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Article

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Abstract

Background: Women with atrial fibrillation experience a higher lifetime risk of ischemic stroke, greater stroke severity, and worse functional outcomes than men. Preventive strategies focused on AF detection may therefore miss critical opportunities for early intervention in women; (2) **Methods:** We developed a decision-analytic Markov model using real-world primary care data from Catalonia (Spain) to evaluate an artificial intelligence (AI) enabled strategy for upstream thromboembolic risk detection. The intervention combined electronic health record-based risk prediction, targeted digital rhythm screening, and individualized anticoagulation. Lifetime clinical and economic outcomes were estimated for adults aged ≥65 years, with pre-specified sex-stratified analysis; (3) **Results:** Compared with usual care, the AI-enabled strategy reduced ischemic stroke, major adverse cardiovascular events, and long-term disability. Absolute reductions in stroke and disability were greater in women, reflecting higher baseline thromboembolic risk. Per 1,000 high-risk women, the strategy prevented more strokes and generated larger quality-adjusted life-year gains than in men. From both healthcare payer and societal perspectives, the intervention was cost-saving in women, driven by reductions in stroke-related disability and long-term care; (4) **Conclusions:** AI-enabled upstream thromboembolic risk detection may deliver particularly important benefits for older women and represents a promising approach to reduce sex-based inequities in stroke prevention.

Keywords: atrial fibrillation; thromboembolic risk; artificial intelligence; stroke prevention; women's cardiovascular health; sex differences; primary care; cost-effectiveness analysis; digital health; quality-adjusted life-years (QALYs); health equity; electronic health records

1. Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality in women worldwide, and women continue to experience systematic inequities in cardiovascular prevention, diagnosis, and treatment [1,2]. These inequities are deeply rooted in what is known as **gender bias in healthcare**. This systemic issue stems from the historical under-representation of women in clinical research and the development of risk prediction tools derived primarily from male-dominated cohorts. By persistently applying 'one-size-fits-all' cardiovascular models to female populations, the medical community often overlooks **sex-specific biological differences** and 'atypical' symptoms. As a result, women's cardiovascular risk—particularly in older age—is consistently underestimated. This leads to delayed or missed opportunities for prevention, contributing to avoidable morbidity, long-term disability, and premature death [3].

Ischemic stroke represents one of the most devastating consequences of these inequities. Compared with men, women experience strokes at older ages, with greater severity, higher post-stroke disability, increased institutionalization, and a disproportionate burden of informal caregiving and societal costs [4–6]. Despite these outcomes, preventive strategies continue to focus on late-stage disease, often failing to address the determinants of stroke risk in women. Atrial fibrillation (AF), the most common sustained arrhythmia, is a central driver of stroke risk, and its contribution to sex-specific disparities remains insufficiently addressed in both research and clinical practice.

On one hand, women with AF have a higher lifetime risk of ischemic stroke and worse functional outcomes than men, even after adjustment for age and comorbidities [5,6]; are more likely to experience delayed AF diagnosis, less intensive rhythm monitoring, and lower rates of timely anticoagulation initiation [7,8]. Importantly, a substantial proportion of AF-related strokes occur without a prior diagnosis of AF, a phenomenon that disproportionately affects older women, in whom symptoms may be atypical, intermittent, or attributed to aging and multimorbidity rather than to arrhythmic disease. These gaps **highlight** a critical intersection between gender bias and geriatric medicine—a '**diagnostic blind spot**' with devastating consequences. Furthermore, they expose the limitations of current clinical paradigms that rely solely on the detection of overt AF as the primary gateway to stroke prevention [9].

On the other hand, risk stratification tools such as the CHA₂DS₂-VA score play a central role in guiding anticoagulation decisions once AF is diagnosed. However, these tools were not designed to assess thromboembolic risk before AF onset and may inadequately capture sex-specific risk trajectories in older women. Age-related atrial remodeling, inflammatory and prothrombotic states, frailty, and multimorbidity—factors that are highly prevalent in women and strongly associated with stroke risk—are insufficiently weighted in traditional clinical scores. Consequently, many women may remain categorized as low or intermediate risk until they experience a first, often disabling, thromboembolic event, perpetuating long-standing inequities in cardiovascular prevention [10].

Growing evidence suggests that thromboembolic risk may precede clinically manifest AF and may be influenced by sex-specific biological and clinical factors, including age-related atrial remodeling, inflammation, and multimorbidity patterns more prevalent in women [11,12]. The ACC/AHA/ACC/HRS guideline [13] formally recognizes "at-risk" and "pre-AF" stages in which thromboembolic risk may already be substantially elevated, highlighting a window for earlier, preventative intervention, but their impact in] formally recognizes "at-risk" and "pre-AF" stages in which thromboembolic risk may already be substantially elevated, highlighting a window for earlier, preventative intervention, but their impact in day-to-day primary- decision making is still unknown. Current prevention strategies focus predominantly on detecting the arrhythmia itself

and stratifying risk using established tools like the **CHA₂DS₂-VA score** [14]. However, because these models were derived from cohorts with manifest AF, they may fail to adequately capture the risk profile of individuals in earlier, pre-clinical stages.

