A COST-EFFECTIVENESS ANALYSIS OF THE CNIC-POLYPILL STRATEGY, COMPARED TO USUAL CARE, IN SECONDARY CARDIOVASCULAR PREVENTION FROM A SPANISH PERSPECTIVE USING DATA FROM THE SECURE TRIAL

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1.INTRODUCTION AND OBJECTIVE

Cardiovascular disease (CVD) is a major cause of morbidity and mortality globally (1). The prevalence of myocardial infarction (MI) is approaching 3M people worldwide and approximately 50% to 75% of patients who experience MI will have a recurrent cardiovascular event within one to three years (2). In Spain, CVD represents 27,9% of deaths, remaining the leading cause (3).

The recommended standard of care (SoC) treatment for the management of patients with a history of major adverse cardiovascular events (MACE) is an antiplatelet agent, statins, and angiotensin-converting enzyme inhibitors, given concomitantly (4). The CNIC-Polypill is a combination pill containing 100 mg acetylsalicylic acid, 20/40 mg atorvastatin, and 2.5/5/10 mg ramipril. The SECURE outcomes trial (phase III, randomised and controlled) has shown the efficacy of the CNIC-Polypill strategy in reducing the risk of recurrent MACE compared with SoC when initiated within six months of a myocardial infarction (5). The CNIC-Polypill is associated with hazard ratios of 0.66 (95% CI: 0.36 to 1.22) and 0.77 (95% CI: 0.50 to 1.19) when compared with SoC for time to stroke and CVD death, respectively. Due to the SECURE results, the European Society of Cardiology included the CNIC-Polypill in the Acute Coronary Syndrome (ACS) 2023 guidelines and it has recently been added to the Essential Medicines List of the World Health Organization (5, 6).

Objective: This analysis aimed to estimate the cost-effectiveness of the CNIC-Polypill strategy vs SoC from a Spanish national healthcare perspective using data from the SECURE trial.

2. METHODS

A Markov cohort model, as outlined in Figure 1, was developed to compare the costs and benefits of the CNIC-Polypill with those of SoC over a lifetime time horizon.

A hypothetical cohort, with the baseline characteristics of the SECURE trial, entered the 'no further event' health state and remained in it until they either experienced a reinfarction or a stroke (disabling or non-disabling). Upon experiencing an event, patients remained in a tunnel state for 12 months (acute 'post-event' phase), to account for higher mortality, higher costs and lower quality of life (QoL) immediately after experiencing an event. After 12 months in the acute 'post-event' phase, patients reached stable 'post-event' health states. It was assumed that patients could not experience more than one reinfarction or stroke.

The monthly probability of a patient within the 'no further event' health state experiencing a reinfarction, stroke or CV death was informed by parametric survival analysis using individual patient-level data, based on the individual components of the composite endpoint of the SECURE trial. Parametric extrapolations were chosen by means of 3 criteria: Goodness of fit statistics, visual inspection and clinical plausibility of the long-term extrapolations. Log-normal, Weibull and Exponential distributions were best fitting for time to reinfarction, stroke and CV death, respectively. The non-CV death was informed by Spanish general population norm (age and gender adjusted) and standardized mortality ratios were applied in the post reinfarction and stroke states. The non-CV death was assumed to be treatment independent throughout the model time horizon.

Patients were at risk of urgent revascularizations throughout the model, which were associated with further costs and disutilities.

Treatment acquisition costs, CV event costs (hospital diagnostic related group codes), and health state-specific healthcare resource utilization (7) were considered (Table 1, table 2 and table 3, respectively). Most recent available costs were used or inflated to 2021 EUR if more recent data was not available.

Table 4 presents the utilities used throughout the model. Utility values were assumed to be equivalent between the 'no further event' and 'post-reinfarction (acute phase)', as patients in the 'no further event' health state were assumed to have experienced an MI within a median of eight days of entering the model. In both health states ('no further event' and 'post-reinfarction' until reaching a stable phase) utility values were assumed to increase during the first year to account for the QoL decrement in the first months after an event. Separate utility values were applied depending on whether patients experienced a disabling or non-disabling stroke. Health state utility values were adjusted (adjustment factor) considering general population utilities to determine age-specific utilities for each health state.

Outcome measures include Life Years (LY), quality-adjusted life-years (QALYs), avoided reinfarctions and strokes, total costs, costs breakdown and Incremental Cost-Effectiveness Ratio (ICER) per QALY gained. Sensitivity analyses considered probabilistic sensitivity analysis (PSA) and scenario analyses. Outcomes were discounted at 3%.

