TIMI bleeding events, and adverse events. Model health state utility values are presented in *Table 3*.

Resource use

All costs are reported in euros (€) and refer to the year 2019. One-off event costs are applied in the cycle of incidence for non-fatal MI, non-fatal stroke, and CV mortality events, in addition to any costs associated with treating treatment-related adverse events in order to capture the associated increase in healthcare resource utilization. Maintenance costs are defined as annual costs and are applied in all subsequent years

Table 3 Health-state utility inputs derived from analysis of EQ-5D-5 L responses mapped to EQ-5D-3 L levels

Country	Sweden Mean (SE)	Germany Mean (SE)	Italy Mean (SE)	Spain Mean (SE)
Utility				
CAD and T2DM, no complications	0.8984 (0.0006)	0.8886 (0.0009)	0.8406 (0.0011)	0.8463 (0.0010)
Utility decrement				
MI event	–0.0272 (0.0032)	–0.0310 (0.0052)	–0.0419 (0.0055)	–0.0346 (0.0053)
Stroke event	–0.0738 (0.0041)	–0.1023 (0.0066)	–0.1393 (0.0071)	–0.1080 (0.0067)
Post MI	–0.0155 (0.0025)	–0.0201 (0.0040)	–0.0269 (0.0043)	–0.0226 (0.0041)
Post stroke	–0.050 (0.0034)	–0.0718 (0.0054)	–0.0996 (0.0058)	–0.0815 (0.0056)
Post stroke & MI	–0.0655 (0.0042)	–0.0919 (0.0068)	–0.1265 (0.0073)	–0.1042 (0.0069)
Amputation[b]	–0.1750 (–0.0175)[a]	–0.1750 (–0.0175)[a]	–0.1750 (–0.0175)[a]	–0.1750 (–0.0175)[a]
TIMI minor bleed/bleeding requiring medical attention	–0.0069 (0.0016)	–0.0093 (0.0027)	–0.0120 (0.0028)	–0.0094 (0.0027)
TIMI major bleed	–0.0325 (0.0038)	–0.0418 (0.0061)	–0.0621 (0.0065)	–0.0526 (0.0062)
Mild/moderate dyspnoea	–0.0060 (0.0012)	–0.0067 (0.0019)	–0.0102 (0.0021)	-0.0087 (0.0020)
Severe dyspnoea	–0.0150 (0.0053)	–0.0316 (0.0086)	–0.0265 (0.0092)	–0.0317 (0.0088)

CAD, coronary artery disease; MI, myocardial infarction; SE, standard error; TIMI, thrombolysis in myocardial infarction; T2DM, type 2 diabetes mellitus.
[a] Assumed 10% of mean value.
[b] Amputation was not monitored in trial as an independent event; value taken from literature.[36]

for patients with a history of MI, stroke, or amputation. TIMI major bleeding events are defined to include intracranial bleeding, overt signs of haemorrhage associated with a drop in haemoglobin of ≥ 5 g/dL, or fatal bleeding events, and TIMI minor bleeding events are defined as overt signs of haemorrhage associated with a drop in haemoglobin of 3 to < 5 g/dL.[32] As these events are serious and likely to require inpatient care, cost inputs were conservatively based on inpatient estimates of the costs associated with managing bleeding events. Less serious bleeding events requiring medical attention but not meeting the criteria for TIMI major and minor bleeds were assumed to require a single primary care visit. Similarly, although patients with mild or moderate dyspnoea may not require any additional medical attention, these events were conservatively assumed to require a single primary care visit; severe events were assumed to incur a cost associated with hospitalization.