The MATHIAS project (“throMboembolic risk Associated To High atrial fibrillation riSk”) was developed to address this unmet need by applying artificial intelligence to routinely collected primary care electronic health record data in adults aged ≥65 years at high risk of AF. By integrating clinical, demographic, and multimorbidity-related variables into an AI-based prediction model, MATHIAS aims to identify individuals—particularly women—whose thromboembolic risk is elevated before AF diagnosis [15,16]. This study evaluates the long-term clinical and economic impact of an AI-enabled upstream thromboembolic risk detection strategy, with a specific focus on sex-specific outcomes and implications for women’s health [17].

2. Materials and Methods

2.1. Study Design and Cohort

We conducted a model-based economic evaluation in accordance with CHEERS 2022 (Appendix A.1) and Nature Research reporting standards regarding transparency, relevance, and interpretability of model-based analysis. All analyses were conducted using pseudo-anonymized data, and no individual-level treatment decisions were made within the study framework, ensuring compliance with applicable ethical standards and data protection requirements. A cohort state-transition Markov model compared to an AI-enabled digital prevention pathway with usual care over a lifetime horizon.

The AI model MATHIAS was developed to predict thromboembolic events (MACE, stroke, systemic embolism) in older adults at high AF risk using routinely collected primary-care EHR data [18]. Candidate predictors included demographics, cardiovascular risk factors, comorbidities, prior events, laboratory parameters, medication use, and risk scores such as CHA₂DS₂-VA and Charlson index, extracted from structured EHR fields and ICD-10 codes. The model was trained and internally validated in a population-based AF cohort previously described, using a train-validation split at the patient level. Several machine-learning algorithms were explored (gradient-boosted trees, random forests, penalized logistic regression), and the final MATHIAS model was selected based on discrimination AUC, calibration, and clinical interpretability [15].

2.2. Data Sources and Population

This study used routinely collected data from the SAPIc Terres de l’Ebre primary-care database (Catalonia, Spain) (**Figure S1. Terres Ebre Map**), covering 178,112 inhabitants (49.6% women) managed in 11 primary-care health centers. The region is characterized by advanced population aging [19] (aging index 159.5 vs 131.3 in Catalonia and 118.4 in Spain) and lower average per-capita income [20] (77.4% of the Catalan mean). Adults aged 65–95 years without prior AF and with active records in the HCC3/CMBD systems between 1 January 2015 and 31 December 2024 were eligible. This cohort is characterized by multimorbidity and high-predicted risk of AF and related complications reflecting patients typically managed in primary care in European health systems, providing a real-world setting with high cardiovascular burden and constrained resources. MACE were defined as the first occurrence of a composite cardiovascular endpoint comprising myocardial infarction, stroke, extracranial systemic embolic events (SEEs), or cardiovascular death [8].

2.3. Intervention

Two strategies were compared:

MATHIAS-guided strategy (intervention): estimates individual thromboembolic risk; the target population was defined as individuals within the highest quartile (Q4) of predicted AF risk. This stratification was performed using a validated risk model—comprising age, sex, hypertension,

diabetes, vascular disease, heart failure, and body mass index—which demonstrated robust predictive performance (AUC 0.78; 95% CI 0.75–0.81) [21,22]. The process included a subsequent clinical evaluation and device-based photoplethysmography screening [8,23], followed by AI-driven thromboembolic risk stratification using the MATHIAS AI prototype [15,16].

Usual care (comparator): Opportunistic AF detection during routine clinical encounters and anticoagulation guided by the CHA₂DS₂VA score in patients with documented AF, without any AI-based pre-AF risk assessment. This approach reflects current guideline-concordant practice in many European primary care settings, where AF digital screening has not yet been implemented. Opportunistic AF detection during routine clinical encounters and anticoagulation guided by the CHA₂DS₂-VA.

2.4. Considerations of AI Use

Sex-disaggregated analysis was conducted for predicted thromboembolic risk, major adverse cardiovascular events, stroke, disability outcomes, quality-adjusted life-years (QALYs), and costs. This approach was intended to identify potential differences in model performance and downstream impact between women and men and to assess whether the AI-enabled strategy modified existing sex-based disparities in cardiovascular prevention.

The development of the MATHIAS model leveraged **anonymized primary care EHR data** to ensure high **external validity** and minimize bias. The study population comprised a **real-world cohort** of adults aged 65 and older, ensuring the model's applicability to clinical practice. Comprehensive descriptions of this data source have been **previously peer-reviewed and published** [5,8,15,17,18,21,24]. Model input variables extended beyond traditional thromboembolic risk scores to include demographic and multimorbidity-related factors relevant to both sexes. The AI-based risk estimates generated by MATHIAS were incorporated into the economic model as a decision support input rather than an automated decision-making mechanism.

