HOSPITALIZATION-DRIVEN ECONOMIC EFFECTS OF NEW TREATMENTS FOR TRANSTHYRETIN AMYLOID CARDIOMYOPATHY IN SLOVAKIA

Ekonomické vplyvy novej liečby transtyretínovej amyloidovej kardiomyopatie vyplývajúce z hospitalizácií na Slovensku

Robert BABELA[1,3], Terezia HLAVATA[2], Peter POLAK[3]

[1]Slovak Medical University, Bratislava, rector Dr.h.c. prof. MUDr. P. Šimko, CSc.
[2]National Institute of Cardiovascular Disease, Department for Congenital Heart Defects in Adults, head of department prof. MUDr. I. Šimková, CSc.
[3]Project HealthCare (PHC), Healthcare Think-Tank, Bratislava

Abstract
Introduction: Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive disease characterized by recurrent cardiovascular-related hospitalizations, with hospitalization costs accounting for 87 – 93% of direct medical expenses. Two randomized trials demonstrated that transthyretin stabilizers (tafamidis in ATTR-ACT; acoramidis in ATTRibute-CM) reduce cardiovascular morbidity and mortality. This study translates these clinical benefits into hospitalization-related economic consequences for the Slovak healthcare system.
Methods: A cohort-based Markov model with monthly cycles was developed from the Slovak public-payer perspective, focusing on cardiovascular-related hospitalization costs. The base-case analysis used a 12-month time horizon with an extended 6.5-year scenario. Clinical inputs were derived from phase III clinical trials: acoramidis reduced annualized cardiovascular-related hospitalization rates to 0.22 versus 0.45 events/patient-year for placebo; tafamidis to 0.48 versus 0.70 events/patient-year. Slovak-specific hospitalization cost was €3,462.94 per admission. Health utilities were 0.80 (alive without hospitalization) and 0.56 (hospitalized). The model calculated total costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs).
Results: In base case, acoramidis saved €2,550 per patient and tafamidis saved €1,905 per patient in hospitalization costs. In the 6.5-year analysis, acoramidis generated total hospitalization costs of €9,719 versus €21,916 for standard therapy (€12,196 saved), while producing 4.82 versus 4.04 QALYs (0.78 QALYs gained), yielding a dominant ICER of –€15,720.22/QALY. Tafamidis generated costs of €16,371 versus €15,933 for standard therapy (€437 incremental), producing 3.45 versus 2.48 QALYs (0.97 QALYs gained), with an ICER of €450.23/per 1 QALY. Both treatments substantially reduced hospitalization probabilities compared to standard care.
Conclusions: Reductions in cardiovascular-related hospitalizations achieved with transthyretin stabilizers translate into meaningful economic savings within the Slovak healthcare system. Acoramidis demonstrated a dominant cost-effectiveness profile (saving costs while improving outcomes), while tafamidis showed highly favorable cost-effectiveness. These

Abstrakt
Úvod: Transtyretínová amyloidová kardiomyopatia (ATTR-CM) je progresívne ochorenie charakterizované opakovanými hospitalizáciami súvisiacimi s kardiovaskulárnym ochorením, pričom hospitalizačné náklady predstavujú 87 – 93 % priamych zdravotníckych výdavkov. Dve randomizované štúdie preukázali, že stabilizátory transtyretínu (tafamidis v ATTR-ACT; akoramidis v ATTRibute-CM) znižujú kardiovaskulárnu morbiditu a mortalitu. Táto štúdia transformuje tieto klinické benefity na ekonomické dôsledky súvisiace s hospitalizáciami pre slovenský zdravotnícky systém.
Metódy: Bol vytvorený kohortový Markovov model s mesačnými cyklami z perspektívy slovenského verejného platcu, zameraný na náklady hospitalizácií súvisiacich s kardiovaskulárnym ochorením (KV hospitalizácií). Základná analýza použila 12-mesačný časový horizont s rozšíreným 6,5-ročným scenárom. Klinické vstupy boli odvodené z klinických štúdií fázy III: akoramidis znížil ročnú mieru KV hospitalizácií na 0,22 verzus 0,45 udalostí/pacient-rok pre placebo; tafamidis na 0,48 verzus 0,70 udalostí/pacient-rok. Slovenské špecifické náklady na hospitalizáciu boli 3462,94 € na prijatie. Zdravotné utility boli 0,80 (nažive bez hospitalizácie) a 0,56 (hospitalizovaný). Model vypočítal celkové náklady, roky života adjustované na kvalitu (QALY) a inkrementálne pomery nákladovej efektívnosti (ICER).
Výsledky: V rámci base case, akoramidis ušetril 2550 € na pacienta a tafamidis ušetril 1905 € na pacienta na hospitalizačných nákladoch. V 6,5-ročnej analýze akoramidis generoval celkové hospitalizačné náklady 9719 € verzus 21 916 € pre štandardnú terapiu (12 196 € úspor), pričom produkoval 4,82 verzus 4,04 QALY (0,78 QALY zisk), čo viedlo k dominantnému ICER – 15 720,22 €/QALY. Tafamidis generoval náklady 16 371 € verzus 15 933 € pre štandardnú terapiu (437 € navyše), produkoval 3,45 verzus 2,48 QALY (0,97 QALY zisk), s ICER 450,23 €/za 1 QALY. Obe liečby výrazne znížili pravdepodobnosti hospitalizácie v porovnaní so štandardnou starostlivosťou.
Závery: Zníženie počtu KV hospitalizácií stabilizátormi transtyretínu sa premieta do významných ekonomických úspor v slovenskom zdravotníckom systéme. Akoramidis preukázal dominantný profil nákladovej efektívnosti (šetrí náklady pri zlepšení