Patients' time on treatment was informed by unadjusted survival curves describing time to premature discontinuation of ticagrelor derived from the THEMIS clinical trial, and discontinuation in the placebo arm of the trial was not considered. All patients were assumed to discontinue treatment with ticagrelor after 4 years, aligned to the follow-up of the THEMIS trial. Ticagrelor treatment costs are applied while the cohort remains on therapy, with patients who have discontinued ticagrelor incurring costs associated with standard care alone. Country-specific costs are reported in Supplementary material online, *Table S1*. Where appropriate, costs were inflated to 2019 values using relevant consumer price indices.[33–35] Costs reported in Swedish Krona (SEK) were converted to euros using an exchange rate of 10.57.

Results

In the overall THEMIS population, the ICER was below established WTP thresholds in Sweden and Spain (*Table 4*), with QALY gains of 0.045 and 0.043 per treated patient, respectively, based on a 4-year treatment period aligned to the duration of the trial, suggesting that ticagrelor may be a cost–effective treatment option for THEMIS-like patients in these countries. In Germany and Italy, the estimated ICER was above commonly used WTP thresholds, suggesting that ticagrelor may not be a cost–effective treatment option in these countries.

In patients with a history of PCI or in patients with a history of PCI and stent, the estimated ICERs were consistently below the commonly cited WTP thresholds (€47 000/QALY in Sweden and €30 000/QALY in Germany, Italy, and Spain), with differences in cost–effectiveness estimates between countries primarily driven by the acquisition cost of ticagrelor. The reduced cost per QALY in patients with a history of PCI and stent is driven by the improved treatment effect observed in THEMIS.[16]

Treatment with ticagrelor was associated with QALY gains ranging between 0.094 and 0.099 in patients with a history of PCI and between 0.120 and 0.126 in patients with a history of PCI and stent. Ticagrelor, in addition to standard therapy, appeared to be a cost–effective treatment for the prevention of MI, stroke, and death in patients with CAD, T2DM with a history of PCI (with or without stent) over a lifetime horizon (*Table 4*).

Sensitivity analysis

Deterministic, or one-way, sensitivity analysis showed that cost–effectiveness was robust to the choice of model input parameters, with no scenarios or population subgroups resulting in an ICER over established WTP thresholds in any of the modelled countries in the THEMIS-PCI and THEMIS-PCI with stent populations (Supplementary material). Higher ICERs in the analysis representing the overall THEMIS trial inclusion criteria mean that conclusions of cost–effectiveness may vary based on the choice of model input parameters in this patient population.

Changes in patient characteristics had the largest impact on cost–effectiveness results, with improved cost–effectiveness in smokers and patients with estimated glomerular filtration rate