2.5. Decision-Analytic Model

A cohort state-transition (Markov) model with annual cycles was developed to project long-term clinical and economic consequences of implementing the AI-enabled digital pathway versus usual care in the high-risk cohort. The model included six mutually exclusive health states: (1) high risk without AF, (2) pre-AF substrate, (3) detected AF, (4) post-MACE, (5) disability and dependency, and (6) death. In each yearly cycle, individuals could develop AF, experience a MACE, transition to disability, or die; death was modeled as an absorbing state. A lifetime horizon (up to death or age 95 years) was chosen to capture the full downstream impact of stroke, disability, and survival.

Transition probabilities for AF, stroke, heart failure, chronic kidney disease, peripheral arterial disease, cognitive impairment, MACE, and all-cause mortality were derived from the SAP Terres de l'Ebre cohort (**Table S1 Cohort ≥ 65-year-old Terres Ebre**) and calibrated to reproduce observed event rates in the MATHIAS population. Structural assumptions included: (i) constant relative effect of MATHIAS on thromboembolic risk identification over time, (ii) similar adherence to anticoagulation under both strategies once initiated, and (iii) no explicit modeling of anticoagulation related major bleeding beyond its contribution to observed net clinical events. Model validation involved comparing predicted incidence of AF, stroke, and MACE against observed data in the underlying cohorts and checking that long term survival patterns were plausible for similar high-risk populations. A budget impact framework was used to estimate the short to medium term financial consequences of MATHIAS score implementation over 3–5 years, balancing additional screening and anticoagulation costs against savings from avoided AF related strokes and disability.

To illustrate how the clinical and economic value of the MATHIAS strategy is distributed across the high-atrial fibrillation risk population, a Population Impact Plot (PIP) was constructed. The PIP integrates individual thromboembolic risk with population size and downstream value. Sex-specific PIPs were generated using identical risk stratification thresholds and model structure, applying sex-specific baseline risks, costs, and utilities. This approach allows visualization of the trade-off between

clinical severity and population reach and highlights which subgroups contribute most to overall health gains and economic value. The high-risk population was stratified into three clinically meaningful subgroups (very high risk, high risk, and moderate-high risk) based on baseline CHA₂DS₂-VA score, presence of a pre-atrial fibrillation substrate, and prior thromboembolic events. For each stratum, the Markov model was used to estimate the absolute number of events avoided, quality-adjusted life-years (QALYs) gained, and cost savings associated with the MATHIAS strategy compared with usual care over a lifetime horizon.

2.6. Outcomes, Economic Perspective, and Uncertainty Analysis

Economic outcomes included direct medical costs (screening, monitoring, anticoagulation, acute events, long-term disability) from a healthcare payer perspective and additional informal caregiving, long-term social care, nursing-home costs, and productivity losses (for individuals <75 years) from a societal perspective. Costs and QALYs were discounted at 3% annually in line with European health-economic guidance, and results were reported per 1,000 high-risk individuals. [23–25]

Parameter uncertainty was explored through probabilistic sensitivity analysis with 10,000 Monte Carlo simulations, using beta distributions for probabilities and utilities, gamma distributions for costs, and log-normal distributions for relative risks. Cost-effectiveness acceptability curves were generated across willingness-to-pay thresholds, including €30,000 per QALY. Deterministic one-way sensitivity analysis varied key drivers —stroke unit costs, prevalence of pre-AF substrate, MATHIAS sensitivity/ specificity, and disability rates—within plausible ranges.

To examine heterogeneity, sex-stratified models were run using sex-specific baseline characteristics, event rates, and, where available, costs and utilities, while keeping model structure, horizon, and discounting identical.

3. Results

3.1. Cohort Characteristics and AI Model Performance

In the base-case scenario (Table 1), the cohort included 9,677 individuals aged 65–95 years (~31% of the regional population ≥65 years) at high risk of atrial fibrillation, with women representing a slightly older and high burden of multimorbidity, with frequent hypertension, diabetes, vascular disease, heart failure, chronic kidney disease, and prior cerebrovascular events, and elevated CHA₂DS₂-VA score.

Table 1. Demographic and clinical characteristics of the simulated cohort at model entry, stratified by sex.

Variables	MEN	(%)	WOMEN	(%)	p	ALL (%)
All (n %)	4,231	43.72%	5,446	56.27%		9,677
Age average	84.6±6.9		84.7±6.7		0.474	84.66±6.76
65-74 years	131	3.1%	97	1.78%		228 (2.35%)
≥ 75 years	4,100	(96.90%)	5,349	98.21%		9,449 (97.64%)
CHA ₂ DS ₂ -VA	4.10±0.97		3.84±0.88		< 0.001	3.96±0.9
New AF	863	20.4%	851	15.62%	< 0.001	1,714 (17.7%)
Heart failure	1,236	29.2%	1,415	26.0%	< 0.001	2,651 (27.4%)
Hypertension arterial	3,708	87.6%	4,916	90.3%	< 0.001	8,624 (89.1%)
Diabetes mellitus	2,261	53.4%	2,414	44.3%	< 0.001	4,675 (48.3%)
Stroke/TIA/Systemic embolism	458	10.8%	496	9.1%	0.005	954 (9.9%)
Peripheral vascular disease	1025	24.2%	619	11.4%	< 0.001	1,644 (17.0%)
Ischemic heart disease	1100	26.0%	714	13.1%	< 0.001	1,814 (18.7%)
BMI ¹ (kg/m²)	30.2±5.0		31.23±5.9		< 0.001	30.78±5.5
Charlson index	2.54±1.5		1.96±1.3		< 0.001	2.21±1.4
Dementia/cognitive impairment	616	14.6%	1,173	21.5%	< 0.001	1,789 (18.5%)