hospitalization-driven savings partially offset treatment costs, though comprehensive economic evaluation requires incorporating drug acquisition costs. Establishing a Slovak ATTR-CM registry is essential for validating these projections and optimizing disease management strategies *(Tab. 7, Ref. 19). Text in PDF www.lekarskyobzor.sk.*
KEY WORDS: transthyretin amyloid cardiomyopathy, hospitalization costs, cost-effectiveness, acoramidis, tafamidis, Markov model.
Lek Obz 2026, 75 (2): 50-57

výsledkov), kým tafamidis ukázal vysokopriaznivú nákladovú efektívnosť. Tieto úspory nákladov na hospitalizácie čiastočne kompenzujú náklady na liečbu, hoci komplexné ekonomické hodnotenie vyžaduje zahrnutie akvizičných nákladov liekov. Vytvorenie slovenského ATTR-CM registra je nevyhnutné pre validáciu týchto projekcií a optimalizáciu stratégií manažmentu ochorenia *(tab. 7, lit. 19). Text v PDF www.lekarskyobzor.sk.*
KĽÚČOVÉ SLOVÁ: transtyretínová amyloidová kardiomyopatia, hospitalizačné náklady, nákladová efektívnosť, akoramidis, tafamidis, Markovov model.
Lek Obz 2026, 75 (2): 50-57

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, life-limiting cardiomyopathy characterized by heart-failure symptoms, recurrent cardiovascular (CV) hospitalizations, and premature death. Contemporary cohort work from the UK National Amyloidosis Centre (NAC) shows stage-dependent survival from diagnosis and substantial healthcare use, underscoring the budgetary implications of admissions in this population. In the NAC staging paper, median survivals were 69.2, 46.7, and 24.1 months for NAC stages I – III, respectively; converting medians to means suggests approximately 8.3, 5.6, and 2.9 years (1). Lane and colleagues reported genotype-specific survival (median 69 months for non-V122I hereditary ATTR-CM, 57 months for wild-type, and 31 months for V122I) and documented high use of hospital services around diagnosis, again emphasizing admissions as a dominant cost driver (2). Economically, ATTR-CM imposes a substantial burden on healthcare systems, with cardiovascular-related hospitalization accounting for approximately 87 – 93% of direct costs, resulting in very high annual per-patient costs (3,4). A study from Sweden analyzed healthcare resource use and direct healthcare costs among patients with ATTR-CM across different stages of disease severity, defined by New York Heart Association (NYHA) class. The total annual healthcare costs per patient increased substantially from early-stage (NYHA II) to advanced-stage (NYHA IV), primarily driven by inpatient hospitalizations. The mean cost across all stages was approximately €21,200 per patient per year, substantially higher than the corresponding costs for other types of heart failure in Sweden. The study also highlighted a prolonged diagnostic delay averaging 3.5 years until ATTR-CM diagnosis (5). Conversely, a study from Spain compared the health and economic impact of correct diagnosis of ATTR-CM to missed diagnosis. Using a probabilistic Markov model with time horizons of 1 to 15 years, the authors demonstrated that correct diagnosis generates life years gained and reduces cardiovascular-related hospitalizations, resulting in cost savings for the Spanish National Health System. These savings increased over time, reaching approximately €2,900 per patient after 15 years (6). Two randomized controlled trials demonstrated that transthyretin stabilizers reduce morbidity and mortality in ATTR-CM. In the ATTR-ACT trial, tafamidis reduced all-cause mortality and cardiovascular-related hospitalizations over 12 months compared with placebo (7). Similarly, in the ATTRibute-CM trial, acoramidis improved a hierarchical composite endpoint and reduced the annualized frequency of cardiovascular-related hospitalization, with separation of event curves by month three (8). The present manuscript translates these clinical benefits into hospitalization-related economic outcomes for the Slovak Republic, where hospital budgets operate within the SK-DRG reimbursement framework. For cost context and reimbursement procedures, we refer to the National Institute for Value and Technologies in Health Care (NIHO) and the public Slovak HTA appraisal for acoramidis (Beyonttra, ZHL175).