Table 4 Cost–effectiveness result

	THEMIS			THEMIS-PCI			THEMIS-PCI with stent		
Outcome	**Ticagrelor**	**Placebo**	**Incremental**	**Ticagrelor**	**Placebo**	**Incremental**	**Ticagrelor**	**Placebo**	**Incremental**
Total LYs	11.063	11.017	0.046	12.012	11.907	0.105	11.904	11.768	0.136
Sweden (WTP €47 000/QALY)									
Total QALYs	9.892	9.848	0.045	10.744	10.645	0.099	10.647	10.521	0.126
Total costs	€27 537	€25 820	€1718	€29 201	€27 381	€1820	€29 015	€27 153	€1862
Treatment	€1914	€209	€1705	€1949	€226	€1723	€1949	€224	€1725
CV events	€4806	€5035	–€229	€4535	€4831	–€296	€4596	€4940	–€344
Adverse events	€858	€831	€28	€955	€935	€20	€943	€923	€20
T2DM management	€19 958	€19 744	€214	€21 762	€21 389	€373	€21 527	€21 066	€461
ICER		€38 428/QALY			€18 449/QALY			€14 751/QALY	
Germany (WTP €30 000/QALY)									
Total QALYs	9.771	9.727	0.045	10.614	10.516	0.098	10.518	10.392	0.126
Total costs	€40 166	€38 348	€1818	€42 499	€40 471	€2028	€42 184	€40 052	€2132
Treatment	€1901	€132	€1769	€1930	€143	€1787	€1930	€141	€1789
CV events	€5894	€6130	–€236	€5238	€5528	–€290	€5307	€5636	–€329
Adverse events	€809	€862	–€53	€918	€976	–€59	€904	€961	–€56
T2DM management	€31 562	€31 224	€338	€34 414	€33 824	€591	€34 043	€33 314	€729
ICER		€40 628/QALY			€20 632/QALY			€16 967/QALY	
Italy (WTP €30 000/QALY)									
Total QALYs	9.222	9.179	0.043	10.020	9.926	0.094	9.929	9.809	0.120
Total costs	€20 060	€18 242	€1818	€21 106	€19 204	€1902	€20 981	€19 044	€1937
Treatment	€2132	€319	€1812	€2177	€345	€1832	€2175	€341	€1834
CV events	€3685	€3838	–€154	€3385	€3579	–€193	€3430	€3651	–€221
Adverse events	€538	€526	€12	€600	€593	€7	€593	€585	€8
T2DM management	€13 705	€13 558	€147	€14 943	€14 687	€256	€14 782	€14 466	€317
ICER		€42 252/QALY			€20 233/QALY			€16 140/QALY	
Spain (WTP €30 000/QALY)									
Total QALYs	9.297	9.254	0.043	10.100	10.006	0.094	10.008	9.888	0.120
Total costs	€21 636	€20 441	€1195	€23 048	€21 804	€1243	€22 920	€21 667	€1253
Treatment	€1629	€364	€1266	€1673	€393	€1280	€1670	€388	€1282
CV events	€4409	€4649	–€239	€4350	€4669	–€319	€4410	€4787	–€378
Adverse events	€674	€665	€9	€753	€750	€3	€744	€740	€4
T2DM management	€14 923	€14 763	€160	€16 272	€15 993	€279	€16 096	€15 752	€345
ICER		€27 894/QALY			€13 228/QALY			€10 431/QALY	

CV, cardiovascular; ICER, incremental cost–effectiveness ratio; QALY, quality-adjusted life-year; T2DM, type 2 diabetes mellitus; WTP willingness-to-pay.

< 60 mL/min/1.73 m^2. The history of coronary artery bypass graft (CABG) and baseline HbA1c level were also influential to cost–effectiveness. In general, ticagrelor was more cost–effective in higher-risk patient populations, such as smokers and patients with impaired renal function, as a result of increased event incidence, leading to a greater number of avoided events than in low-risk patient populations.

Probabilistic sensitivity analysis showed that ticagrelor was cost–effective in 59% of simulations in the overall THEMIS population at a WTP threshold of €47 000/QALY in Sweden, and 32%, 30%, and 54% of simulations at a WTP threshold of €30 000/QALY in Germany, Italy, and Spain, respectively. In subgroup analysis, 92%, 78%, 78%, and 91% of simulations were cost–effective in the THEMIS-PCI subgroup and 98%, 91%, 91%, and 97% of simulations were cost–effective in the THEMIS-PCI with stent subgroup, for analysis in Sweden, Germany, Italy, and Spain, respectively (*Figure 2*).

Discussion

This analysis demonstrates that ticagrelor may be a cost-effective treatment option for the prevention of CV events and death when used in addition to standard care in patients with stable CAD and T2DM in Sweden and Spain and is likely to be cost–effective in patients with prior PCI (with or without stent) across the four countries studied (Sweden, Germany, Italy, and Spain). Results were