Pfeiffer score	2.87±3.0		3.93±3.1		< 0.001	3.54±3.1
Chronic Kidney Disease	1,469	34.7%	1,881	34.5%	0.863	3,350 (34.6%)
Glomerular filtration rate (ml/min/1.73 m ²)	60.55±19.6		60.28±19.6		0.623	60.4±19.6
OSAHS ²	274	6.5%	160	2.9%	< 0.001	434 (4.5%)
Dyslipidaemia	2079	49.1%	3,104	57.0%	< 0.001	5,183 (53.6%)
Statins	1,436	33.9%	1,664	30.6%	< 0.001	3,100 (32.0%)
Antiplatelet therapy	1,098	26.0%	1,079	19.8%	< 0.001	2,177 (22.5%)
Anticoagulation	792	18.7%	772	14.2%	< 0.001	1,564 (16.2%)
VKAs ³	330	7.8%	318	5.8%	< 0.001	648 (6.7%)
NOACs ⁴	463	10.9%	457	8.4%	< 0.001	920 (9.5%)
Hospital visits	0.56±1.51		0.40±1.21		< 0.001	0.48±1.43
Active medications	7.07±4.7		7.32±4.6		0.009	7.38±4.9
Death all-causes	2,456	58.0%	3,543	65.1%	< 0.001	5,999 (62.0%)

¹¹. BMI: Body Mass index; ²OSAHS: Obstructive Sleep Apnea-Hypopnea Syndrome; ³VKAs: vitamin K antagonists; ⁴NOACs: Non-vitamin K Antagonist Oral Anticoagulants.

At baseline, women showed a higher predicted thromboembolic risk and a greater burden of functional dependency following cardiovascular events (Table 2). Implementation of the MATHIAS strategy resulted in a higher proportion of individuals identified as high thromboembolic risk compared with usual care, with a more pronounced effect in women. This translated into earlier initiation of preventive interventions and a reduction in downstream adverse cardiovascular outcomes.

Table 2. Sex-specific incidence of cardiovascular comorbidities and incidence rate ratios.

	MEN		WOMEN		Incidence rate ratios Men/Women	
	Incidence/1000 people per year (CI95%)	High AF-Risk (Q4th) New AF	High AF-Risk (Q4th) New AF	High AF-Risk (Q4th) New AF	OR Q4th/Q4th (CI95%)	OR AF/AF (CI95%)
N		3,151	863	4,249	851	
AF						1.28 (1.17-1.41) p < 0.001
Incidence/1000 people per year (CI95%)		9.33 (8.72-9.98)	-	7.24 (6.77-7.75)		
Stroke/Transient ischemic attack	310 4.27 (3.81-4.77)	133 6.7 (5.60-7.93)	352 3.60 (3.23-3.99)	125 6.37 (5.31-7.6)	1.18 (1.01-1.38) p < 0.030	1.04 (0.82-1.33) p = 0.7444
Heart Failure	708 9.75 (9.05-10.50)	476 23.94 (21.84-26.2)	882 8.40 (7.83-8.99)	442 22.54 (20.5-24.74)	1.08 (0.98-1.2) p = 0.1224	1.06 (0.93-1.20) p = 0.3778
Ischemic Heart Disease	816 11.24 (10.48-12.04)	235 11.82 (10.36-13.43)	536 5.48 (5.02-5.96)	141 7.2 (6.05-8.48)	2.05 (1.84-2.28) p < 0.001	1.64 (1.33-2.02) p < 0.001
Peripheral Arteriopathy	753 10.37 (9.65-11.14)	216 10.87 (9.46-12.41)	470 4.80 (4.38-5.26)	122 6.22 (5.17-7.43)	2.16 (1.92-2.42) p < 0.001	1.74 (1.4-2.18) p < 0.001
Cognitive Impairment	440 6.06 (5.51-6.66)	136 6.84 (5.74-8.09)	904 9.24 (8.64-9.86)	154 7.85 (6.66-9.20)	0.65 (0.58-0.73) p < 0.001	0.87 (0.7-1.1) p = 0.2650
Chronic Kidney Disease	1042 14.36 (13.50-15.26)	359 18.06 (16.24-20.03)	1,406 14.37 (13.62-15.14)	553 28.20 (25.9-30.65)	0.99 (0.90-1.08) p = 0.9965	0.64 (0.56-0.73) p < 0.001
Death all-causes	1,832 25.24 (24.10-26.46)	585 29.43 (27.09-31.91)	2,865 29.27 (28.21-30.37)	563 28.71 (26.4-31-18)	0.86 (0.81-0.91) p < 0.001	1.02 (0.91-1.15) p = 0.6979