Methods

Perspective, Horizon, and Scope

The present analyses adopt the Slovak public-payer and hospital perspective, focusing exclusively on the direct medical costs associated with cardiovascular and heart failure-related hospitalizations. This perspective aligns with the primary decision-making context for reimbursement evaluations within the Slovak healthcare system. The base-case analysis employs a 12-month time horizon. Additionally, a scenario analysis extends the survival time horizon to 6.5 years, representing the central estimate derived from mean survival projections based on the National Amyloidosis Centre (NAC) staging system. The extended horizon inputs are informed by established prognostic frameworks (1) and validated survival data from contemporary cohort studies (2).

Model Structure

A cohort-based state-transition (Markov) model was developed to capture the disease trajectory and associated economic burden. The model employs monthly cycles and half-cycle correction to minimize discretization bias. The model comprises four mutually exclusive health states: (1) Alive without hospitalization; (2) Hospitalized due to cardiovascular or heart failure events; (3) Alive post-discharge; and (4) Dead.

Cardiovascular and heart failure-related hospitalizations are modeled as recurrent events, with each admission incurring both direct medical costs and within-cycle health utility decrements. Transitions between states

are governed by time-dependent probabilities derived from trial data and supplemented by real-world evidence, where appropriate. Patients experiencing hospitalization events transition from the 'Alive without hospitalization' state to the 'Hospitalized' state, subsequently progressing to the 'Alive post-discharge' state upon survival through the hospitalization period. The post-discharge state captures the elevated risk profile and altered cost trajectory following hospitalization events.

This modeling framework reflects established methodological approaches in cardiovascular economic evaluations, where hospitalization events constitute the primary drivers of both economic burden and health-related quality of life decrements. The structure adheres to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Medical Decision Making (SMDM) consolidated guidance for state-transition modeling (9). The methodological foundation draws upon seminal works in decision-analytic modeling (10) and contemporary best-practice recommendations for cardiovascular disease modeling (11 – 13). These sources provide formal theoretical underpinnings for state-transition model development, parameter estimation, and the derivation of cycle-specific transition probabilities from available clinical data.

Model Assumptions and Limitations

The model incorporates several key structural assumptions that warrant explicit acknowledgment. First, the Markov assumption implies that transition probabilities depend solely on the current state and not on the pathway by which that state was reached. Second, the model assumes that all events occurring within a cycle are realized at its midpoint, necessitating a half-cycle correction. Third, competing risks of mortality are represented through state-specific transition probabilities, with cardiovascular mortality incorporated within hospitalization-related transitions and background mortality applied uniformly across all living states.

Rate-to-Probability Conversion

Clinical trial publications typically report event data as either annualized rates (events per patient-year) or fixed-horizon cumulative risks. To operationalize these parameters within the discrete-time Markov framework, conversion to cycle-specific transition probabilities is required. This conversion assumes a constant hazard rate within each interval, a standard assumption in health economic modeling when individual patient data are unavailable (Tab. 1).

We convert to per-cycle probabilities using a standard constant-hazard embedding (Tab. 1):

- From **rate** λ to **probability** over Δt years: $p = 1 - e^{-\lambda \Delta t}$
- From **risk** over horizon T (e.g., 12-month mortality P_t) to **rate**: $\lambda = -\ln(1 - Pt)/T$

Figure 1. Formulas 1 and 2.

Formula 1: From rate λ to probability over Δt years

$$p = 1 - e^{-\lambda \Delta t}$$

Formula 2: From risk over horizon T to rate

$$\lambda = -ln(1 - P_T) / T$$

where e is Euler's number (≈2.71828) and ln denotes the natural logarithm

This methodological approach aligns with established practices in state-transition modeling and is explicitly endorsed in contemporary guidance documents (11, 13). These references, among others, provide detailed worked examples illustrating both the mathematical derivation and the practical implementation of these conversions.

Clinical Input Parameters

The model incorporates treatment-specific event rates derived from pivotal randomized controlled trials. The more recent trial evaluated acoramidis versus placebo (ATTRibute-CM trial). The annualized cardiovascular hospitalization rate was 0.22 events per patient-year in the acoramidis arm, compared with a model-derived placebo rate of 0.45 events per patient-year, based on the detailed analysis published in the Journal of the American College of Cardiology. Alternative estimates suggest rates of approximately 0.50 events per patient-year when back-calculated from relative risk ratio reported in the New England Journal of Medicine publication. All-cause mortality at 30 months was 19.3% with acoramidis versus 25.7% with placebo (8). The earlier trial, published in 2018, evaluated tafamidis versus placebo (ATTR-ACT trial). The annualized cardiovascular hospitalization rate was 0.48 events per patient-year with tafamidis versus 0.70 events per patient-year with placebo. The all-cause mortality at 30 months reached 29.5% and 42.9% in the tafamidis and placebo groups, respectively (7).