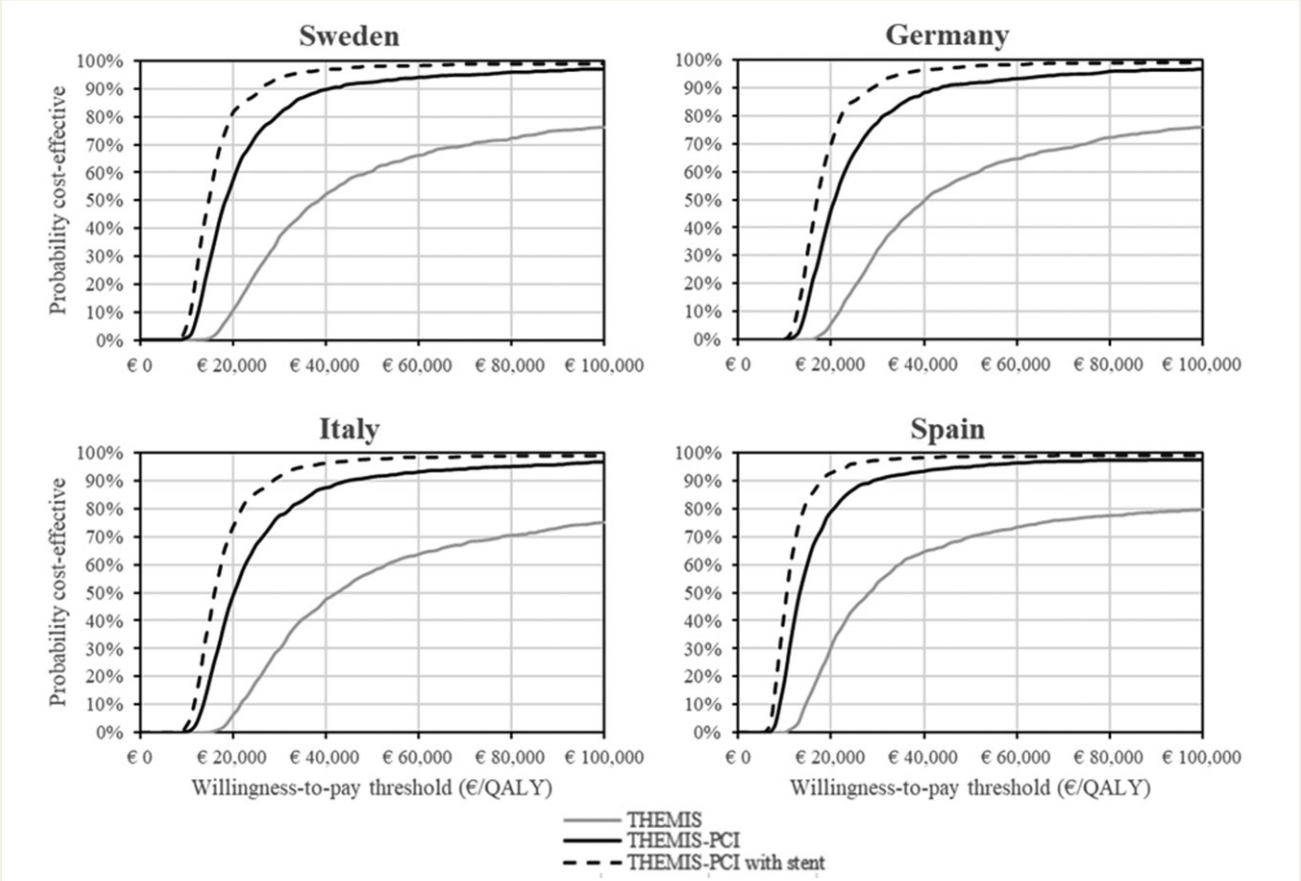

Figure 2 Cost–effectiveness acceptability curve.

principally driven by improved life expectancy as a result of lower mortality within trial follow-up and secondary reductions in mortality as a result of reduced CV event incidence, with larger benefits being observed in patients with prior PCI, with the magnitude of the health benefit comparing favourably to previously published estimates for antithrombotic treatments.[36] This translated into significant QALY gains for patients treated with ticagrelor. In the patient population with prior PCI, ticagrelor reduced the incidence of CV events, with fewer non-fatal MI and stroke events, fewer CV deaths, but increased TIMI major bleeds. The avoidance of CV events was associated with modest QALY gains but contributed to cost savings, which partially offset the additional cost of treatment with ticagrelor. In order to assess the cost–effectiveness of treatment with ticagrelor over a lifetime horizon, there is a requirement to extrapolate outcomes beyond the observations of the THEMIS clinical trial, and this inherently introduces uncertainty. Deterministic sensitivity analysis, however, showed that the cost–effectiveness of ticagrelor was robust to the choice of model input parameters and influential patient characteristics.