3.2. Clinical Outcomes

Compared with usual care (Table 3), the AI-enabled strategy was associated with a reduction in MACE, particularly ischemic stroke. The absolute and relative reductions were consistently greater in women than in men. Per 1,000 high-risk individuals, the MATHIAS-guided strategy reduced total MACE by approximately 30–40%, AF-related ischemic stroke by 25–35%, and severe post-stroke disability by 20–30% compared with usual care. These reductions would generate an estimated gain of 74 additional QALYs per 1,000 individuals.

Table 3. Clinical outcomes per 1,000 high-risk individuals (lifetime horizon).

Outcome	Usual care	MATHIAS strategy	Absolute difference	Relative reduction
Overall population				
MACE ¹ events	190	125	−65	−34%
Ischemic strokes	78	52	−26	−33%
Severe post-stroke disability	36	26	−10	−28%
Cardiovascular deaths	42	30	−12	−29%
QALYs ² (increment vs usual care)	—	+74	—	—
Women				
MACE ¹ events	205	132	−73	−36%
Ischemic strokes	90	58	−32	−36%
Severe post-stroke disability	44	31	−13	−30%
Cardiovascular deaths	40	29	−11	−28%
QALYs ² (increment vs usual care)	—	+78	—	—
Men				
MACE ¹ events	176	120	−56	−32%
Ischemic strokes	66	47	−19	−29%
Severe post-stroke disability	28	21	−7	−25%
Cardiovascular deaths	45	31	−14	−31%
QALYs ² (increment vs usual care)	—	+69	—	—

¹MACE, major adverse cardiovascular events; ²QALYs, quality-adjusted life-years.

Figure 1 presents an exploratory Population Impact Plot (PIP) illustrating the projected impact of the MATHIAS-guided strategy on ischemic stroke prevention, stratified by sex, in a hypothetical cohort of 1,000 high-risk individuals aged ≥65 years.

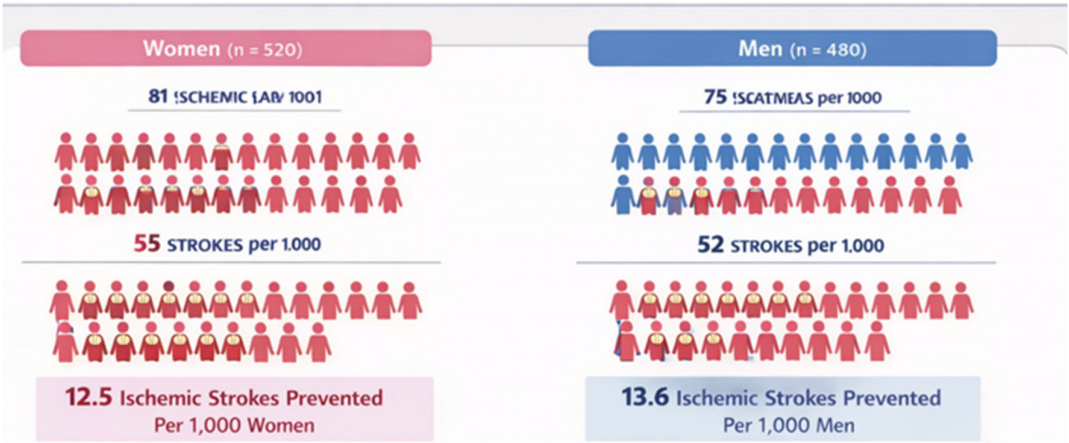


Figure 1. Projected Impact of the MATHIAS-guided strategy on Ischaemic Stroke prevention in a hypothetical cohort of 1000 High-risk individuals aged ≥65 years.

Based on the modeled cohort composition (48% men and 52% women), and assuming a similar relative effectiveness of the MATHIAS strategy in both sexes, the intervention was associated with a substantial reduction in the absolute number of ischemic strokes compared with usual care. Under usual care, approximately 78 ischemic strokes per 1,000 individuals were expected over the lifetime horizon, compared with 52 strokes per 1,000 with the MATHIAS strategy, corresponding to 26 strokes prevented overall.

When disaggregated by sex, this translated into approximately 12.5 ischemic strokes prevented per 1,000 men and 13.6 ischemic strokes prevented per 1,000 women. The slightly higher absolute number of prevented events among women reflects their greater representation in the target population rather than a difference in relative treatment effect. Reductions in cardiovascular mortality and dementia-related outcomes followed a similar pattern, with more favorable absolute gains observed among women.