Post-hospitalization conditional mortality, applicable to transitions from the hospitalized state, was estimated by synthesizing safety data from the ATTRibute-CM trial and applying methodological bracketing informed by the ATTR-ACT experience. This parameter has a secondary influence on overall model outcomes, as the primary treatment effect operates through a reduction in hospitalization frequency rather than modification of case-fatality risk (14).

Health State Utility Values

Health-related quality of life parameters were derived from contemporary ATTR-CM-specific sources. The base-case utility value for patients in the 'Alive without hospitalization' state was set at 0.80, based on EQ-5D-5L measurements from recent quality of life studies in ATTR-CM populations. During hospitalization cycles, utility was reduced to 0.56, reflecting the acute functional and symptomatic burden of cardiovascular decompensa-

tion. This magnitude of decrement is consistent with published evidence from acute heart failure populations and corresponds to utility values reported in the Nordic PROACT ATTR-CM observational study (15).

Cost Parameters (Slovak Healthcare System)

The analysis incorporates Slovakia-specific healthcare cost data to ensure relevance to the national decision-making context. Unit Cost per cardiovascular or heart-failure-related admission: €3,462.94 (base case). This estimate is anchored to the Slovak Health Technology Assessment (HTA) framework and reflects the total episode cost, including emergency department presentation, inpatient stay, diagnostic procedures, pharmacological management, and discharge planning. Comprehensive documentation supporting this costing approach is available in the public appraisal dossier of the National Institute for Value and Technologies in Health Care (NIHO) for acoramidis (Beyonttra, ZHL175; NIHO reference documentation).

Discounting

Scenario analyses applied an annual discount rate of 5% to both costs and health outcomes for projections extending beyond one year. This rate reflects the societal time preference for current versus future health benefits and aligns with international standards for health economic evaluation. The base-case 12-month analysis presents undiscounted outcomes due to the short time horizon, whereas the extended 6.5-year scenario applies discounting from the second year onward.

Table 1. Comprehensive inputs table with focus on hospitalization.

Input	Base value	Cycle	Rationale / source
P(hospitalized, year) – Standard (acoramidis trial)	0.443	year	(8)
P(hospitalized, year) – Acoramidis	0.252	year	(8)
P(death, year) – Standard (acoramidis trial)	0.112	year	(8)
P(death, year) – Acoramidis	0.082	year	(8)
P(hospitalized, year) – Standard (tafamidis trial)	0.503	year	(7)
P(hospitalized, year) – Tafamidis	0.381	year	(7)
P(death, year) – Standard (tafamidis trial)	0.201	year	(7)
P(death, year) – Tafamidis	0.131	year	(7)
P(discharge alive | hospitalized, year)	0.876	year	(7)
Utility, Alive-not-hospitalized	0.80	month	(15)
Utility, Hospitalized	0.56	month	(15)
Mean survival (scenario)	6.5	year	Within NAC-based range; used for long-term scenario.
Unit cost per CV/HF admission	€3,462.94	1 event	Slovak HTA appraisal context (NIHO, Beyonttra ZHL175)
Discounting (costs and effects)	5%	year	MoH Decree, No. 422/2011

Results

Acoramidis Treatment Arm Analysis

The model utilizes annualized transition probabilities derived directly from the ATTRibute-CM trial data, as detailed in Table 2.

Table 2. Transition probabilities for standard therapy in the acoramidis study (8).

		TO		
		Alive/NoHsptl*	Hospitalised	Dead
FROM	Alive/NoHsptl*	0.445	0.443	0.112
	Hospitalised	0.876	0.000	0.124
	Dead	0.000	0.000	1.000

* NoHsptl = no hospitalization

For patients receiving standard therapy, the annual transition probabilities were 0.445 for remaining alive without hospitalization, 0.443 for experiencing a cardiovascular hospitalization, and 0.112 for death. These probabilities sum to one, ensuring internal model consistency. The hospitalized state applies conditional annual probabilities, relevant only to those experiencing hospitalization within a given year. These were 0.876 for survival to discharge and 0.124 for in-hospital or immediate post-discharge death, corresponding to a conditional annual mortality rate of approximately 12.4%.

For patients treated with acoramidis, the corresponding annual probabilities demonstrate a substantial treatment benefit: 0.666 for remaining alive without hospitalization, 0.252 for hospitalization, and 0.082 for death, again summing to unity (Tab. 3).

Table 3. Transition probabilities for acoramidis in the acoramidis study (8).

