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Economic burden of coronary arteries reintervention after previous percutaneous coronary intervention; predictors and financial implications

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Patras, Greece, May 2026

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Abstract

Cardiac coronary arteries percutaneous interventions (i.e. non-surgical) are the most frequently performed invasive medical interventions worldwide. The goal is to diagnose, identify, quantify and treat coronary arteries stenoses and depending on the clinical context to improve quality of life, angina and all-cause death. Nonetheless, these are costly procedures which necessitate significant resources. It is estimated that 10% of these procedures are performed for patients who had had previous coronary arteries percutaneous interventions.

The aim of this study is to investigate the economic impact of cardiac reinterventions in Greece and identify potential clinical predictors associated with the need for reintervention. Identifying predictors of increased risk for reintervention will provide the background for more actively and aggressively addressing these factors to mitigate the risk of need for future reintervention and having a comprehensive estimation of the magnitude of the economic burden and also give the opportunity to reallocate resources more efficiently.

This study will be conducted in order to demystify the financial burden of coronary reinterventions in Greece. Economic data will be extracted from patients' datasheets in liaison with the Finance department of a tertiary, high Interventional Cardiology volume centre in Greece ensuring patients' anonymity and in accordance with the Helsinki declaration for ethical principles in medical research.

Keywords

PCI, repeat revascularization economics, coronary artery disease

Περίληψη

Οι διαδερμικές (μη χειρουργικές) επεμβάσεις στις στεφανιαίες αρτηρίες της καρδιάς αποτελούν τις συχνότερες επεμβατικές ιατρικές πράξεις παγκοσμίως. Στόχος τους είναι η διάγνωση, αναγνώριση, ποσοτικοποίηση και θεραπεία των στενώσεων στις στεφανιαίες αρτηρίες και ανάλογα με το κλινικό σενάριο, η βελτίωση της ποιότητας ζωής, της στηθάγχης και της συνολικής θνησιμότητας. Ωστόσο, πρόκειται για δαπανηρές διαδικασίες που απαιτούν σημαντικούς πόρους. Εκτιμάται ότι το 10% αυτών των επεμβάσεων αφορά σε ασθενείς που έχουν ήδη υποβληθεί σε προηγούμενες παρεμβάσεις.

Σκοπός της παρούσας μελέτης είναι η διερεύνηση του οικονομικού αντίκτυπου των καρδιακών επανεπεμβάσεων στην Ελλάδα και ο εντοπισμός πιθανών κλινικών προγνωστικών παραγόντων που σχετίζονται με επανεπέμβαση. Η αναγνώριση των παραγόντων που προβλέπουν τον αυξημένο κίνδυνο για επανεπέμβαση θα αποτελέσει τη βάση για την πιο ενεργή και επιθετική αντιμετώπισή τους, με στόχο τη μείωση του κινδύνου ανάγκης για επανεπέμβαση, καθώς και για μια ολοκληρωμένη εκτίμηση του μεγέθους της οικονομικής επιβάρυνσης, δίνοντας παράλληλα τη δυνατότητα ορθολογικότερης ανακατανομής των πόρων.

Η μελέτη αυτή θα πραγματοποιηθεί με στόχο την αποσαφήνιση του οικονομικού βάρους των στεφανιαίων επανεπεμβάσεων στην Ελλάδα. Τα οικονομικά δεδομένα θα αντληθούν από τα αρχεία ασθενών σε συνεργασία με το Οικονομικό Τμήμα ενός τριτοβάθμιου κέντρου υψηλού όγκου επεμβάσεων στην Ελλάδα, διασφαλίζοντας την ανωνυμία των ασθενών και σύμφωνα με τη Διακήρυξη του Ελσίνκι για τις ηθικές αρχές στην ιατρική έρευνα.

Λέξεις – Κλειδιά

Αγγειοπλαστική, οικονομικά μεγέθη επανεπέμβασης στεφανιαίων αγγείων, στεφανιαία νόσος

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List of Abbreviations & Acronyms

Abbreviation	**Term**
AUC	Area under the curve
CAD	Coronary artery disease
CI	Confidence intervals
DRG	Diagnosis-related group
EMR	Electronic medical record
IQR	Interquartile range
LOS	Length of stay
PCI	Percutaneous coronary intervention
ROC	Receiver operating curve
VIF	Variance inflation factor

1. Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide with a substantial and persistent burden on healthcare systems (Dalen et al., 2014; Mensah et al., 2019; Bauersachs et al., 2019; Tsao et al., 2023). Over the past decades, percutaneous coronary intervention (PCI) has emerged as the cornerstone in the management of CAD, offering a minimally invasive approach to restoring myocardial perfusion and improving patients' outcomes (Pottle et al., 2023; Kumar et al., 2026). Advances in stent technology, pharmacotherapy, and procedural techniques have significantly enhanced the success rates of PCI (Asano et al., 2022). Nonetheless, despite these improvements it is estimated that in developed countries a considerable proportion of patients undergo repeat revascularization due to restenosis, disease progression, or stent-related complications (Stolker et al., 2012; Kwok et al., 2020). These reinterventions introduce an additional layer of complexity, both clinically, technically and financially.

Repeat coronary interventions following an initial PCI often times represent a critical challenge in contemporary cardiovascular care. From a clinical standpoint, patients undergoing reintervention often exhibit more complex disease profiles, including diffuse atherosclerosis, multivessel involvement, and higher comorbidity burden including but not limited to diabetes mellitus or chronic kidney disease (Parasca et al., 2016). These factors not only complicate subsequent procedures but also contribute to worse prognostic outcomes. From an economic perspective, the need for repeat interventions amplifies healthcare expenditures through increased hospital admissions and procedural costs, extended pharmacological treatments, and long-term follow-up care.

The economic burden associated with coronary artery reinterventions is multifaceted, encompassing direct medical costs as well as indirect costs such as loss of productivity and impaired quality of life. Healthcare systems, particularly those operating with limited resources and under constraints, must balance the benefits of advanced interventional therapies with their financial sustainability. As the global population ages and the prevalence of cardiovascular risk factors continue to rise, understanding and mitigating the economic impact of repeat PCI procedures becomes increasingly important.

Identifying predictors of coronary reintervention is therefore a crucial step towards optimizing patient management and reducing unnecessary healthcare expenditures. These predictors may include patient-related factors such as age, comorbidities, and lifestyle

behaviours, as well as procedural variables like stent type, lesion characteristics, and operator experience. The ability to stratify patients based on their risk of requiring future interventions allows clinicians to tailor therapeutic strategies more effectively, potentially improving outcomes while minimizing costs.

Furthermore, the financial implications of reintervention extend beyond individual patient care to influence broader healthcare policy and resource allocation decisions. Cost-effectiveness analyses and economic evaluations play a vital role in guiding clinical guidelines, reimbursement policies, and investment in new technologies. By examining the interplay between clinical predictors and economic outcomes, this paper aims to provide a comprehensive assessment of the burden imposed by coronary artery reinterventions after prior PCI.

In this context, the present study seeks to explore the determinants and economic consequences of repeat coronary interventions, to inform clinical decision-making and promote a more efficient use of healthcare resources. Through a detailed analysis of predictors and associated costs, this research aspires to contribute to the development of strategies that not only enhance patient care but also alleviate the growing financial strain on healthcare systems.

2. Background

2.1 Coronary Artery Disease: Epidemiology and Global Burden

CAD remains the leading cause of morbidity and mortality worldwide despite substantial advances in cardiovascular prevention, diagnosis, and treatment (Dalen et al., 2014; Roth et al. 2020). CAD develops through a chronic atherosclerotic process characterized by progressive accumulation of lipid-rich plaques within the coronary arteries, eventually leading to impaired myocardial perfusion and clinical manifestations ranging from stable angina to acute coronary syndromes. Although mortality from cardiovascular disease has declined in many developed countries during the last three decades, the absolute number of patients living with CAD continues to increase because of population ageing, improved survival following myocardial infarction, and the growing prevalence of cardiovascular risk

factors such as diabetes mellitus, obesity, hypertension, dyslipidaemia, and smoking (Virani et al., 2021; Knuuti et al., 2020; Timmis et al. 2022).

The epidemiological burden of CAD extends beyond mortality. Patients frequently require repeated hospitalizations, long-term pharmacological therapy, outpatient monitoring, and invasive procedures, all of which substantially increase healthcare expenditure. Recent estimates indicate that cardiovascular diseases account for one of the largest proportions of healthcare spending worldwide, with coronary artery disease representing the largest contributor among cardiovascular conditions (Timmis et al., 2022). The increasing prevalence of multimorbidity further amplifies this burden, as many patients undergoing coronary revascularization also suffer from chronic kidney disease, diabetes mellitus, heart failure, or peripheral arterial disease, conditions associated with worse clinical outcomes and greater healthcare resource utilization.

The burden of CAD is particularly important in Europe, where cardiovascular diseases remain responsible for millions of deaths annually and consume a considerable proportion of national healthcare budgets (Timmis et al., 2022). Beyond direct medical costs, CAD generates substantial indirect costs through productivity losses, disability, early retirement, and reduced quality of life. Consequently, modern cardiovascular care increasingly emphasizes not only improvements in survival but also optimization of healthcare efficiency and resource allocation.

Within this context, the concept of value-based cardiovascular care has gained increasing attention during the last decade. Healthcare systems are expected to maximize patient outcomes while simultaneously minimizing unnecessary healthcare expenditure. This transition has significantly increased interest in evaluating the economic consequences of invasive cardiovascular procedures, particularly percutaneous coronary intervention (PCI), which has become one of the most frequently performed invasive procedures worldwide.

2.2 Evolution of Percutaneous Coronary Intervention

Since its introduction by Andreas Grüntzig in 1977, PCI has revolutionized the management of coronary artery disease (Grüntzig et al. 1978). Initially performed using plain balloon angioplasty, PCI substantially improved myocardial perfusion but was limited by high rates of acute vessel closure and restenosis. The subsequent introduction of bare-metal stents represented a major technological advancement by reducing elastic recoil and improving

procedural success (Serruys et al., 1994). Nevertheless, neointimal hyperplasia resulted in restenosis rates approaching 20–30%, frequently necessitating repeat revascularization.

The development of first-generation drug-eluting stents (DES) dramatically reduced restenosis by inhibiting neointimal proliferation through local antiproliferative drug delivery (Stone et al., 2004). Continuous improvements in stent architecture, thinner struts, more biocompatible polymers, and newer antiproliferative agents have progressively enhanced long-term outcomes while reducing both restenosis and stent thrombosis (Moses et al. 2003; Byrne et al. 2015). Contemporary second- and third-generation DES now represent the standard of care according to current European and American clinical practice guidelines (Lawton et al., 2022, Neumann et al., 2019).

Simultaneously, PCI has evolved from a relatively straightforward procedure toward increasingly complex interventions involving chronic total occlusions, bifurcation lesions, heavily calcified vessels, multivessel disease, and left main coronary artery disease. These developments have been facilitated by intravascular imaging modalities such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), as well as physiological assessment techniques including fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR). Such technologies improve lesion characterization, optimize stent deployment, and contribute to better long-term clinical outcomes (Mintz et al., 2001; Kang et al., 2015; Ali et al., 2016; Tonino et al., 2009; Davies et al., 2017; Lin et al., 2024).

More recently, artificial intelligence and machine learning have begun influencing PCI planning and procedural decision-making. Predictive algorithms increasingly support clinicians by estimating procedural risk, identifying high-risk lesions, and predicting long-term adverse cardiovascular outcomes. These innovations are expected to improve personalized treatment strategies while potentially reducing healthcare costs through more efficient patient selection and procedural optimization.

2.3 Repeat Percutaneous Coronary Intervention

Despite remarkable technological progress, repeat coronary revascularization continues to represent one of the major challenges in contemporary interventional cardiology (Buccheri et al., 2016). Repeat PCI refers to a subsequent percutaneous coronary intervention performed following a previous coronary revascularization procedure. Although the

incidence of restenosis has substantially declined with contemporary DES, repeat interventions remain relatively common because of multiple mechanisms including disease progression, neoatherosclerosis, stent thrombosis, incomplete revascularization, and the development of new coronary lesions.