The analysis may also underestimate incremental costs for patients treated with ticagrelor plus standard therapy, as consistent with health technology assessment guidelines, future costs unrelated to T2DM or CAD are not captured; for example, increased life expectancy will lead to more time at risk of hospitalization for other non-CV causes. Conversely, this analysis is likely to overestimate the costs associated with bleeding events, as model cost inputs conservatively assume that all TIMI major and minor bleeding events will require inpatient care, which is unlikely to be the case in real-world clinical practice. An additional consideration is that while CV events use risk equations that adjust for age, events such as TIMI major/minor bleeds, dyspnoea, and amputation are modelled as non-time-dependent incident events, where individuals are at equivalent risk irrespective of age. This could be viewed as a limitation if events were more likely to be fatal/high-risk in an elderly individual.

The probabilistic analysis also showed that when accounting for the uncertainty inherent in health economic modelling, ticagrelor is likely to be cost-effective in patients with a history of PCI, with or without stent. As a result of the size of the patient population with CAD and T2DM in Europe and the complex nature of managing the disease and its sequelae, these comorbidities impose a significant burden on patients and healthcare payers. Any reduction in the burden of disease through avoided CV events will have significant consequences on society in terms of reduced indirect costs, which were not captured within this study. Furthermore, this study did not explore the potential impact of avoided CV events on service delivery and the potential for the reduction of adverse clinical events to ameliorate pressure on strained healthcare services. The objective of this study was to evaluate ticagrelor across major European

countries, and as such, the results of this study do not necessarily generalize to the rest of the world, particularly those countries that have different healthcare systems or reimbursement frameworks. However, the consistency of the findings across the included countries suggests that conclusions of cost–effectiveness may be applicable to other countries with similar healthcare systems.

Of note, this cost–effectiveness analysis was not designed to address the clinical value of ticagrelor in patients with type 2 diabetes and CAD, which has been described in detail in the overall trial population[15] and in the subgroup with a history of prior PCI.[16] In the overall population,[15] the absolute risk increase in TIMI major bleeding was numerically higher than the absolute benefit in ischemic outcomes. The incidence of a prespecified composite outcome of irreversible harm (death from any cause, myocardial infarction, stroke, fatal bleeding, or intracranial haemorrhage) was similar in the ticagrelor group and the placebo group. In patients with prior PCI,[16] the benefit to risk balance was more favourable, and there was a significant interaction between the history of prior PCI and the balance of risk and benefit measured by the net irreversible harm outcome. It is noteworthy that, while ticagrelor has been approved in patients with stable CAD (with or without diabetes) in the USA (and the Food and Drug Administration detailed their analysis for doing so[37]) and in patients with T2DM and prior PCI in Canada, it is not approved in Europe, and the present analysis should not be viewed as encouraging off-label use in Europe. The European Medicines Agency concluded that '*the benefit-risk balance in the new indication proposed remains currently negative for the population with CAD and T2DM without any history of MI or stroke*'.[38] Yet, it is important that the present cost–effectiveness analyses pertaining to European countries be available in the public domain.

In conclusion, this analysis suggests that the cost–effectiveness of ticagrelor in addition to standard care in patients with stable chronic CAD and T2DM varies according to country and WTP threshold. However, in T2DM patients with prior PCI, ticagrelor is likely to represent a cost–effective option for the prevention of CV events across Swedish, German, Italian, and Spanish healthcare systems.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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