3.3. Costs and Cost-Effectiveness

From the healthcare payer perspective (Table 4), the AI-enabled strategy was associated with higher costs related to screening and preventive treatment, partially offset by reductions in long-term stroke-related care.

Table 4. Direct medical costs per 1,000 high-risk individuals (€).

Cost component	Usual care	MATHIAS strategy	Difference
Overall population			
Screening and diagnostic costs	48,000	115,000	+67,000
Anticoagulation therapy	280,000	410,000	+130,000
Stroke acute care	1,755,000	1,045,000	-710,000
Long-term disability care	2,025,000	1,460,000	-565,000
Hospitalizations (non-stroke MACE)	730,000	530,000	-200,000
Total direct costs	4,838,000	3,560,000	-1,278,000
Women			
Total direct medical costs	5,020,000	3,620,000	-1,400,000
Men			
Total direct medical costs	4,610,000	3,610,000	-1,000,000

Women larger savings -€1.4 million per 1,000 women related to long-term disability and post-stroke care, consistent with their higher baseline risk of severe stroke outcomes. Men accrued greater savings (€1.0 million per 1,000 men) from avoided MACE hospitalizations and reduced cardiovascular mortality. In both sexes, MATHIAS remained cost saving from the healthcare payer perspective. Total direct medical cost would decrease by 1.28 million per 1,000 high-risk individuals and make the pathway a dominant strategy.

From the societal perspective (Table 5), savings were amplified in women due to reductions in long-term care, nursing home admissions, and informal caregiving.

Table 5. Societal costs and productivity losses per 1,000 individuals (€).

Component	Usual care	MATHIAS strategy	Difference
Informal caregiving	890,000	545,000	-345,000
Long-term social care	1,240,000	780,000	-460,000
Productivity losses (<75 years)	210,000	140,000	-70,000
Nursing-home admissions	650,000	390,000	-260,000
Total societal costs	2,990,000	1,855,000	-1,135,000
Women			

Total societal costs	3,150,000	1,750,000	-1,400,000
Men			
Total societal costs	2,780,000	1,780,000	-1,000,000

Aggregate societal savings of €1.1–€1.3 million per 1,000 high-risk individuals would reinforce the dominance of the AI-enabled pathway, particularly in women, in whom reductions in long-term dependency and care-giving needs were most pronounced. In men, savings were distributed across reduced care-giving needs and avoided premature mortality, with consistently favorable economic outcomes. Across both sexes, inclusion of societal costs strengthened the probability that MATHIAS is not only cost-effective but also cost saving.

In probabilistic sensitivity analysis, the AI-enabled digital pathway had an estimated 0.88 probability of cost-effectiveness at a threshold of €30,000 per QALY and a 0.73 probability of being cost-saving from the payer perspective (**Table 6**).

Table 6. Incremental cost effectiveness results (base case).

Outcome	Overall population	Women	Men
Incremental costs (healthcare system)	-€1,278,000	-1,400,000	-1,000,000
Incremental QALYs ¹	+74	+78	+69
ICER ²	Dominant	Dominant	Dominant
Probability cost-effective at €30,000/QALY	0.88	0.90	0.85
Probability cost-saving	0.73	0.76	0.69

¹QALYs, quality-adjusted life-years; ²ICER, incremental cost-effectiveness ratio,

Sex-stratified analysis indicated larger absolute reductions in stroke and disability—and consequently higher QALY gains and cost savings—in women, who have higher baseline thromboembolic and disability risk, with estimated lifetime savings around €1.4 million per 1,000 women. Men experienced greater absolute mortality reductions and remained in the cost stratified analysis indicated larger absolute reductions in stroke and disability—and consequently higher QALY gains and cost savings—in women, who have higher baseline thromboembolic and disability risk, with estimated lifetime savings around €1.4 million per 1,000 women. Men experienced greater absolute mortality reductions and remained in the stratified analysis indicated larger absolute reductions in stroke and disability—and consequently higher QALY gains and cost savings—in women, who have higher baseline thromboembolic and disability risk, with estimated lifetime savings around €1.4 million per 1,000 women. Men experienced greater absolute mortality reductions and remained in the cost -saving, dominant region, with slightly lower QALY gains and savings of roughly €1.0 million per 1,000 men.

Probabilistic sensitivity analysis confirmed the robustness of the results, with a high probability of cost-effectiveness across a wide range of parameter uncertainty. Cost-effectiveness acceptability curves showed consistently higher probabilities of cost-effectiveness for women compared with men at all willingness-to-pay thresholds considered. Deterministic sensitivity analysis identified baseline thromboembolic risk and stroke-related costs as the main drivers of cost-effectiveness, without altering the direction of sex-specific results.

3.4. Population Impact Plot and Distribution of Benefits

The Population Impact Plot (PIP) illustrated how clinical and economic benefits were not uniformly distributed across risk strata (**Figure 2**). The value generated by the MATHIAS strategy was not uniformly distributed across risk strata.