Current evidence indicates that repeat revascularization should not be viewed solely as a procedural failure (Alfonso et al., 2014). Instead, it reflects the chronic progressive nature of atherosclerosis and the cumulative effect of patient-related risk factors. Consequently, modern research has shifted its focus from purely procedural determinants toward comprehensive patient risk stratification (Cassese et al., 2014; Cutlip et al. 2007).

Recent systematic reviews have demonstrated that prediction models for in-stent restenosis and repeat PCI generally achieve acceptable discriminatory performance, although many published models remain limited by small sample sizes, inadequate external validation, and substantial methodological heterogeneity. These limitations highlight the continuing need for large, real-world observational studies capable of integrating demographic, clinical, procedural, and economic variables within a single analytical framework.

2.4 Clinical Predictors of Repeat Percutaneous Coronary Intervention

Repeat PCI is a multifactorial clinical outcome resulting from the interaction between patient-related characteristics, lesion complexity, procedural factors, pharmacological treatment, and the natural progression of coronary atherosclerosis (Casses et al., 2014). Contemporary evidence suggests that the need for repeat coronary revascularization cannot be attributed to a single determinant but rather to the cumulative effect of multiple biological and clinical processes. Consequently, recent research has shifted from investigating isolated predictors toward the development of multivariable risk prediction models capable of identifying patients at increased risk of recurrent coronary intervention.

Age

Age has traditionally been considered an important determinant of cardiovascular prognosis. However, its relationship with repeat PCI is not straightforward (Cassese et al., 2014). Older patients generally present with more diffuse coronary artery disease and multiple comorbidities, yet younger patients often undergo repeat revascularization because they survive longer after the index procedure and therefore remain exposed to progressive

atherosclerosis for a longer period. Several observational studies have reported that younger age may paradoxically be associated with higher repeat PCI rates, reflecting a more aggressive form of coronary disease rather than protection from adverse outcomes. This observation is particularly relevant to the interpretation of the present study, in which patients requiring repeat intervention were younger than those undergoing their first PCI.

Sex

Sex-related differences in PCI outcomes remain controversial (Cassese et al., 2014). Women generally present at older ages, often with more atypical symptoms and smaller coronary vessel diameters, whereas men usually experience coronary artery disease earlier in life and undergo PCI more frequently. Although male sex has been associated with increased repeat revascularization in several registries, other studies have failed to demonstrate an independent association after adjustment for cardiovascular risk factors and lesion complexity. Consequently, sex is increasingly viewed as a surrogate marker reflecting differences in disease presentation rather than an independent causal predictor.

Diabetes Mellitus

Among all cardiovascular risk factors, diabetes mellitus represents one of the strongest and most consistently reported predictors of repeat coronary intervention (Kosiborod et al., 2005). Hyperglycaemia promotes endothelial dysfunction, chronic inflammation, oxidative stress, vascular smooth muscle proliferation, and accelerated atherosclerosis (Beckman et al., 2002). These mechanisms increase both restenosis and progression of disease in untreated coronary segments.

Diabetic patients typically exhibit diffuse multivessel disease, smaller coronary arteries, and more complex lesions requiring longer stents and multiple devices (Banning et al., 2010). Consequently, they experience higher rates of target lesion failure, target vessel revascularization, and repeat PCI than non-diabetic patients. Even with contemporary drug-eluting stents, diabetes remains an independent predictor of adverse long-term outcomes following PCI.

Hypertension

Hypertension contributes substantially to endothelial injury and progression of coronary atherosclerosis (Yusuf et al., 2004). Nevertheless, evidence regarding its independent association with repeat PCI remains inconsistent. Several studies report significant associations in univariate analyses, whereas hypertension frequently loses statistical significance after multivariable adjustment because of its strong correlation with age,

diabetes, obesity, and chronic kidney disease. Therefore, hypertension is currently regarded as an important background cardiovascular risk factor rather than a consistently independent determinant of repeat coronary intervention.

Dyslipidaemia

Elevated low-density lipoprotein cholesterol (LDL-C) plays a central role in plaque formation and progression of coronary artery disease (Ference et al., 2004). Although intensive lipid-lowering therapy has substantially reduced recurrent cardiovascular events, inadequate lipid control remains associated with higher rates of repeat revascularization. Contemporary evidence emphasizes that residual inflammatory risk persists even after optimal lipid management, explaining why recurrent coronary events continue to occur despite widespread statin use.

Smoking

Smoking remains one of the most modifiable predictors of recurrent coronary disease (Ambrose et al., 2004). Tobacco exposure accelerates endothelial dysfunction, platelet activation, thrombosis, inflammation, and oxidative stress while simultaneously impairing vascular healing following stent implantation. Smokers demonstrate higher rates of restenosis, recurrent myocardial infarction, and repeat coronary intervention compared with non-smokers. Importantly, smoking cessation following PCI has been associated with substantial reductions in long-term cardiovascular events, highlighting the importance of secondary prevention programmes.

Chronic Kidney Disease

Chronic kidney disease (CKD) has emerged as one of the strongest predictors of adverse PCI outcomes (Go et al., 2004). Patients with impaired renal function typically present with diffuse coronary calcification, accelerated vascular ageing, systemic inflammation, and impaired endothelial repair mechanisms. These pathophysiological changes substantially increase procedural complexity and predispose patients to recurrent coronary interventions (Ndrepepa et al., 2024). CKD also increases hospitalization costs because of longer hospital stays, higher complication rates, and increased need for post-procedural monitoring.

Lesion Complexity

Beyond patient-related characteristics, anatomical lesion complexity plays a crucial role in determining long-term PCI outcomes (Farooq et al., 2013). Multivessel coronary artery disease, bifurcation lesions, chronic total occlusions, severe calcification, long lesions, and left main disease have all been associated with increased repeat revascularization rates

(Serruys et al., 2009). Lesion complexity frequently requires multiple stents, prolonged procedural times, greater use of intravascular imaging, and more expensive consumable materials, thereby increasing both procedural risk and hospital expenditure.

Procedural Characteristics

Several procedural factors have also been linked with repeat PCI. Inadequate stent expansion, incomplete lesion coverage, residual stenosis, stent underexpansion, and geographic miss remain important mechanisms leading to target lesion failure. The widespread implementation of IVUS and OCT has significantly reduced these technical failures by improving stent optimization and procedural precision (Mintz et al., 2001; Kang et al., 2015; Ali et al., 2016).

More recently, physiological lesion assessment using FFR and iFR has further improved patient selection by avoiding unnecessary stent implantation and reducing future repeat procedures (Tonino et al., 2009; Davies et al., 2017; Lin et al., 2024).

Multivariable Risk Prediction

During the last decade, cardiovascular research has increasingly focused on comprehensive multivariable prediction models rather than isolated predictors. Logistic regression remains the most commonly employed analytical technique because of its ability to estimate adjusted odds ratios while simultaneously controlling for confounding variables. Recent studies have additionally explored machine learning algorithms, including random forests, gradient boosting, neural networks, and explainable artificial intelligence models, aiming to improve individualized risk prediction after PCI (Johnson et al., 2018; Krittanawong et al. 2019). Although many machine learning models demonstrate excellent predictive performance, their integration into routine clinical practice remains limited by issues of external validation, interpretability, and implementation.

2.5 Economic Burden of Repeat Percutaneous Coronary Intervention

The economic burden associated with CAD extends far beyond the costs of the initial hospitalization. Although advances in interventional cardiology have substantially improved procedural success and reduced short-term complications, repeat PCI continues to represent an important driver of healthcare expenditure worldwide (Luengo-Fernandez et al., 2023; Leal et al., 2006). Recurrent hospitalizations, repeated invasive procedures,

prolonged pharmacological treatment, outpatient follow-up, and management of complications collectively generate considerable direct medical costs while simultaneously increasing indirect societal costs through productivity loss, disability, and reduced quality of life (Cohen et al., 2004; Greenberg et al., 2004; Fearon et al., 2013; Magnuson et al., 2013; Osnabrugge et al., 2015; Bagust et al., 2006; Kaiser et al., 2005; Jacobson et al., 2007; Clark et al., 2004).

Economic evaluations have consistently demonstrated that cardiovascular disease accounts for one of the largest components of healthcare expenditure in developed countries (Luengo-Fernandez et al., 2023; Leal et al., 2006). Within this context, coronary revascularization procedures represent a major contributor because they require highly specialized personnel, technologically advanced catheterization laboratories, expensive medical devices, and intensive post-procedural monitoring (Cowper et al., 2000). Consequently, even modest reductions in repeat PCI rates may translate into substantial savings for healthcare systems. Unlike the initial PCI procedure, repeat interventions frequently involve considerably greater procedural complexity. Patients requiring reintervention often present with diffuse coronary artery disease, multivessel involvement, chronic total occlusions, severe coronary calcification, or previous multiple stent implantations. These characteristics frequently prolong procedure duration, increase fluoroscopy time, require additional guidewires, balloons, drug-eluting stents, intravascular imaging devices, and adjunctive pharmacological therapy, thereby substantially increasing hospital expenditure.

From the provider's perspective, repeat PCI is associated with greater consumption of hospital resources. Additional catheterization laboratory time, increased utilization of disposable materials, longer inpatient stays, more frequent laboratory investigations, repeated imaging examinations, and greater pharmaceutical consumption all contribute to higher procedural costs. Furthermore, patients undergoing repeat interventions are generally older, present with greater comorbidity burden, and exhibit higher complication rates, factors that further increase resource utilization.

From the payer's perspective, healthcare expenditure extends beyond the hospitalization episode itself. National reimbursement systems must finance outpatient medication, cardiac rehabilitation, repeated specialist consultations, emergency department visits, diagnostic investigations, and treatment of future cardiovascular events. Consequently, the true economic burden of repeat PCI cannot be adequately captured by procedural costs alone but requires evaluation across the entire continuum of cardiovascular care.

This distinction has become increasingly important in health economic research. Contemporary economic evaluations therefore recommend adopting multiple analytical perspectives, including the hospital provider perspective, the healthcare payer perspective, and the broader societal perspective. Each perspective captures different cost components and therefore addresses different policy questions. Hospital administrators are primarily interested in procedural resource utilization, whereas national healthcare systems seek to estimate total expenditure associated with cardiovascular disease management.

Another important concept emerging from recent literature is that of cost drivers**.** Rather than considering total hospitalization cost as a single outcome, recent investigations increasingly attempt to identify which individual components contribute most substantially to overall expenditure. These cost drivers commonly include stent implantation, intracoronary imaging, pharmacological agents, intensive care utilization, prolonged hospitalization, management of peri-procedural complications, and readmissions. Understanding the relative contribution of each component allows healthcare organizations to identify opportunities for improving efficiency without compromising clinical quality.

Several studies have demonstrated that procedural materials account for the largest proportion of PCI-related expenditure. DES, guide catheters, balloons, IVUS, OCT, atherectomy devices, and thrombectomy systems represent high-cost technologies whose utilization varies according to lesion complexity. Consequently, patients undergoing repeat PCI frequently generate disproportionately higher procedural costs compared with those receiving their first intervention.

Hospital length of stay (LOS) represents another important determinant of economic burden. Although contemporary PCI increasingly allows same-day discharge for selected low-risk patients, repeat interventions often require prolonged hospitalization because of greater procedural complexity, advanced age, multiple comorbidities, renal dysfunction, or post-procedural complications. Numerous economic analyses have consistently identified LOS as one of the strongest independent predictors of total hospitalization cost.

Pharmaceutical expenditure also contributes substantially to the economic burden of repeat coronary intervention. Beyond procedural anticoagulation and antiplatelet therapy, patients frequently require prolonged dual antiplatelet treatment, intensive lipid-lowering therapy, antihypertensive medication, diabetes management, and secondary prevention strategies. These long-term treatment requirements extend healthcare expenditure well beyond the

index hospitalization and highlight the importance of considering lifetime costs rather than isolated procedural expenses.