		TO		
		Alive/NoHsptl*	Hospitalised	Dead
FROM	Alive/NoHsptl*	0.666	0.252	0.082
	Hospitalised	0.875	0.000	0.125
	Dead	0.000	0.000	1.000

* NoHsptl = no hospitalization

Derivation, Cross-Check and Validation

These transition probabilities reflect annualized conversion of trial-reported event rates, providing internal consistency and empirical validation of the modeling approach. The placebo arm exhibited an annual probability of experiencing at least one cardiovascular hospitalization of 0.44; whereas acoramidis reduced this to 0.25. Likewise, the annual probability of death declined from 0.112 in the placebo arm to 0.082 with acoramidis, precisely reproducing the matrix values above and confirming the coherence of the model's rate-to-probability derivation (14).

Tafamidis Treatment Arm Analysis

Parallel calculations were performed for the tafamidis comparison using data from the ATTR-ACT trial, applying the same rate-to-probability conversion methodology.

From the "Alive-without-hospitalization" state, patients receiving standard therapy had annual transition probabilities of 0.296 for remaining alive without hospitalization, 0.503 for hospitalization due to cardiovascular events, and 0.201 for death (Tab. 4).

Table 4. Transition probabilities for standard therapy in the tafamidis study (7).

		TO		
		Alive/NoHsptl*	Hospitalised	Dead
FROM	Alive/NoHsptl*	0.296	0.503	0.201
	Hospitalised	0.777	0.000	0.223
	Dead	0.000	0.000	1.000

* NoHsptl = no hospitalization

For tafamidis-treated patients, the corresponding annual probabilities were 0.488 for remaining alive without hospitalization, 0.381 for hospitalization, and 0.131 for death (Tab. 5).

Table 5. Transition probabilities for tafamidis in the tafamidis study (7).

		TO		
		Alive/NoHsptl*	Hospitalised	Dead
FROM	Alive/NoHsptl*	0.488	0.381	0.131
	Hospitalised	0.824	0.000	0.176
	Dead	0.000	0.000	1.000

* NoHsptl = no hospitalization

These transition probabilities maintain consistency with the annualized cardiovascular hospitalization rates (0.48 versus 0.70 in the tafamidis and placebo groups, respectively) and with the 30-month all-cause mortality risks (29.5% versus 42.9% in the tafamidis and placebo groups, respectively) reported in the ATTR-ACT trial (7).

Extended Time Horizon Cost-Effectiveness Results

Acoramidis Cost-Effectiveness Results

The extended-horizon analysis, which incorporates long-term survival projections based on National Amyloidosis Centre (NAC) staging data, reveals a markedly favorable economic profile for acoramidis when evaluated from the hospitalization cost perspective (Tab. 6).

Over the 6.5-year analytic horizon, the acoramidis strategy incurs total hospitalization costs of €9,719 per patient, compared with €21,916 for standard therapy, resulting in cost savings of €12,196. At the same time, acoramidis produces 4.82 QALYs versus 4.04 QALYs under standard care, representing an incremental gain of 0.78 QALYs.

The concurrent reduction in costs (€12,196 saved) and improvement in health outcomes (0.78 QALYs gained) positions acoramidis as a dominant strategy in health economic terms. The resulting negative incremental cost-effectiveness ratio (ICER) of - €15,720.22 per QALY gained indicates that acoramidis both saves costs and improves outcomes—a scenario representing exceptional value from a health technology assessment perspective.

Table 6. Cost-effectiveness results for acoramidis and standard therapy from the perspective of hospitalization impact.

Acoramidis	**Results**
COSTS	€ 9,719
QALYs	4.82
Standard therapy	
COSTS	€ 21,916
QALYs	4.04
ICER	
Incremental Costs	€ (12,196)
Incremental Effectiveness	0.78
ICER (per 1 QALY gained)	€ (15,720.22)

Tafamidis Cost-Effectiveness Results

The parallel extended-horizon analysis for tafamidis over 6.5-year demonstrates a distinctly different economic profile compared with the acoramidis. The tafamidis strategy generates total hospitalization costs of €16,371 per patient versus €15,933 for standard therapy, resulting in incremental costs of €437 (Tab. 7).

This marginal cost increase persists despite a reduction in hospitalization frequency, suggesting that the extent of admission reduction is insufficient to fully offset other cost dynamics over the long term. Tafamidis produces 3.45 QALYs versus 2.48 QALYs for standard therapy, corresponding to an incremental effectiveness of 0.97 QALYs.

The ICER for tafamidis compared with standard therapy is €450.23 per QALY gained, indicating that tafamidis improves outcomes at a modest incremental cost when assessed from the hospitalization perspective alone. This highly favorable ratio lies well below conventional European willingness-to-pay thresholds (typically €20,000-50,000 per QALY), underscoring the cost-effectiveness of tafamidis within this evaluative framework.

Head-to-Head Indirect Economic Comparison

The indirect mathematical economic comparison between acoramidis and tafamidis reveals hypothetical differentiation in favor of acoramidis when assessed from the hospitalization cost perspective over the 6.5-year horizon. In this mathematical scenario, acoramidis

seems to demonstrate improved clinical effectiveness, generating 4.82 QALYs versus 3.45 QALYs for tafamidis, corresponding to an incremental benefit of 1.36 QALYs. Concurrently, acoramidis incurs lower total hospitalization costs (€9,719 versus €16,371). However, in the absence of direct comparative studies involving both technologies, any such analysis remains highly hypothetical. Consequently, these findings cannot be readily translated into clinical practice and may not accurately reflect actual clinical outcomes.