Figure 1. Markov Model with 6 mutually exclusive health states. 12 monthly event-specific tunnel health states account for different mortality risk in the 1st year post-event

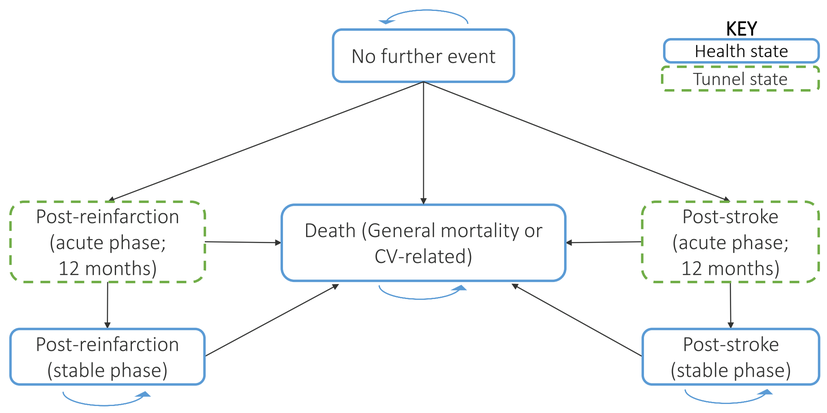

Table 1. Medication acquisition costs

Weighted average treatment costs (p/cycle)	
Treatment	Cost (€)
Polypill (Average AAR40/AAR20)	€ 15,31
Standard Care	€ 17,67

Table 2. Cardiovascular event costs

Post-event costs (immediately after event)	
Reinfarction	Deterministic
Non-fatal	€ 6.288,30
Fatal	€ 12.025,80
Stroke	Deterministic
Non-fatal	€ 5.204,00
Fatal	€ 7.473,10
Distribution of CVD deaths in SECURE trial	Proportion
Reinfarction	97%
Stroke	3%
Weighted cost of CV death	€ 11.872

Table 3. Health state costs

Health state costs	
Health state	Cost per cycle
No further event	€ 31,33
Post reinfarction	€ 31,33
Post stroke	€ 97,36

Table 4. Utilities.

Health state utility values (applied per monthly cycle)		
First month 'post-reinfarction' and 'no further event'	0.68	AF: 0.75
2 to 6 months 'post-reinfarction' and 'no further event'	0.78	AF: 0.86
7 months 'post-reinfarction' and 'no further event' until death	0.82	AF: 0.91
'Post-stroke' (non-disabling)	0.81	AF: 0.89
'Post-stroke' (disabling)	0.45	AF: 0.50
Stroke (weighted average of non-disabling and disabling)	NA	AF: 0.68
Disutilities (applied as one-off per even per cycle)		
PCI decrement	0.06	

Abbreviations: AF: Adjustment factor; NA: Not applicable. PCI: Percutaneous Coronary Intervention.

3. RESULTS

- **Base Case Analysis**: Results over a lifetime time horizon show that the CNIC-Polypill is dominant (less costly and more effective) when compared with standard care (Table 5). The CNIC-Polypill is also associated with fewer reinfarctions and strokes compared to SoC (Table 6). As the urgent revascularisation rate is not treatment dependant, slightly more events are found in the CNIC-polypill arm as patients are at risk longer (due to incremental LY gained).
- **PSA**: In line with the Base Case Analysis, the CNIC-Polypill was dominant in 82% of the iterations. The probabilities of the CNIC-Polypill being cost effective, considering a willingness to pay cost-effectiveness threshold of €30,000 per QALY gained, and cost saving are 88.7% and 99.5%, respectively (Figure 2).
- **Scenario Analyses**: In all 8 different scenarios tested the CNIC-Polypill remained dominant (seven scenarios) or cost-saving (one scenario). Scenarios considered were: Second-best fitting distributions for parametric survival curves; gradual and instant treatment wanning effect; treatment discontinuation; societal perspective; time horizon limited to 4 years mimicking the SECURE follow-up length; alternative utility values; no treatment effect on all efficacy parameters; equivalent dosages across arms.

Table 5: Base Case Economic evaluation results over a lifetime horizon (per patient)

	CNIC-Polypill	SoC	Difference
Total cost discounted	€10,945	€11,537	-€592
Total QALYs discounted	6.70	6.62	0.08
Total LY discounted	9.29	9.19	0.10
Total LY undiscounted	11.40	11.26	0.14
ICER			Dominant
Net monetary benefit at a WTP threshold of € 30,000 per QALY			€2,956

Table 6: Base Case Predicted number of events over a lifetime horizon (per patient)

	CNIC-Polypill	SoC	Difference
Number of reinfarctions	0.077	0.093	-0.016
Number of strokes	0.036	0.053	-0.017
Number of urgent revascularisations	0.090	0.089	0.001

Figure 2. Cost-effectiveness plane presenting the results of the probabilistic sensitivity analysis with 1,000 iterations.

4. CONCLUSIONS

The CNIC-Polypill is a dominant strategy (improving health outcomes and reducing costs) in patients after acute coronary syndrome when compared to SoC from the perspective of the Spanish healthcare system and, therefore, should be considered at hospital discharge as a therapeutic strategy of choice for patients in secondary prevention.

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REFERENCES

1. Setoguchi, S. et al., Journal of the American College of Cardiology, 51, 1247-1254, 2008.
2. ANDRES, E. et al., Revista Española de Cardiología (English Edition), 65, 414-420, 2012.
3. INFORME ANUAL DEL SISTEMA NACIONAL DE SALUD, 2020-2021
4. Byrne RA, et al. Eur Heart J. 2023 Aug 25;ehad191; 2023 ESC Guidelines for the management of acute coronary syndromes.
5. Castellano JM et al. N Engl J Med. 2022 Sep 15;387(11):967–77.
6. Web Annex A. WHO Model List of Essential Medicines – 23rd List, 2023.
7. BOE (ESTADO, 2013). núm. 180, de 29 de julio de 2013, páginas 55225 a 55251. Inflated from 2013 to 2021 prices