Importantly, the economic consequences of repeat PCI are not limited to healthcare providers. Society incurs additional indirect costs arising from temporary work disability, reduced productivity, caregiver burden, premature retirement, and diminished quality of life. Although these costs are often excluded from hospital-based economic evaluations because of limited data availability, they may equal or even exceed direct medical costs in younger working populations.

Recent health economic literature has increasingly emphasized value-based healthcare, a concept advocating optimization of patient outcomes relative to healthcare expenditure (Weintraub et al., 2017). Within this framework, repeat PCI represents an important quality indicator because successful prevention of recurrent coronary intervention simultaneously improves patient prognosis and reduces healthcare costs. Consequently, identifying patients at increased risk of repeat PCI has both clinical and economic importance.

Despite considerable progress in understanding the economic burden of repeat coronary intervention, several important limitations remain within the existing literature. First, most available evidence originates from North American healthcare systems, whose reimbursement mechanisms differ substantially from those operating in Europe. Second, many studies estimate costs using administrative reimbursement data rather than actual hospital accounting records, potentially underestimating true resource utilization. Third, relatively few investigations combine detailed economic evaluation with multivariable clinical risk prediction within the same analytical framework.

These limitations are particularly relevant for Greece, where published evidence regarding the financial consequences of repeat PCI remains scarce. Differences in Diagnosis Related Group (DRG) reimbursement mechanisms, hospital financing, healthcare organization, and resource allocation make direct extrapolation of international findings problematic. Consequently, country-specific analyses are required to accurately estimate the economic impact of repeat coronary intervention and support evidence-based healthcare planning.

The present study directly addresses this gap by integrating clinical and financial data obtained from a high-volume tertiary cardiac centre in Greece. Unlike many previous investigations, the study evaluates hospital costs from two complementary perspectives, thereby providing a more comprehensive estimation of the economic burden associated with repeat PCI. This dual-perspective approach contributes novel evidence to the existing

literature and may assist clinicians, hospital administrators, and policymakers in optimizing cardiovascular resource allocation while improving long-term patient outcomes.

2.6 Methodological Approaches Used in Previous Studies

The investigation of repeat PCI has evolved considerably during the last two decades, not only regarding clinical knowledge but also with respect to methodological approaches (Cutlip et al., 2007). Improvements in data availability, electronic medical records, national cardiovascular registries, and hospital administrative databases have enabled researchers to employ increasingly sophisticated epidemiological and statistical techniques for evaluating clinical outcomes and healthcare costs (Brennan et all., 2013). Consequently, contemporary research combines traditional biostatistical methods with advanced econometric and machine-learning techniques to better understand predictors of repeat revascularization and its associated economic burden.

Retrospective Observational Cohort Studies

The overwhelming majority of published studies investigating repeat PCI have adopted retrospective observational cohort designs (Wall et al., 2017; Hannan et al., 2013). This methodological approach allows investigators to evaluate large populations using routinely collected clinical and administrative data without influencing patient management or exposing participants to additional clinical risks.

Retrospective cohort studies offer several important advantages. They are relatively inexpensive, allow inclusion of thousands of patients, accurately reflect routine clinical practice, and provide high external validity because patients are not selected according to strict randomized trial eligibility criteria. Particularly in health economic research, retrospective analyses are considered highly appropriate because they evaluate actual resource utilization rather than hypothetical estimates.

Nevertheless, retrospective studies also possess important limitations. Selection bias, residual confounding, missing data, and heterogeneous documentation practices may influence observed associations. Consequently, careful statistical adjustment is required to minimize these biases and improve the validity of estimated effects.

The present study follows this internationally accepted methodological framework by analysing consecutive PCI procedures performed within a tertiary cardiac centre using routinely collected clinical and financial information.

Hospital Registries and Administrative Databases

Large cardiovascular registries have become fundamental sources of evidence regarding PCI outcomes (James et al., 2009; Yeh et al., 2016; Austin et al., 2011). National registries such as the National Cardiovascular Data Registry (NCDR), the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), and other European multicentre databases have enabled investigators to evaluate hundreds of thousands of procedures over prolonged follow-up periods.

Administrative hospital databases offer additional advantages because they contain detailed information regarding admissions, DRGs, hospital reimbursement, pharmaceutical expenditure, procedural materials, and length of hospital stay. Such databases are particularly valuable for economic evaluation because they permit estimation of actual healthcare costs rather than relying exclusively on reimbursement tariffs.

However, registry-based research frequently lacks detailed angiographic characteristics, laboratory measurements, or patient-reported outcomes. Therefore, combining electronic medical records with financial databases—as undertaken in the present study—represents a particularly robust methodological approach that captures both clinical and economic dimensions of patient care.

Descriptive Statistical Methods

Descriptive statistics constitute the first stage of nearly every investigation examining repeat PCI. Continuous variables are summarized using means with standard deviations when normally distributed or medians with interquartile ranges (IQR) when skewed. Because healthcare cost data rarely follow a normal distribution, medians are generally preferred as measures of central tendency.

Categorical variables are typically presented as frequencies and percentages. Baseline comparisons between patients undergoing first-time PCI and repeat PCI allow investigators to identify differences in demographic characteristics, cardiovascular risk factors, and clinical presentation before multivariable modelling.

The statistical approach employed in the present dissertation follows these recommendations by presenting continuous variables using both medians (IQR) and means (standard deviations), thereby facilitating comparison with previous investigations.

Comparative Statistical Analysis

Comparison between independent patient groups represents one of the most common objectives of PCI research. Selection of the appropriate statistical test depends primarily on the distribution of continuous variables.

Because healthcare expenditure usually demonstrates considerable positive skewness, most published studies employ non-parametric statistical procedures. The Mann–Whitney U test has therefore become the preferred method for comparing hospitalization costs between independent patient groups when assumptions of normality are violated.

Conversely, normally distributed variables are generally compared using independent-samples t-tests, whereas categorical variables are analysed using Pearson's Chi-square test or Fisher's exact test when expected frequencies are small.

The methodological choices adopted in the present study are therefore fully consistent with contemporary statistical practice reported within the international literature.

Binary Logistic Regression

Binary logistic regression has become the standard analytical technique for identifying independent predictors of repeat PCI because the outcome of interest is inherently dichotomous (repeat intervention versus first intervention) (Hosmer et al., 2013). Unlike univariate analyses, logistic regression simultaneously evaluates multiple explanatory variables while controlling for potential confounding effects.

Most published studies initially estimate crude odds ratios using separate univariate logistic regression models before constructing multivariable models incorporating demographic characteristics, cardiovascular risk factors, angiographic findings, and procedural variables. The results are generally reported as adjusted odds ratios (OR) together with 95% confidence intervals, allowing assessment of both statistical significance and clinical relevance.

The present study adopts precisely this internationally accepted analytical strategy by estimating both crude and adjusted odds ratios, thereby facilitating direct comparison with previously published evidence.

Assessment of Model Performance

Beyond estimating regression coefficients, contemporary methodological standards emphasize evaluation of model quality (Harrell et al., 1996). Three complementary domains are typically examined:

Model Calibration

Calibration refers to the agreement between predicted probabilities and observed outcomes. The Hosmer–Lemeshow goodness-of-fit test remains the most widely employed calibration procedure in cardiovascular prediction models. Non-significant test results indicate satisfactory agreement between observed and predicted event frequencies.

Model Discrimination

Discrimination describes the ability of a prediction model to distinguish between patients who will experience repeat PCI and those who will not. Receiver Operating Characteristic (ROC) curves and the Area Under the Curve (AUC) constitute the standard measures of discriminatory performance.

An AUC above 0.70 generally indicates acceptable discrimination, whereas values exceeding 0.80 suggest excellent predictive performance.

Multicollinearity

Because predictor variables frequently correlate with one another, multicollinearity may produce unstable regression coefficients and misleading interpretations. Variance Inflation Factors (VIF) are therefore routinely examined prior to final model estimation. Values below conventional thresholds indicate that multicollinearity is unlikely to compromise model validity.

The inclusion of Hosmer–Lemeshow statistics, ROC analysis, and VIF assessment in the present dissertation demonstrates adherence to internationally recognized standards for multivariable prediction modelling.

Survival Analysis and Cox Regression

Although binary logistic regression dominates studies focusing on repeat PCI occurrence, investigations evaluating long-term follow-up commonly employ survival analysis techniques. Cox proportional hazards regression allows estimation of hazard ratios while accounting for differences in follow-up duration between patients (Cox, 1972).

Survival analysis is particularly useful when the timing of repeat revascularization represents the primary outcome rather than its simple occurrence. Kaplan–Meier survival curves are frequently presented to illustrate cumulative event-free survival following PCI.

Because the present study focuses on whether patients required repeat intervention rather than the exact timing of recurrence, binary logistic regression constitutes the most appropriate analytical approach.

Propensity Score Matching

Observational studies are inherently susceptible to confounding because treatment allocation is not randomized. To reduce selection bias, many contemporary investigations employ propensity score matching or inverse probability weighting.

These techniques attempt to create comparable patient groups by balancing observed baseline characteristics before outcome analysis. Although propensity methods cannot eliminate unmeasured confounding, they substantially improve internal validity when randomized controlled trials are impractical.

However, propensity score analyses require detailed covariate information and large sample sizes and are therefore mainly encountered in multicentre registry studies.

2.7 Evolution of Research on Repeat Percutaneous Coronary Intervention (2010–2025)

The scientific understanding of repeat PCI has undergone substantial transformation during the past fifteen years. Although repeat revascularization has always been recognized as an important clinical outcome following PCI, the focus of cardiovascular research has progressively shifted from technological aspects of coronary stenting toward comprehensive patient-centred management integrating clinical outcomes, healthcare economics, and personalized risk prediction.

Early period (2010–2014):

At the beginning of the previous decade, most investigations primarily evaluated the comparative performance of bare-metal stents and first-generation DES (Stone et al., 2010; Palmerini et al., 2013; Navarese et al., 2014). Restenosis represented the principal mechanism responsible for repeat coronary intervention, and research mainly concentrated on improving stent technology through modifications in polymer composition, antiproliferative drug delivery, and stent architecture (Stolker et al., 2012).

Clinical studies conducted during this period consistently demonstrated that first-generation DES significantly reduced angiographic restenosis and target lesion revascularization compared with bare-metal stents. Consequently, technological innovation was widely considered the primary strategy for reducing repeat PCI.

Economic evaluations published during this period largely focused on comparing the acquisition costs of different stent platforms with the anticipated savings resulting from

lower repeat revascularization rates. Cost-effectiveness analyses frequently concluded that the higher initial cost of drug-eluting stents was justified by reductions in future hospitalizations and repeat procedures.

Despite these advances, investigators increasingly recognized that improvements in stent technology alone could not eliminate recurrent coronary events because disease progression frequently occurred outside previously treated coronary segments.

Intermediate Period (2015–2019):

Following the widespread implementation of second-generation drug-eluting stents, the incidence of restenosis declined considerably (Bangalore et al., 2018; Elgendy et al., 2017). Consequently, the scientific focus gradually shifted from device performance toward patient-related determinants of recurrent coronary disease (Koskinas et al., 2016).

Research increasingly emphasized the role of diabetes mellitus, chronic kidney disease, smoking, obesity, chronic inflammation, multivessel disease, and complex coronary anatomy as major predictors of repeat coronary intervention. During this period, investigators acknowledged that repeat PCI reflects not only procedural success but also the chronic progressive nature of atherosclerosis.

Large observational registries and multicentre cohort studies became increasingly common, allowing researchers to evaluate outcomes in real-world populations rather than highly selected randomized clinical trial participants. These studies demonstrated that clinical outcomes observed under routine practice conditions often differed from those reported in randomized trials because of greater patient complexity and comorbidity burden.