Table 7. Cost-effectiveness results for tafamidis and standard therapy from the perspective of hospitalization impact.

TAFAMIDIS	**Results**
COSTS	€ 16,371
QALYs	3.45
Standard therapy	
COSTS	€ 15,933
QALYs	2.48
ICER	
Incremental Costs	€ 437
Incremental Effectiveness	0.97
ICER (per 1 QALY gained)	€ 450.23

Discussion

The translation of randomized controlled trial (RCT) outcomes into discrete-time transition probabilities within a Markov framework demonstrates that both acoramidis and tafamidis significantly reduce cardiovascular and heart-failure – related hospitalizations in patients with transthyretin amyloid cardiomyopathy (ATTR-CM). When evaluated using Slovak diagnosis-related group (SK-DRG) reimbursement rates, these reductions in hospitalization frequency translate into meaningful per-patient cost savings over the trial-concordant time horizon. The magnitude of savings correlates with the differential treatment effects observed in the pivotal trials, with acoramidis yielding approximately €2,550 saved per patient and tafamidis €1,905 per patient. The extended 6.5-year analysis further amplifies these differences, with acoramidis demonstrating a dominant cost-effectiveness profile (saving €12,196 while gaining 0.78 QALYs), and tafamidis maintaining a highly favorable ICER of €450.23 per 1 QALY gained when viewed solely from the hospitalization-cost perspective. Under the assumption that these modeled per-patient savings remain consistent across a broader population, treating 100 patients with acoramidis might yield approximately €1.2 million in cumulative hospitalization-related cost savings over the 6.5-year period compared to standard therapy, suggesting the potential for substantial economic impact of treatment selection decisions at the population level, though real-world outcomes may vary depending on patient heterogeneity and healthcare system dynamics. From a patient-centered perspective, the potential 0.78 QALY gain with acoramidis from the perspective of hospitalizations, translates to approximately 9.4 months of perfect health equivalent or a 19.3% improvement in quality-adjusted life expectancy over 6,5 years (the percentage improvement over standard therapy using standard therapy as the baseline), reflecting both reduced hospitalization burden and enhanced overall health status throughout the treatment period.

The methodological framework employed in this analysis aligns with international best practices for economic evaluations in chronic cardiovascular disease, where recurrent hospitalization events are key determinants of both economic burden and quality-of-life loss (11 – 14,16 – 19). The state-transition modeling approach, incorporating rate-to-probability conversions under constant-hazard assumptions, follows ISPOR – SMDM consolidated recommendations and has been validated across multiple cardiovascular indications (9). The convergent evidence from the ATTRibute-CM and ATTR-ACT trials, each demonstrating consistent reductions in cardiovascular hospitalization despite differences in design and population, supports the external validity of focusing on admission-driven economic consequences within the Slovak healthcare context. This hospitalization-centric analytical perspective reflects the clinical reality of ATTR-CM management, where acute decompensation episodes dominate healthcare resource utilization and substantially impair patient-centered outcomes.

The observed differences of cardiovascular related hospitalizations in absolute rate reduction between trials (0.23 events per patient-year for acoramidis versus 0.22 for tafamidis) must be interpreted in light of considerable cross-trial heterogeneity (7, 8). These studies enrolled distinct patient cohorts with variable disease severity, applied differing endpoints definitions and adjudication methods, and reported markedly different baseline event rates in control arms. Such heterogeneity precludes any definitive comparative conclusions without either head-to-head evidence or advanced indirect comparison methods using individual patient data (IPD). The economic trends identified here are directionally favorable for both treatments when viewed from the restricted hospitalization perspective, yet a comprehensive cost-effectiveness evaluation would also require inclusion of pharmaceutical acquisition costs, follow-up care, outpatient resource use, and broader societal impacts, including productivity loss and caregiver burden.

Several important limitations affect the interpretation and generalizability of these findings. First, the exclusive focus on hospitalization-related costs represents a methodological simplification that limits the scope of the analysis. The results should not be interpreted as a full cost-effectiveness assessment suitable for reimbursement decisions without incorporation of drug acquisition and broader healthcare resource costs. Second, the transferability of SK-DRG-based cost parameters warrants careful scrutiny, as tariffs and lengths of stay vary across Slovak hospitals. The base unit cost of €3,462.94 per cardiovascular admission, though consistent with national reimbursement schedules, requires

local validation and may underestimate the true cost of complex ATTR-CM admissions involving intensive or rehabilitative care. Third, the extended 6.5-year horizon, although anchored in NAC staging evidence and survival literature, remains an extrapolation without direct validation in Slovak ATTR-CM cohorts. The absence of national registry data necessitates reliance on international evidence, which may not fully capture Slovak patient characteristics, treatment patterns, or healthcare system dynamics. Fourth, the indirect comparison between acoramidis and tafamidis is subject to residual confounding and population heterogeneity. Without access to IPD, techniques such as matching-adjusted indirect comparison (MAIC) could not be applied, limiting the ability to control for between-trial differences.