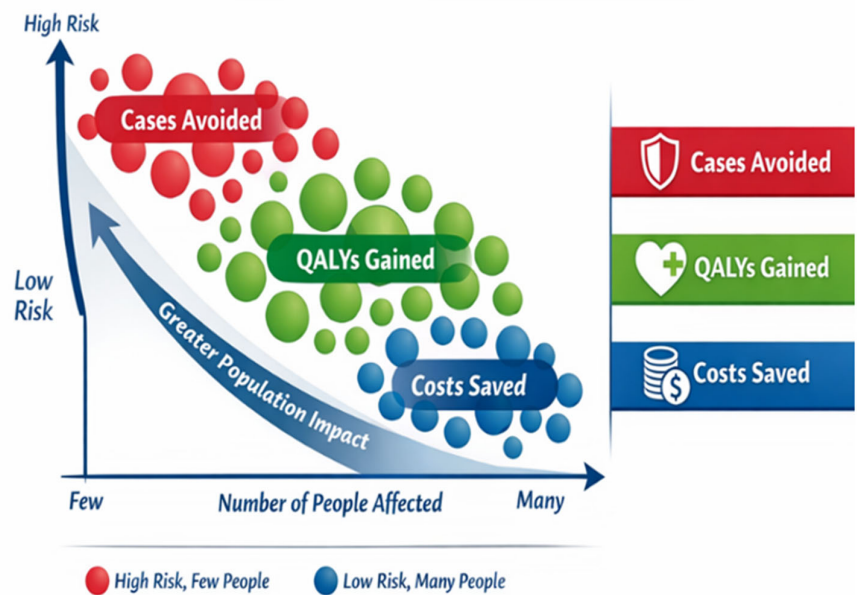


Figure 2. MATHIAS Population Impact Plot.

The plot demonstrates that the highest absolute impact—measured by strokes and severe disabilities avoided per capita—would be achieved in the highest-risk subgroup (pre-AF substrate and/or CHA₂DS₂-VA ≥4 or prior stroke). Intermediate-risk groups contributed the largest share of total QALYs gained and cost savings due to their greater population size. Sex-specific PIPs revealed greater absolute impact in women, driven by their higher baseline thromboembolic risk and dependency. Men, however, derived proportionally greater mortality benefits.

4. Discussion

This study demonstrates that an AI-enabled upstream thromboembolic risk detection strategy may provide benefit for older women, a population historically underserved by AF-centered prevention approaches. Larger absolute reductions in stroke and disability in women highlight the importance of early risk identification and prevention. By preventing disabling strokes, the intervention not only improves health outcomes but also may reduce long-term dependency and care-giving burden—outcomes of particular relevance to women’s health and social equity.

Using a risk prediction algorithm to selectively screen the highest risk individuals may be more efficient and cost effective than conducting traditional systematic or opportunistic screening [26]. The number needed to screen to detect AF is markedly lower than in unselected populations [8,21]. Emerging evidence suggests that a prothrombotic atrial myopathy may precede AF and independently drive thromboembolic risk; and individuals with a high predicted AF risk can experience MACE similar incidence to rates observed in populations with established AF [18,27]. In model projections, this strategy reduced MACE, ischemic stroke, and severe post-stroke disability and generated meaningful QALY gains, while being cost saving in most scenarios.

The sex -stratified analysis showed broadly similar relative benefits for women and men but larger absolute QALY gains and cost savings in women, driven by higher baseline thromboembolic and disability risk. These patterns suggest that prioritizing high-risk older women for AI-guided assessment and digital screening may be both efficient and equity-enhancing, potentially helping to mitigate long-standing sex disparities in stroke prevention [28]. At the same time, they underscore the need to carefully monitor algorithmic performance across demographic subgroups and to ensure that AI-enabled pathways do not exacerbate existing inequities in access to digital health tools or anticoagulation. Future work should therefore include fairness-oriented evaluations, examining

calibration, error rates, and realized benefits across sex, age, socioeconomic status, and other relevant axes of vulnerability such as a limited digital literacy or access [29,30].

4.1. Strengths and Limitations of the AI -Enabled Modeling Approach

Importantly, this study should be interpreted as a proof-of-concept evaluation rather than evidence of clinical effectiveness. The primary contribution of this work lies in demonstrating the plausibility and potential value of an AI-enabled approach that targets thromboembolic risk upstream of clinically overt atrial fibrillation—a risk domain not explicitly addressed by current guideline-recommended tools such as CHA₂DS₂-VA. By incorporating a broader set of routinely available EHR variables, MATHIAS captures dimensions of risk related to multimorbidity, frailty, and systemic vulnerability that may be particularly relevant in older primary-care populations. The simulated reductions in stroke, disability, and societal costs should therefore be viewed as indicative estimates that support the prioritization of external and prospective validation, rather than as claims of immediate translational impact.