Economic research also evolved substantially during this period. Rather than comparing individual devices, investigators increasingly analysed healthcare resource utilization, hospital efficiency, readmission rates, and long-term healthcare expenditure associated with recurrent coronary interventions.

Contemporary period (2020–2025):

The last five years have witnessed another major transformation in cardiovascular research (Khera et al., 2021). Contemporary investigations increasingly integrate clinical cardiology, epidemiology, health economics, artificial intelligence, and implementation science into a unified research framework.

Rather than focusing solely on procedural outcomes, current studies aim to identify patients at highest risk of recurrent coronary intervention using multivariable prediction models

incorporating demographic characteristics, laboratory findings, angiographic complexity, procedural variables, and socioeconomic factors (Condello et al., 2023).

Machine learning algorithms have recently emerged as promising tools for individualized cardiovascular risk prediction. Random forests, gradient boosting, neural networks, and explainable artificial intelligence have demonstrated encouraging predictive performance in identifying patients likely to require repeat PCI. Nevertheless, widespread clinical implementation remains limited because many published models lack external validation and prospective evaluation.

Simultaneously, increasing healthcare expenditure associated with ageing populations has substantially strengthened interest in economic evaluation (Lawton et al., 2022). Contemporary health policy emphasizes value-based healthcare, requiring optimization of patient outcomes while ensuring efficient resource allocation. Consequently, recent publications increasingly examine repeat PCI not only as a clinical endpoint but also as an indicator of healthcare quality, efficiency, and sustainability.

Hospital administrators and policymakers now require evidence regarding the financial implications of repeat coronary intervention to optimize reimbursement systems, allocate limited healthcare resources, and improve long-term cardiovascular care.

2.8 Identification of the Research Gap

The literature reviewed above demonstrates that repeat PCI remains a major clinical and economic challenge despite substantial technological advances in interventional cardiology. Nevertheless, several important knowledge gaps continue to limit current evidence.

Most previous investigations have concentrated either on clinical outcomes or on economic evaluation, with relatively few studies integrating both dimensions within the same analytical framework. Consequently, limited evidence exists regarding the relationship between patient characteristics, repeat coronary intervention, and detailed hospital expenditure.

Furthermore, the overwhelming majority of economic evaluations originate from the United States or Northern Europe. Published evidence from Greece remains scarce despite important differences in healthcare financing, hospital reimbursement mechanisms, and organization of cardiovascular services. International findings therefore cannot be directly extrapolated to the Greek healthcare system without locally generated evidence.

An additional limitation concerns the analytical methods adopted in previous investigations. Although many studies identify clinical predictors of repeat PCI, fewer evaluate model performance comprehensively through calibration, discrimination, and assessment of multicollinearity. Similarly, relatively few investigations integrate detailed financial information with multivariable clinical prediction models.

The present dissertation addresses these limitations by combining clinical, procedural, and hospital financial data obtained from a high-volume tertiary cardiac centre in Greece. Using multivariable logistic regression, the study identifies independent predictors of repeat PCI while simultaneously quantifying the associated economic burden from complementary healthcare perspectives.

Consequently, the present research contributes to the existing literature in three important ways:

1. **Clinical contribution:** identification of independent predictors of repeat PCI in a real-world Greek population.
2. **Methodological contribution:** integration of robust multivariable statistical modelling with comprehensive model validation.
3. **Economic contribution:** estimation of the hospital financial burden associated with repeat PCI using detailed cost data rather than reimbursement estimates alone. These contributions provide evidence that may support clinicians in identifying high-risk patients, assist hospital administrators in optimizing resource utilization, and inform policymakers responsible for planning sustainable cardiovascular healthcare services.

3. Methodology

This chapter outlines the methodological framework which has been adopted in the current investigation, including the purpose and research questions which will guide the work, the design rationale, the sampling strategy, the data sources on which the information will be extracted, and the statistical techniques to be employed in the analysis. The last section deals with issues of research ethics.

3.1 Purpose and Research Questions

The overall aim of the study was to measure the economic burden of repeat PCI that is, PCI performed in patients who had already received a coronary stent, and to compare it with that of patients who did not have previously received a coronary stent. A secondary purpose was to determine demographic and clinical factors, which may be associated with increased risk for reintervention, with a view to inform future risk-stratification decisions. The conception of the work was in the wider context of an observation, which has been repeatedly noted in the international literature, that approximately 10% of all PCI procedures are repeat procedures on patients who had had a previous stent and that these procedures are very wasteful of healthcare resources the magnitude of which has not been precisely defined in the Greek setting.

This purpose was operationalized in three particular research questions:

Q1. Does the total in-hospital cost of a PCI procedure differ between patients who have previously received a coronary stent and those who have not, when cost is measured both as the sum of the Diagnosis-related group (DRG)-based reimbursement amount plus out-of-hospital cost components (Total Cost M) and as the sum of inpatient materials and inpatient pharmaceutical expenditure (Total Cost N)?

Q2. Which demographic characteristics (age, sex) and classic cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking) are independently associated with increased risk for repeat revascularization, i.e. belonging in the previous-stent group, after mutual adjustment?

Q3. What is the magnitude and dispersion of each of the individual cost components contributing to the two cost summaries, and where in the cost structure does any between-group difference originate?

The a priori formulated directional hypothesis was the hypothesis that prior stenting would be related to a higher in-hospital cost, or an indication of more complex procedures when re-intervention was the case. The test of hypothesis was done separately on each of the two definitions of cost, to enable the analysis to capture potentially divergent signals between the standardized reimbursement system and the actual inpatient resource use.

3.2 Research Methodology

The methodological approach followed was a quantitative one, based on the assumption that the research questions involve objectively measurable economic and clinical quantities, that the results can be given in numerical terms, and that the objective of the analysis is to test a directional hypothesis through the use of inferential statistical methods (Creswell and Creswell, 2018). The qualitative or mixed-methods design would have been inappropriate to the nature of the data and the type of inference that was needed.

The quantitative paradigm of this study assumed retrospective observational cohort study with a comparative structure in two groups. They were extracted ex post facto from clinical and financial records which had been generated in the normal course of patient care, and patients were put into two mutually exclusive groups depending on whether they had a coronary stent placed during a prior episode of patient care or not. The methodological standard of studies of resource use and cost in healthcare is the retrospective design, since it allows the inclusion of large unselected samples representative of routine clinical practice, avoids the selection biases that might affect prospective enrolment, and eliminates the ethical concerns that may arise with randomization in the context of cost-comparison (Drummond et al., 2015).

The study adhered to principles outlined in the STROBE Statement of how observational studies should be reported (von Elm et al., 2007). Specifically, operational definitions of all variables, eligibility criteria to be part of the source population, time window of inclusion, and the method of analysis were defined before data extraction and were reported in detail in the present chapter.

3.3 Sample and Sampling Method

The research was undertaken in a tertiary, high- PCI-volume cardiac centre in Greece. The source population consisted of all consecutive adult patients undergoing a PCI at the participating centre during the period 3 March 2024 to 6 April 2026, a time window of about twenty-five months that was chosen to provide a sample large enough to identify clinically meaningful differences in cost without pushing the limits of data extraction outside feasibility constraints.

A consecutive (also called census) sampling design was employed: all PCI episodes occurring during the period of eligibility were enrolled in the study, and no random

subsampling. Instead of probability sampling, consecutive sampling was used due to its ability to minimize selection bias in administrative data and generate a sample that is representative of the natural case mix of the participating centre at the time of observation (Field, 2018).

Inclusion mandated a recorded PCI procedure within the eligibility window (ii) complete clinical and financial information on the cost categories of interest (iii) demographic and risk-factor data. Any case with missing cost or demographic information would have been excluded; in fact, there was no eligible case that was excluded due to missing data.

The final analytic sample consisted of 1,736 PCI episodes of which 312 (18.0%) belonged to the reintervention group (patients with a previous stent) and 1,424 (82.0%) compared to the comparison group (patients without a previous stent). The disproportionality of the two groups is the reflection of the natural occurrence of cases of reintervention within the source population. The obtained sample size is large enough to consider the achievement of the conventional rule-of-thumb minimum of ten events per predictor variable to be able to estimate multivariable logistic regression models with a great degree of stability (Hosmer et al., 2013), and sufficient power to detect moderate between-group differences in cost.

3.4 Research Instrument

The current research did not use a questionnaire-based or interview-based tool since the research questions addressed objective economic and clinical measures which are captured in the electronic information systems of the participating centre, as opposed to de novo data collection of the study participants.

Two data sources that are complementary were employed. Electronic Medical Records (EMR) of the centre were used to extract clinical and demographic data, and the respective accounting and reimbursement records were used to extract economic data. The two sources were combined at the level of the individual hospitalization episode using the case-record identifier, all identifying information was then removed before analysis.

Table 1 shows the variables abstracted in each PCI episode. They were classified into four groups, namely demographic information (age, sex), classic cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking), hospitalization parameters (admission, discharge date, length of stay (LOS), DRG code and description) and economic data (the six individual components of costs and the two derived cost summaries).

Variable	Type	Operational definition
Group (PreviousStent)	Binary (0/1)	1 if any prior coronary stent at the index PCI; 0 otherwise
Sex	Binary (1/2)	1 = male; 2 = female
Age	Continuous	Age in years at the time of admission
Hypertension	Binary (0/1)	1 = present; 0 = absent / not documented
Diabetes mellitus	Binary (0/1)	1 = present; 0 = absent / not documented
Dyslipidaemia	Binary (0/1)	1 = present; 0 = absent / not documented
Smoking	Binary (0/1)	1 = current smoker; 0 = absent / not documented
Length of stay (LOS)	Continuous	Duration of hospitalization in days
DRG / DRG description	Categorical	Diagnosis-related group code and label
Reimbursement	Continuous (€)	DRG-based reimbursement amount
Inpatient materials	Continuous (€)	In-hospital materials cost
Inpatient drugs	Continuous (€)	In-hospital drug expenditure
Out-of-hospital drugs	Continuous (€)	Pharmaceutical cost outside the inpatient stay
Out-of-hospital ETIP	Continuous (€)	Out-of-hospital ETIP-coded cost
Out-of-hospital materials	Continuous (€)	Materials cost outside the inpatient stay
Total Cost M	Continuous (€)	Reimbursement + Out-of-hospital drugs + ETIP + Materials
Total Cost N	Continuous (€)	Inpatient materials + Inpatient drugs

Table 1. *Variables abstracted from the electronic clinical and financial records of the participating centre.*

The analysis of the variables in the form of two summary cost variables was obtained. The total cost M was defined as the amount of the DRG-based reimbursement amount plus the three out-of-hospital cost components (out-of-hospital drugs, ETIP and materials) and was thus intended to reflect the cost in the perspective of the third-party payer. Total Cost N was defined as the amount of inpatient materials and inpatient drug spending and was thus expected to capture cost on the side of the providing institution. The dual definition is based

on the principle that the concept of relevant cost depends on the perspective (analytical perspective) adopted, and that economic assessments must report results of more than one perspective when the perspectives may differ (Drummond et al., 2015).

3.5 Data Collection and Analysis

There were two phases of data extraction. The clinical case-record system in the centre provided a list of all the PCI hospitalization episodes within the eligibility window in the first stage. The second step involved retrieving and compiling the demographic, clinical and economic data concerning each of the identified episodes into a single operative dataset. The internal hospital case-record identifier was used to exchange data between the clinical and financial systems before the analysis and was later replaced with an anonymized study identifier.

The four binary cardiovascular risk factors were initially captured in the original datasheets as present (codes 1) or blank (no entry). To conduct the analysis, empty entries were operationalized as the lack of the respective factor and coded with 0. This convention is explicitly documented because it influences the interpretation of the prevalence estimates: under-documentation of risk factors in the source system would under this convention lead to underestimation of true prevalence and would, under this convention, attenuate any association between a risk factor and reintervention status.