Most critically, Slovakia currently lacks a dedicated ATTR-CM registry that would enable accurate mapping of patient journeys, documentation of real-world outcomes, and characterization of healthcare utilization. This data gap constrains the ability to validate model assumptions, calibrate them to local conditions, and assess external validity of trial-based projections.

The establishment of a national ATTR-CM registry therefore represents an urgent policy priority for optimizing disease management and supporting evidence-based reimbursement decisions. Such a registry should systematically collect data on hospital admissions, length of stay, readmissions, outpatient utilization, and longitudinal quality-of-life outcomes using validated instruments. Regular updates of DRG costing methodologies specific to cardiovascular admissions would improve the accuracy of economic evaluations and ensure that reimbursement rates reflect the clinical and logistical complexity of ATTR-CM management.

As Slovak-specific evidence accumulates, periodic re-estimation of hospitalization-related economic impacts will be essential to refine understanding of treatment value in the national context. The National Institute for Value and Technologies in Health Care (NIHO) provides an established institutional framework for integrating real-world evidence into HTA processes. Linking registry data with formal economic models would enable dynamic reassessment of treatment value as clinical practice evolves and long-term outcomes mature. Collaboration with international ATTR-CM registries could further facilitate benchmarking of Slovak results within the broader European experience, while maintaining focus on nationally relevant cost structures and treatment patterns.

Conclusion

Reductions in cardiovascular and heart-failure hospitalizations observed in modern transthyretin stabilizer trials translate into tangible hospital budget savings in Slovakia. Using standard rate-to-probability conversions, this analysis demonstrates that the annual probability of hospitalization declines meaningfully for both acoramidis and tafamidis, producing clear, event-driven cost offsets under SK-DRG reimbursement rates. Over the patient's survival horizon, both agents reduce admissions with savings proportional to their trial-specific event-rate differences. Because trial populations and endpoints differ, indirect comparisons should be interpreted cautiously. Establishing a Slovak ATTR-CM registry and refining hospital unit cost methodologies will be essential for developing more definitive, system-specific economic assessments in the future.*

*__Declarations__

Ethics approval and Consent to participate: Author confirms that the research did not involve human participants or human biological material; it exclusively utilized aggregated administrative healthcare cost data. No personally identifiable data were obtained or used, and therefore, ethical committee approval was not required. Informed consent to participate was also not applicable. Author further confirms that all methods were conducted in accordance with relevant guidelines and regulations, including Slovak Law 153/2013. Law on the national healthcare information system and on the amendment and supplementation of certain laws, which does not mandate ethical committee approval for the use of such datasets.

Funding: This researchers-initiated study was supported by an unrestricted grant from Bayer Slovakia. The sponsor had no role in study design, data collection, analysis, interpretation, manuscript preparation, or publication decisions. The authors maintained complete independence and full editorial control throughout the research process. PP-BEY-SK-0022-1 1/2026

Competing interests: The authors declare no competing interests.

References

1. GILLMORE JD, DAMY T, FONTANA M, HUTCHINSON M, LACHMANN HJ, MARTINEZ-NAHARRO A, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J (Internet) 2018, 39: 2799 – 806. Doi.org/10.1093/eurheartj/ehx589
2. LANE T, FONTANA M, MARTINEZ-NAHARRO A, QUARTA CC, WHELAN CJ, PETRIE A, et al. Natural History, Quality of Life, and Outcome in Cardiac Transthyretin Amyloidosis. Circulation (Internet) 2019, 140: 16 – 26. Doi.org/10.1161/CIRCULATIONAHA.118.038169
3. DELGADO D, DABBOUS F, SHIVAPPA N, MAZHAR F, WITTBRODT E, SHRIDHARMURTHY D, et al. Epidemiology of transthyretin (ATTR) amyloidosis: a systematic literature review. Orphanet J Rare Dis (Internet) 2025, 20: 29. Doi.org/10.1186/s13023-025-03547-0
4. GILLMORE J, HAHN K, GUSTAV SMITH J, CONCEIÇÃO I, TIAN Z, et al. Rationale and Design of ANTHOLOGY, an ATTR Amyloidosis Real-World Evidence Program Aiming to Address Gaps in Amyloidosis Care (Internet). Adis Journals 2025: 1139822800 Bytes. Doi.org/10.6084/M9.FIGSHARE.28497332
5. HJALTE F, NORLIN JM, ALVERBÄCK-LABBERTON L, JOHANSSON K, WIKSTRÖM G, ELDHAGEN P. Health care resource use, diagnostic delay and disease burden in transthyretin amyloid cardiomyopathy in Sweden. Ann Med (Internet) 2023, 55: 2292686. Doi.org/10.1080/07853890.2023.2292686
6. FORMIGA F, GARCÍA-PAVÍA P, MARTÍN SÁNCHEZ FJ, NAVARRO-RUIZ A, RUBIO-TERRÉS C, PERAL C, et al. Health and economic impact of the correct diagnosis of transthyretin cardiac amyloidosis