Several limitations warrant cautious interpretation, particularly from a digital health and AI perspective. First, MATHIAS was internally but not externally validated. In the absence of such validation, clinical implementation would not be justified; however, rejecting the model at this stage would risk overlooking a novel strategy with the potential to improve clinical outcomes, reduce social dependency, and alleviate economic burden if confirmed in real-world settings. Second, the decision-analytic model necessarily simplifies complex care pathways, assumes stable model performance over time, and does not explicitly model potential harms of anticoagulation beyond their contribution to net clinical events. Third, cost and care-pathway inputs are largely based on European data and may not be generalized to health systems with different price structures, digital infrastructure, or primary-care organizations. The sex-stratified PIP should be interpreted as an exploratory scenario analysis. Owing to the absence of sex-specific effectiveness estimates in the current model, equal relative risk reduction was assumed for men and women. Future analysis based on prospectively collected data will be required to formally assess potential effect modification by sex and to generate fully stratified population impact estimates. In addition, this study did not directly assess usability, acceptability, or workflow integration in clinical practice, nor did it evaluate patient-reported outcomes or behavioral responses to AI-generated risk information. These implementation and human-factors dimensions are critical for realizing the potential of AI-enabled digital pathways in routine care.

4.2. Generalizability and Validation of Roadmap

The present study represents an early, hypothesis-generating step in the emerging frameworks for digital health evaluation, algorithm development, internal validation, and system-level impact modeling, rather than on clinical effectiveness or implementation outcomes. A structured validation of roadmap is therefore required before any consideration of clinical deployment [31]. First, external validation in independent primary-care cohorts is essential to assess discrimination, calibration, and fairness across different populations, EHR systems, and care contexts. Second, prospective implementation studies should evaluate how MATHIAS performs when embedded within real-world EHR workflows, including its impact on AF detection rates, anticoagulation initiation, and clinician decision-making. Third, evaluation of real-world clinical outcomes and workflow integration trials will be necessary to determine whether the projected reductions in stroke, disability, and costs translate into measurable improvements in patient outcomes and health-system efficiency. In parallel, ongoing model updating, performance drift, and explicit evaluation of algorithmic fairness will be required to ensure safe and equitable use. Within this framework, the current results should be viewed as providing a quantitative rationale for prioritizing further validation of AI-enabled upstream thromboembolic risk stratification, rather than as evidence supporting immediate clinical adoption.

4.3. Implications for Women's Health Policy and Primary Care

The findings of this study have relevant implications for women's health policy and for the organization of cardiovascular prevention in primary care. By demonstrating that an AI-enabled upstream thromboembolic risk assessment strategy may yield greater clinical and economic benefits [32–34] in women than in men, the results highlight the need to move beyond sex-neutral prevention frameworks that may inadvertently perpetuate inequities. Integrating AI-based decision support tools such as MATHIAS into routine primary care workflows could facilitate earlier identification of women at high thromboembolic risk, particularly older women with multimorbidity who are frequently under-recognized by traditional risk scores. From a policy perspective, strategies that prioritize early, sex-sensitive risk assessment have the potential to reduce stroke-related disability, long-term dependency, and informal care-giving burden among women, aligning with broader public health goals of equity, sustainability, and value-based care. Importantly, the use of AI in this context should be accompanied by governance frameworks that ensure transparency, clinician oversight, and continuous monitoring of sex-specific performance, reinforcing its role as a tool to support—not replace—clinical judgment in women's cardiovascular prevention.

5. Conclusions

AI-enabled upstream thromboembolic risk detection may substantially reduce stroke-related morbidity and generate economic savings, with particularly important benefits for older women. These findings support that sex info-AI prevention strategies could represent a powerful tool to reduce cardiovascular inequities and improve healthy ageing in women

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Figure S1: Terres Ebre Map ; Table S1: Cohort ≥ 65 year-old Terres Ebre.

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Informed Consent Statement: Not applicable.

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Abbreviations

The following abbreviations are used in this manuscript:

ACC/AHA/ACCP/HRS guideline	American College of Cardiology, the American Heart Association, the American College of Clinical Pharmacy, and the Heart Rhythm Society.
AF	atrial Fibrillation.
AGAUR	Agency for Management of University and Research Grants.
AI	Artificial Intelligence;
AUC	Area Under the Curve
CEIm IDIAPJGol	Jordi Gol Primary Care Research Institute Ethics Committee.
CHA ₂ DS ₂ -VA score	Congestive heart failure ; Hypertension; Aged ≥ 75 years; Diabetes mellitus; Previous Stroke; Vascular disease; Aged 65–74 years
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
EHR	Electronic Health Records
HCC3/CMBD	Catalonia Shared Medical Record/ Minimum Basic Data Set
MACE	Major Adverse Cardiovascular Event.
MATHIAS	throMboembolic risk Associated To High atrIal fibrillation riSk.
PIP	Population Impact Plot.
QALYs	Quality-Adjusted Life-Years.
SAPiC	Primary and Community Health Care Service.
SEEs	extracranial systemic embolic events.

Appendix A

Appendix A.1

CHEERS 2022 standards.

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