All the statistical analysis was conducted using IBM SPSS Statistics (IBM Corp., 2023). The continuous variables were summarized using the median and interquartile range (IQR) since the distribution of all cost variables was found to depart significantly, on the Shapiro-Wilk test (Shapiro & Wilk, 1965); means with standard deviations were also reported since this is complete. Categorical variables were summarized in terms of counts and percentages. Between-group comparisons of continuous variables were performed using the Mann-Whitney U test, the appropriate non-parametric procedure for comparing two independent groups when the assumption of normality is not tenable (Mann & Whitney, 1947). The corresponding effect size was computed as $r = |Z| / \sqrt{N}$ and interpreted according to Cohen's (1988) conventional thresholds ($r \approx 0.10$ small, $r \approx 0.30$ medium, $r \approx 0.50$ large). For categorical variables, between-group comparisons were performed using Pearson's chi-square test, with Fisher's exact test reported as a secondary check. As a sensitivity analysis for the cost comparisons, an independent-samples t-test was also fitted to the natural-

logarithm-transformed cost values, in order to verify that the conclusions did not depend on the choice of inferential test (Field, 2018).

Two complementary regression analyses were performed to determine the relationship between candidate predictors and previous-stent group membership. Crude (unadjusted) odds ratios were first determined separately in a univariate binary logistic regression, with the 95 percent confidence interval (CI). A multivariate binary logistic regression model (ENTER method) was then used to concurrently enter into the model the complete set of candidate predictors, yielding the adjusted odds ratio of each variable, conditional on all the rest (Hosmer et al., 2013). The adequacy of models was measured by the omnibus likelihood-ratio test, the Cox and Snell and Nagelkerke pseudo-R^2 coefficients, and the Hosmer-Lemeshow goodness-of-fit test (Hosmer and Lemeshow, 1980). The multivariate model was tested by the area under the receiver operating characteristic (ROC) curve as a measure of the discriminative power of the model. Variance inflation factors (VIF) were also checked to eliminate problematic multicollinearity with a value of more than 5 being the traditional level of concern.

All inferential tests were two sided and a probability value of less than 0.05 was considered to indicate statistical significance throughout. In all cases where possible, the results of the analysis are reported in the form of effect size and CI instead of p-values alone, to avoid the famous pitfall when any large sample size turns any small difference into a statistically significant value (Field, 2018).

3.6 Ethical Considerations

The research was carried out in compliance with the ethical principles of medical research that involves human subjects as provided in the Declaration of Helsinki (World Medical Association, 2013). Though the retrospective and non-interventional nature of the work meant that no clinical risk was exposed to the participants over and above the risk that they would encounter under normal care, the principles of beneficence, non-maleficence and respect of autonomy were observed throughout the design, conduct and reporting of the study.

The key ethical issue was that of patient confidentiality. The information systems of the participating centre were accessed by a member of the personnel who was authorized to access such records as a normal part of their daily duties. Direct identifiers, such as names,

dates of birth, residential addresses and an original hospital case-record identifier, were then removed before building the analytic dataset, and were replaced by an anonymized study identifier, so that no particular patient could be re-identified out of the working dataset. The processing of personal data was in compliance with the provisions of Regulation (EU) 2016/679 on the protection of natural persons in as far as the processing of personal data is concerned (the General Data Protection Regulation; European Parliament and Council, 2016) and the corresponding Greek implementing law.

Since the study was retrospective, involving only routinely collected and fully anonymized data, and no direct contact with patients was involved or any intervention, the need to obtain individual informed consent was waived in line with the practice established concerning the use of this type of research.

Lastly, the analytic data, the syntax of all statistical procedures, will be stored in a secure local environment, with the purpose of reproducibility and verification, and will be made available, in fully anonymized form, on reasonable request in accordance with applicable data protection legislation. Regardless of their direction, including the ones that do not support the original a priori hypothesis, the findings of the study are also reported in their entirety, as per the principle of complete and transparent reporting in scientific research.

4. Results

4.1 Sample Description

The final analytic dataset comprised 1,736 consecutive patients undergoing a PCI procedure at the participating tertiary, high-volume PCI centre during the study period. The patients were divided into two mutually exclusive groups based on a previous coronary stent procedure: a reintervention group (patients who had previously received a coronary stent) and a comparison group (patients who had not previously received a coronary stent). Table 2 shows the composition of the sample.

Group	n	Percentage (%)	Cumulative (%)
Without previous stent	1,424	82.0	82.0

Group	n	Percentage (%)	Cumulative (%)
With previous stent	312	18.0	100.0
Total	**1,736**	**100.0**	**-**

Table 2. *Distribution of the study sample by group (N = 1,736).*

As indicated in Table 2, most of the cases (n = 1,424; 82.0%) had not a history of a prior coronary stent implantation whereas 312 patients (18.0%) had undergone a prior stent implantation and were therefore considered reintervention cases. This reintervention rate of 18% is in line with the previously reported rate of about 10% in the international literature, but slightly higher in the present cohort, perhaps because of the referral profile of the participating tertiary centre. The relatively imbalanced sample sizes were expected and considered when choosing the inferential procedures used in the following sections.

4.1.1. Data Collection Period

The retrospective data were obtained using the electronic clinical and financial records of the hospital of all eligible PCI cases performed between 3 March 2024 and 6 April 2026 and provided an observation window of about 25 months. The earliest admission date in the dataset was 3 March 2024 and the latest discharge date was 6 April 2026. The two groups were selected within the same time window: in the comparison group admissions were between 3 March 2024 and 27 March 2026, and in the reintervention group between 4 March 2024 and 29 March 2026, such that any between-group differences in cost or clinical characteristics cannot be due to a different temporal sampling.

4.1.2. Handling of Missing Values

Since the dataset was built literally off of administrative and clinical records, all variables of interest had complete data available. Table 3 summarizes the validity status of every variable which was used in the further analyses.

Variable	Valid (n)	Missing (n)	Missing (%)
Group (PreviousStent)	1,736	0	0.0
Sex	1,736	0	0.0
Age	1,736	0	0.0

Variable	Valid (n)	Missing (n)	Missing (%)
Hypertension	1,736	0	0.0
Diabetes mellitus	1,736	0	0.0
Dyslipidaemia	1,736	0	0.0
Smoking	1,736	0	0.0
Length of stay (LOS)	1,736	0	0.0
Total Cost M	1,736	0	0.0
Total Cost N	1,736	0	0.0

Table 3. *Validity and missingness across analytic variables (N = 1,736).*

As Table 3 indicates, no missing values were identified in any of the variables that were included in the analysis plan, including the demographic information (sex, age). The lack of missingness is directly due to the data abstraction strategy: the four binary risk factors were originally coded as either present (1) or absent (blank cell) in the source datasheets, and absent values were operationalized as "0 = absent" before import. This ruling should be borne in mind when interpreting the prevalence of risk factors that will be reported in the following sections because it does not differentiate between an absent one being documented and an absent one remaining undocumented. There were no imputation procedures involved, and all 1,736 cases were included in all analyses that are presented in the chapters that follow.

4.2 Demographic and Clinical Characteristics

The comparability of the two groups was measured prior to testing the primary hypothesis on cost differences across demographic variables (sex, age) and the four classic cardiovascular risk factors measured in the dataset (arterial hypertension, diabetes mellitus, dyslipidaemia, smoking). Continuous variables were summarized using the median and IQR since the Shapiro-Wilk test rejected the assumption of normality of the age distribution in either group ($W = 0.978$ and $W = 0.957$; $p < 0.001$ in each) and group comparisons were made using the Mann-Whitney U test. The counts and column percentages were used to summarize the categorical variables and compare them using Pearson’s chi-square test. A

p-value of less than 0.05 was deemed statistically significant with a two-sided p-value. Table 4 gives the entire comparison of the baseline.

Characteristic	Without previous stent (n = 1,424)	With previous stent (n = 312)	Test	p-value
Demographics				
Age, years, median (IQR)	57.0 (48.0–69.0)	53.5 (40.8–66.5)	M-W U	< **0.001**
Range (min–max)	*25–84*	*28–79*	-	-
Sex, n (%)			χ^2	**0.031**
Male	758 (53.2%)	187 (59.9%)		
Female	666 (46.8%)	125 (40.1%)		
Cardiovascular risk factors, n (%)				
Hypertension	432 (30.3%)	94 (30.1%)	χ^2	0.942
Diabetes mellitus	424 (29.8%)	104 (33.3%)	χ^2	0.216
Dyslipidaemia	425 (29.8%)	93 (29.8%)	χ^2	0.989
Smoking	428 (30.1%)	86 (27.6%)	χ^2	0.383

Table 4. *Baseline demographic and cardiovascular characteristics by group (N = 1,736). Continuous variables: median (IQR). Categorical variables: n (%). Bold p-values denote statistical significance at $\alpha = 0.05$. M-W U = Mann–Whitney U test; χ^2 = Pearson's chi-square test.*

The two groups as indicated in Table 4 showed significant difference with regard to age. The mean age of patients who had a previous stent was lower than in the comparison group with a median age of 53.5 years (IQR 40.8 - 66.5) versus 57.0 years (IQR 48.0 - 69.0) in the comparison group ($p < 0.001$). Figure 1 demonstrates the age distribution of each group, with the shift of the central tendency in the reintervention group being obvious. The finding has a clinical implication in that patients who later have a coronary reintervention are more likely to develop disease earlier than the overall population of patients receiving PCI, and

the finding could reflect more aggressive underlying atherosclerosis or earlier exposure to risk factors that are not well represented in the current data set.

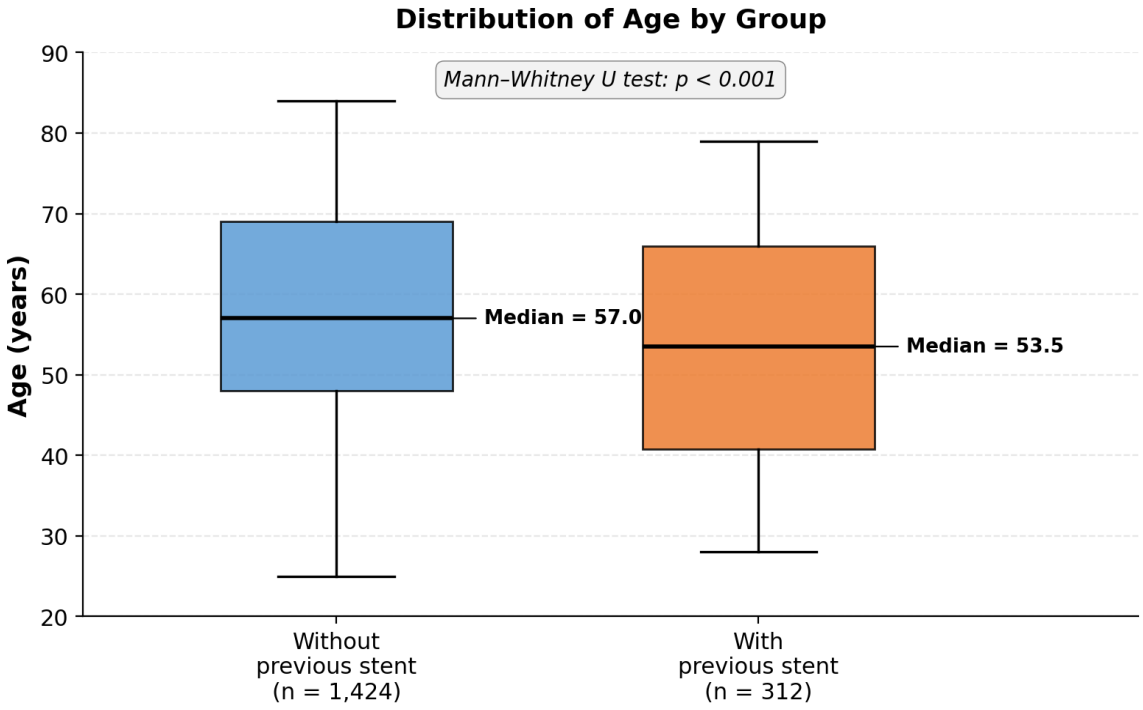

Figure 1. *Boxplot of patients age (years) by group. Boxes represent the interquartile range, horizontal lines indicate the median, and whiskers extend to the minimum and maximum values within 1.5 × IQR.*

In terms of sex, a small yet statistically significant majority of the reintervention group consisted of male patients (59.9% vs 53.2; p = 0.031). Conversely, the four cardiovascular risk factors that were studied did not show any significant difference between the two groups. The prevalence of arterial hypertension (30.3% vs 30.1%; p = 0.942), diabetes mellitus (29.8% vs 33.3%; p = 0.216), dyslipidaemia (29.8% vs 29.8%; p = 0.989) and current smoking (30.1% vs 27.6%; p = 0.383) was virtually identical between groups. The visual comparison of demographic and cardiovascular profiles is provided in Figure 2.