in Spain. Expert Rev Pharmacoecon Outcomes Res (Internet) 2021, 21: 1127 – 1133. Doi.org/10.1080/14737167.2021.1933948
7. MAURER MS, SCHWARTZ JH, GUNDAPANENI B, ELLIOTT PM, MERLINI G, WADDINGTON-CRUZ M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med (Internet) 2018, 379: 1007 – 1016. Doi.org/10.1056/NEJMoa1805689
8. GILLMORE JD, JUDGE DP, CAPPELLI F, FONTANA M, GARCIA-PAVIA P, GIBBS S, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. N Engl J Med (Internet) 2024, 390: 132 – 142. Doi.org/10.1056/NEJMoa2305434
9. SIEBERT U, ALAGOZ O, BAYOUMI AM, JAHN B, OWENS DK, COHEN DJ, et al. State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. Value Health (Internet) 2012, 15: 812 – 820. Doi.org/10.1016/j.jval.2012.06.014
10. SONNENBERG FA, BECK JR. Markov Models in Medical Decision Making: A Practical Guide. Med Decis Making (Internet) 1993, 13: 322 – 338. Doi.org/10.1177/0272989X9301300409
11. GIDWANI R, RUSSELL LB. Estimating Transition Probabilities from Published Evidence: A Tutorial for Decision Modelers. PharmacoEconomics (Internet) 2020, 38: 1153 – 1164. Doi.org/10.1007/s40273-020-00937-z
12. O'MAHONY JF, NEWALL AT, VAN ROSMALEN J. Dealing with Time in Health Economic Evaluation: Methodological Issues and Recommendations for Practice. Pharmaco Economics (Internet) 2015, 33: 1255 – 1268. Doi.org/10.1007/s40273-015-0309-4
13. JONES E, EPSTEIN D, GARCÍA-MOCHÓN L. A Procedure for Deriving Formulas to Convert Transition Rates to Probabilities for Multistate Markov Models. Med Decis Making (Internet) 2017, 37: 779 – 789. Doi.org/10.1177/0272989X17696997
14. JUDGE DP, ALEXANDER KM, CAPPELLI F, FONTANA M, GARCIA-PAVIA P, GIBBS SDJ, et al. Efficacy of Acoramidis on All-Cause Mortality and Cardiovascular Hospitalization in Transthyretin Amyloid Cardiomyopathy. J Am Coll Cardiol (Internet) 2025, 85: 1003 – 1014. Doi.org/10.1016/j.jacc.2024.11.042
15. ELDHAGEN P, LEHTONEN J, GUDE E, GUSTAFSSON F, BAGGER BAHNSEN A, VAKEVAINEN M, et al. Health‐related quality of life among transthyretin amyloid cardiomyopathy patients. ESC Heart Fail (Internet) 2023, 10: 1871 – 1882. Doi.org/10.1002/ehf2.14350
16. ZHAO Q, XIE R, ZHONG W, LIU W, CHEN T, QIU X, et al. Cost-effectiveness analysis of adding durvalumab to chemotherapy as first-line treatment for advanced biliary tract cancer based on the TOPAZ-1 trial. Cost Eff Resour Alloc (Internet) 2023, 21: 19. Doi.org/10.1186/s12962-023-00429-9
17. MILLER DK, HOMAN SM. Determining Transition Probabilities: Confusion and Suggestions. Med Decis Making (Internet) 1994, 14: 52 – 58. https://doi.org/10.1177/0272989X9401400107
18. WELTON NJ, ADES AE. Estimation of Markov Chain Transition Probabilities and Rates from Fully and Partially Observed Data: Uncertainty Propagation, Evidence Synthesis, and Model Calibration. Med Decis Making (Internet) 2005, 25: 633 – 645. Doi.org/10.1177/0272989X05282637
19. FLEURENCE RL, HOLLENBEAK CS. Rates and Probabilities in Economic Modelling: Transformation, Translation and Appropriate Application. Pharmaco Economics (Internet) 2007, 25: 3 – 6. Doi.org/10.2165/00019053-200725010-00002

Accepted for publication November 10, 2025.

Corresponding author:
Prof. Robert Babela, FISAC
Slovak Medical University
Limbova 12
833 03 Bratislava
E-mail: *robert.babela@szu.sk*