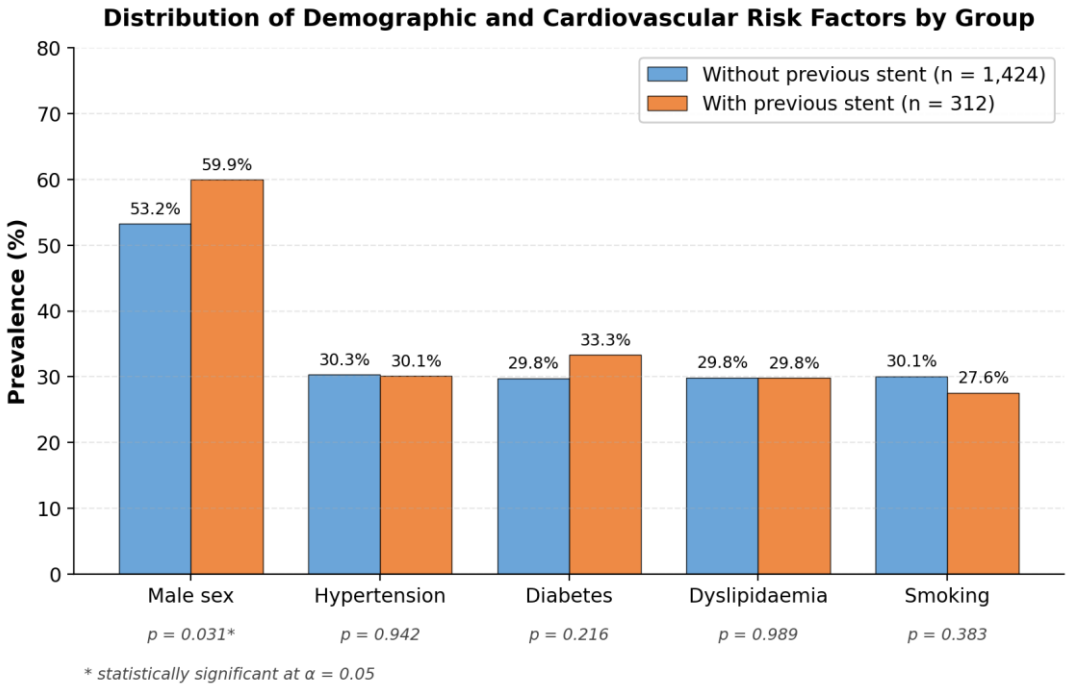

Figure 2. *Prevalence of male sex and of the four cardiovascular risk factors (hypertension, diabetes, dyslipidaemia, smoking) in the two study groups. p-values from Pearson's chi-square test are shown beneath each pair of bars; the asterisk indicates statistical significance at α = 0.05.*

Collectively, these results indicate that there were no significant differences between the two groups at baseline in terms of the recorded cardiovascular risk profile, but there were significant differences between the two groups in terms of age and sex. These two demographic characteristics will have to be controlled in the multivariate analysis conducted in Section 4.4.2, to separate their independent effect on the variables of interest. The fact that the four cardiovascular risk factors did not differ in the cohort is in itself a worthwhile observation, and may be indicative of anatomical, procedural or adherence-related factors that were not represented in the available data. This should, however, be interpreted in the light of the coding decision which is described in Section 4.1, that blank entries in the source datasheets were operationalized as the absence of the corresponding risk factor; under-documentation could therefore have attenuated otherwise detectable group differences.

4.3 Financial Burden - Main Case

4.3.1 Normality Assessment

Prior to the selection of a suitable inferential test to be used in the comparison of total hospitalization costs in the two groups, the distribution of the two outcome variables, Total Cost M and Total Cost N, were evaluated with regard to normality in each group separately. The test was a combination of a formal statistical test (Shapiro-Wilk test, with Kolmogorov-Smirnov / Lilliefors as a secondary test), graphical analysis of histograms with an overlaid theoretical normal curve, and analysis of parameters of the shape of the distribution (skewness). The Shapiro-Wilk test was chosen as the main normality test due to its higher statistical power in a broad scope of sample sizes.

Variable	Group	Shapiro–Wilk W	p-value	Skewness
Total Cost M	Without previous stent	0.902	< **0.001**	+1.20
	With previous stent	0.877	< **0.001**	+0.96
Total Cost N	Without previous stent	0.744	< **0.001**	+3.11
	With previous stent	0.811	< **0.001**	+2.20

Table 5. *Shapiro–Wilk test of normality and skewness coefficients for the two cost variables, in each group (N = 1,736). All p-values from the Shapiro–Wilk test are below 0.001, indicating significant deviation from normality.*

In both groups, Table 5 shows that the null hypothesis of normality was rejected in both instances of Total Cost M and Total Cost N (Shapiro-Wilk $p < 0.001$ in all four analyses). This fact is further confirmed by the skewness coefficients: all four distributions are strongly skewed to the right (positively skewed), with skewness values of +0.96 to +3.11. With skewness set to zero as a benchmark, values of skewness greater than ±1.0 are traditionally considered a significant deviation of skewness. The deviation is also excessively pronounced in the case of Total Cost N in the comparison group (skewness = +3.11) due to the presence of a long right tail that is caused by a small set of extreme cost values.

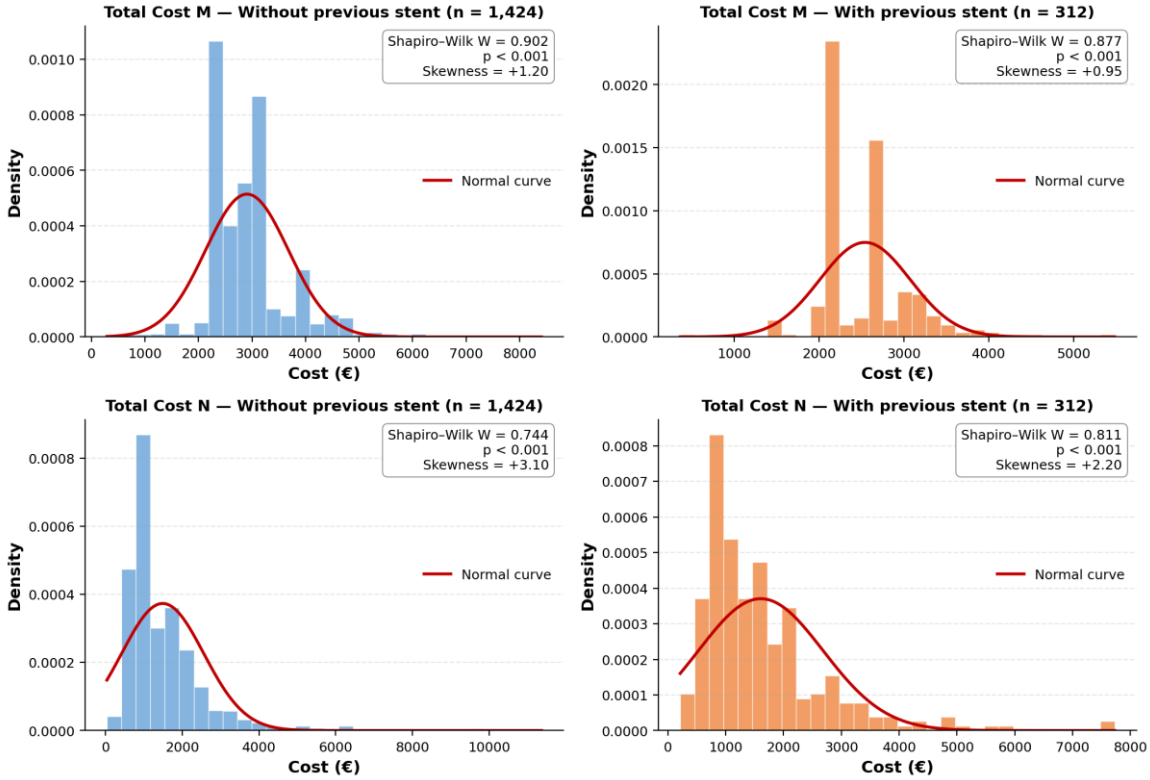

Figure 3. *Histograms of Total Cost M (top row) and Total Cost N (bottom row) by group, with the theoretical normal density curve (red) overlaid for visual comparison. In all four panels the empirical distribution is markedly right-skewed, with a concentration of cases at lower cost values and a long right tail.*

Formal results in Table 5 are visually supported by the histograms in Figure 3. In each of the four panels, the empirical distribution can be seen to contain a clear concentration of the values to the lower-to-moderate cost levels and a strong right tail that is far extended relative to the symmetric reference curve. This is common to healthcare cost data where a relatively small percentage of complex or complicated cases is generating disproportionately large expenditures. Figure 4 also uses some Q-Q plots that give another, more complementary visualization.

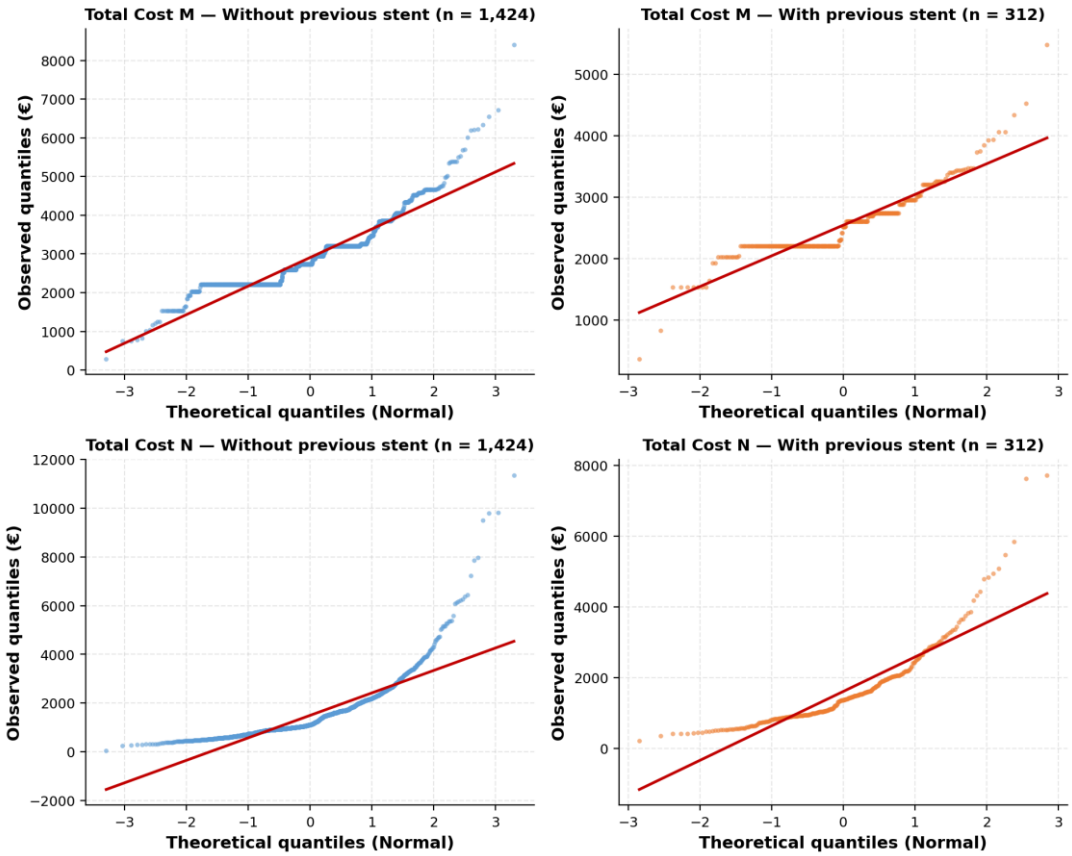

Figure 4. *Normal Q–Q plots of Total Cost M (top row) and Total Cost N (bottom row) by group. The solid red line represents the expected linear pattern under perfect normality. Systematic deviation of the points from the reference line, particularly the upward bow at the upper tail, confirms the non-normality already established by the Shapiro–Wilk test.*

In all of the Q-Q panels in Figure 4, the points are systematically off-trace with a typical upward curvature at the upper end. This trend is the visual fingerprint of skewed data rightwards and supports the formal tests findings. A natural-logarithm transformation applied to both cost variables (to avoid overly large or small numbers) was a sensitivity measure to restore normality, but the transformed distributions still failed the Shapiro-Wilk test in most subsets ($p < 0.001$ to $p = 0.003$), indicating that even a simple monotonic transformation does not fully restore normality.

On these converging lines of evidence, the assumption of normality required by the parametric tests like the independent samples t-test cannot be held tenable in either of the cost variables. Even though it is known that the t-test is reasonably robust in large samples, it is a common practice to apply the t-test routinely to such strongly skewed data, which is methodologically inadvisable in comparing means, because the mean is itself is a poor summary of a highly skewed distribution. In this regard, the non-parametric Mann-Whitney

U test was chosen as the main inferential test in the between-group comparison of Total Cost M and Total Cost N and these are reported using the median and interquartile range instead of the mean and standard deviation throughout Sections 4.3.2 and 4.3.3.

4.3.2 Comparison of Total Cost M (Reimbursement plus Out-of-Hospital Components)

The first element of the main research question, which is discussed in this section, is whether patients with prior coronary stent incur a different total Cost M compared to patients who have not had a prior stent. Total cost M is defined as the sum of the amount reimbursed under the DRG-based system and the three out-of-hospital cost items (out-of-hospital pharmaceuticals, out-of-hospital ETIP and out-of-hospital materials). The non-parametric Mann-Whitney U test was chosen as the primary inferential procedure based on the normality assessment reported in Section 4.3.1 and the cost distributions are summarized below using both the median with IQR (the appropriate non-parametric descriptors) and the mean with standard deviation (provided for reference).

Descriptive statistic	Without previous stent (n = 1,424)	With previous stent (n = 312)
***Central tendency and dispersion** (non-parametric)*		
Median (€)	**2,744**	**2,518**
Interquartile range, IQR (€)	997 (2,207 – 3,204)	537 (2,207 – 2,744)
Range, min – max (€)	289 – 8,409	366 – 5,486
***Mean and dispersion** (for reference)*		
Mean (€)	2,906.50	2,543.23
Standard deviation (€)	775.62	532.32
95% CI for mean (€)	2,866.18 – 2,946.82	2,483.93 – 2,602.53

Table 6. *Descriptive statistics for Total Cost M by group. Median, IQR (with Q1 – Q3) and range are the primary descriptors; mean, standard deviation and 95% CI for the mean are reported for reference. All values are in euros (€).*

Table 6 demonstrates that Total Cost M was lower in patients with a prior stent (median €2,518; IQR €537) as compared to patients without prior stenting (median €2,744; IQR €997). The difference direction is also in the same direction for the mean values (€2,543.23 vs €2,906.50) and the 95% CI of the two means are also not overlapping, which is an early sign of a between-group difference. It is also interesting to note that the dispersion is significantly smaller in the reintervention group: the IQR is smaller, as well as the standard deviation, and the maximum value is also much less. Both IQR and standard deviation are half that of the comparison group, and the maximum value is also significantly smaller (€5,486 vs €8,409). It implies that it is not only that Cost M in patients undergoing reintervention is lower on average but also it is less variable across the cases.

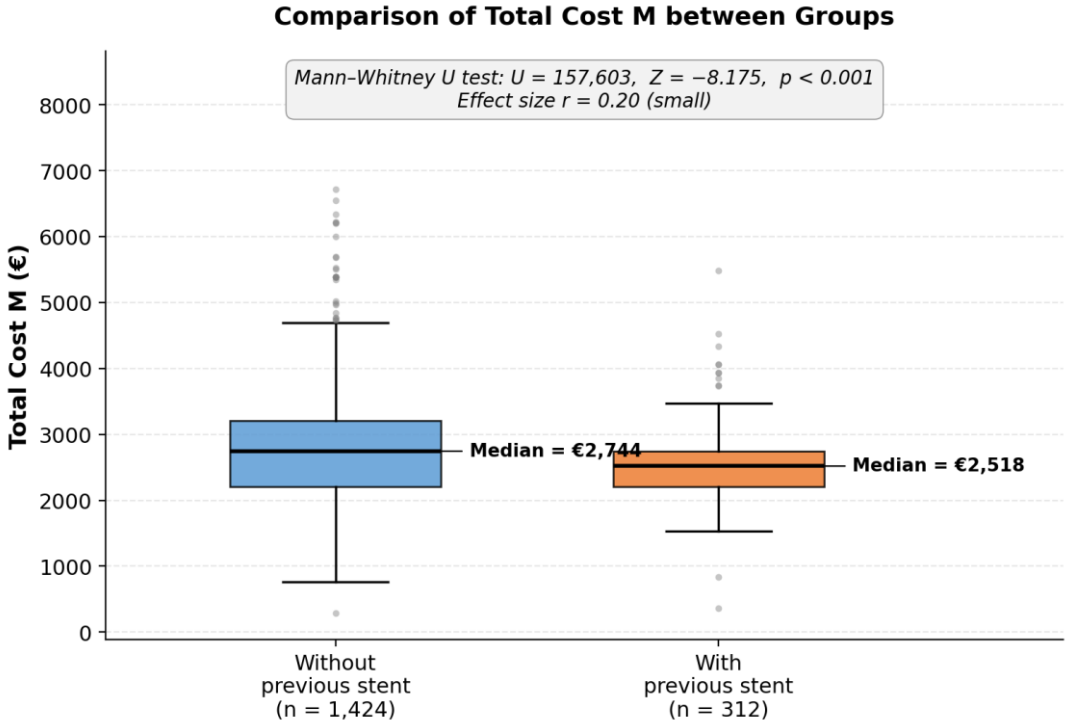

Figure 5. *Boxplots of Total Cost M by group. Boxes represent the interquartile range, horizontal lines indicate the median, and whiskers extend to the most extreme value within 1.5 × IQR; individual points beyond the whiskers are plotted as outliers. The Mann–Whitney U test result and the effect size are reported on the figure.*

The descriptive pattern is confirmed by the visual comparison in Figure 5: the entire box of the reintervention group is lower than the one of the comparison group, although the two boxes are largely overlapping. Mann-Whitney U test showed that the difference in the distribution of Total Cost M between the two groups is statistically significant (U = 157,603; Z = -8.175; p = 0.001), with the mean ranks of patients without a previous stent being higher

(913.82 vs 661.64). The observed effect size r = |Z|/√N = 0.20 falls within the small range based on the conventional thresholds, meaning that though the difference is highly statistically significant, a result that is partly due to the large sample size, the magnitude of the between-group separation is modest in practice. To confirm the same tendency as the previous independent-samples t-test on the natural-logarithm-transformed cost validated the same tendency (Welch t = 8.42; df = 516.84; p =<0.001), which confirms how strong the conclusion is.

It should be stated that the direction of this difference is opposite to that which would be predicted under the working hypothesis of the study which proposed that the previous stent placement would be related to a higher economic burden. To the case of Total Cost M, it is seen that instead of a median cost of M, the present data show that the median cost of the patients with a previous stent is somewhat lower. We shall attempt to give a detailed interpretation in the Discussion, but two preliminary considerations may be briefly indicated at this point. First, Total Cost M is dominated by the DRG based reimbursement component, which is largely procedure specific and standardized, as opposed to being based on individual case complexity; this may weaken or actually reverse cost differentials, which would arise in components that are more directly linked to the procedure itself. Second, the comparison group has a very large range of clinical presentations, some of which can be more complex than a typical re-PCI case and thus yield a higher reimbursable cost. The complementary analysis of the Total Cost N which reflects inpatient drug and material consumption is presented in the following section and is required for a complete picture of the economic burden.

4.3.3 Comparison of Total Cost N (Inpatient Materials and Drugs)

This part will answer the second part of the research question which is whether patients who had been previously stented with a coronary stent incur a different Total Cost N than those who have not previously been stented. Total Cost N is defined as the sum of the inpatient materials and the inpatient drug expenditure and thus represents the resource consumption which can be most directly attributed to the in-hospital management of each case. According to the allocation of Total Cost N in both groups, as determined in Section 4.3.1, there is a marked right-skew on the distribution of Total Cost N in both groups, and the Mann-Whitney U test was therefore employed as the primary inferential procedure. As the major

non-parametric measures of central tendency, Table 7 presents the resultant median with IQR, and also presents the resultant mean with standard deviation as a reference.

Descriptive statistic	Without previous stent (n = 1,424)	With previous stent (n = 312)
Central tendency and dispersion (non-parametric)		
Median (€)	**1,109.50**	**1,363.00**
Interquartile range, IQR (€)	932 (884 – 1,815)	1,102 (912 – 2,014)
Range, min – max (€)	39 – 11,360	213 – 7,728
Mean and dispersion (for reference)		
Mean (€)	1,492.15	1,606.32
Standard deviation (€)	1,069.40	1,077.22
95% CI for mean (€)	1,436.55 – 1,547.74	1,486.32 – 1,726.32

Table 7. *Descriptive statistics for Total Cost N by group. Median, IQR (with Q1 – Q3) and range are the primary descriptors; mean, standard deviation and 95% CI for the mean are reported for reference. All values are in euros (€).*

As shown in Table 7, Total Cost N was higher in patients with a previous stent (median €1,363; IQR €1,102) than in patients without prior stenting (median €1,109.50; IQR €932). The same direction is observed for the mean values (€1,606.32 vs €1,492.15), although the 95% CI for the two means partly overlap. Both distributions are highly variable, with standard deviations of similar magnitude (≈ €1,070 in each group) and very wide ranges, particularly in the comparison group, which contains a small number of extreme high-cost cases reaching up to €11,360. This variability reflects the fact that inpatient drug and material consumption is heavily influenced by case complexity and length of stay, both of which are themselves variable across the cohort.

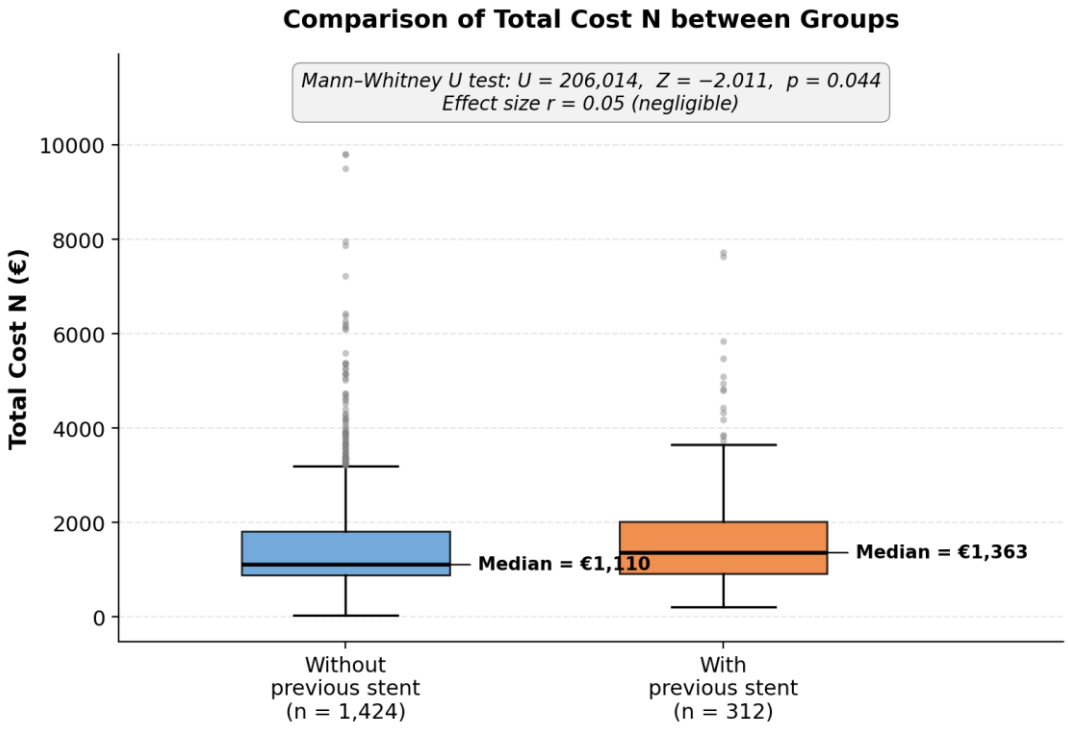

Figure 6. *Boxplots of Total Cost N by group. Boxes represent the interquartile range, horizontal lines indicate the median, and whiskers extend to the most extreme value within 1.5 × IQR; individual points beyond the whiskers are plotted as outliers. The Mann–Whitney U test result and the effect size are reported on the figure.*

Figure 6 demonstrates that the box of the reintervention group is moved slightly upwards in comparison with that of the comparison group, but this does not mean that the two boxes do not overlap greatly over most of their range. The Mann-Whitney U test showed statistically significant difference between the two distributions (U = 206,014; Z = -2.011; p = 0.044), and the mean ranks of the patients with a previous stent were higher (920.20 vs 857.17). The effect size, however, $r = |Z|/\sqrt{N} = 0.05$ is far less than the traditional threshold of a small effect (r = 0.10) and is better described as small. As a sensitivity analysis, an independent samples t-test on the natural-logarithm-transformed cost confirmed the same direction and a similar level of significance (t = -2.087; df = 1,734; p = 0.037) which supports the soundness of the test result.

The direction of such difference is in line with the working hypothesis of the study, which is that patients who have a previous stent have a higher in-hospital cost of materials and drugs. But the practical importance of the finding is far less than the statistical importance of the finding implies. The p-value is close enough to the traditional 0.05 significance level and the effect size is small enough to be statistically significant just because of the high

statistical power available through the large sample size. The between-group difference of about €254 is small in comparison with the overall variability of Total Cost N (interquartile ranges of €932 and 1,102) and is not likely to be of major importance at the level of the individual case. At the institutional level, however, even a small difference per case will work up into a quantifiable budgetary impact when multiplied across the annual number of reintervention cases. The following section gives a more granular break-down of individual cost components, which makes up Total Cost N.

4.3.4 Component-Level Analysis of the Two Cost Definitions

In Section 4.3.2 and 4.3.3, it was established that the two cost summaries, Total Cost M and Total Cost N move in opposite directions between groups. To make clearer where these aggregate differences are founded, the present section disaggregates each of these summaries into its constituent parts and compares them between groups using the Mann-Whitney U test. The LOS is also reported as auxiliary clinical variable as LOS of a hospitalization is one of the key drivers of inpatient resource use and may assist in interpreting the cost results. All the comparisons are given in Table 8.

Cost component	Without previous stent Median (IQR)	With previous stent Median (IQR)	Z	p-value
Components of Total Cost M (€)				
Reimbursement	2,210 (1,533 – 2,530)	1,533 (1,533 – 2,210)	−8.100	< **0.001**
Out-of-hospital drugs	0 (0 – 0)	0 (0 – 0)	0.000	1.000
Out-of-hospital ETIP	674 (674 – 674)	674 (674 – 674)	−1.845	0.065
Out-of-hospital materials	0 (0 – 0)	0 (0 – 0)	−0.468	0.640
Components of Total Cost N (€)				
Inpatient materials	1,011 (884 – 1,815)	1,301 (843 – 1,960)	−2.524	**0.012**
Inpatient drugs	66 (36 – 95)	60 (31 – 80)	−4.288	< **0.001**
Auxiliary clinical variable				
Length of stay (days)	1 (1 – 6)	1 (1 – 2)	−8.211	< **0.001**

Table 8. *Component-level comparison of the two cost definitions, plus the auxiliary clinical variable Length of Stay. Median and interquartile range (Q1 – Q3) are reported for each group, with the corresponding Z statistic and two-sided p-value from the Mann–Whitney U test. Bold p-values denote statistical significance at α = 0.05.*

In Total Cost M, the only element that significantly varied across the groups was the amount of reimbursement based on DRG, which was also significantly lower in patients with a previous stent (median of the reimbursement amount based on DRG, which amounted to significantly lower in patients with a previous stent, was 1,533 vs. 2,210; Z = -8.100; p = 0.001). The three out-of-hospital components, drugs, ETIP and materials, did not have any clinically significant between-group difference: out-of-hospital drugs, out-of-hospital ETIP and out-of-hospital materials have a median of no such cost in either group, a tendency that is statistically insignificant (p=0.065). It then follows that the lower Total Cost M that is observed in the reintervention group and which is reported in Section 3.3.2 is basically a reflection of a lower reimbursement amount rather than of differences in the auxiliary out-of-hospital expenditures.

In the Total Cost N, the direction change was mainly influenced by inpatient materials, which were significantly higher in the reintervention group (median €1,301 and €1,011; Z = -2.524; p = 0.012). The opposite of this (an increase in inpatient drug expenditure) also differed in opposite directions (median increase of €60 versus €66; Z = 0.4288; p = 0.001), but the absolute value of this difference is very small (a few euros at the median) and therefore it contributes little to the aggregate Cost N. The stronger signal is thus the increased consumption of materials by patients undergoing a reintervention, which is found to be consistent with the interpretation that the procedure itself is more resource-intensive in this group, even when the overall episode of hospitalization is otherwise simpler. Figure 7 presents the median value of each cost component side by side, which gives a visual overview of the location of where the differences lie.

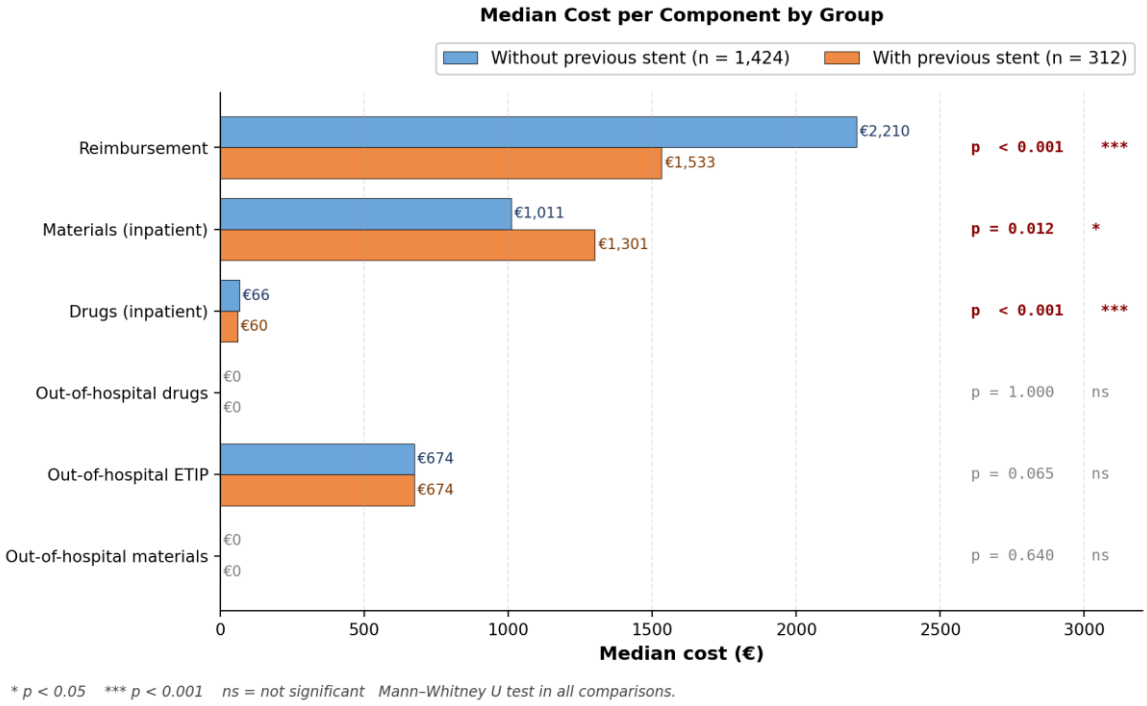

Figure 7. *Median value of each cost component by group. Asterisks indicate the level of statistical significance from Mann–Whitney U tests (* $p < 0.05$, *** $p < 0.001$, ns = not significant). Components on which the two groups differ correspond to the upper part of the chart (Reimbursement, Inpatient materials, Inpatient drugs); the three out-of-hospital components show essentially no between-group separation.*

The results on the component level are consistent with each other when the auxiliary variable LOS is considered. As Table 8 shows, patients with a previous stent had a significantly shorter hospitalization, with a median of 1 day and IQR of 1 - 2 days, being significantly shorter than 1 day and 1 - 2 days in the comparison group (Z = -8.211; p = 0.001). The difference is further shown in the cumulative distribution provided in Figure 8 where more than 70 percent of reintervention cases were discharged on the same calendar day, in comparison with approximately 51 percent of cases in the comparison group and very few reintervention patients stayed longer than five days.

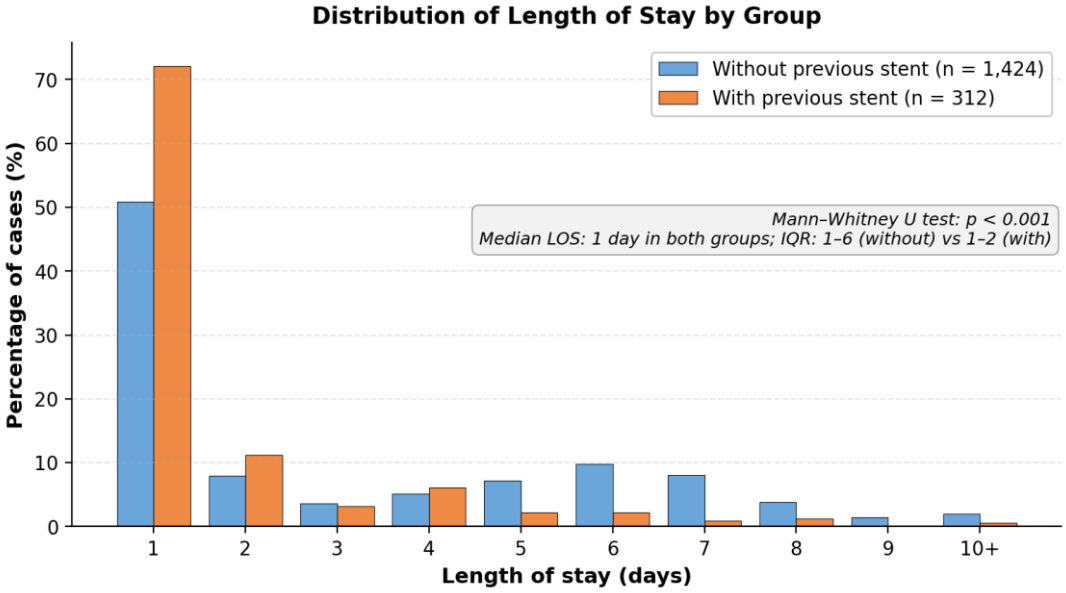

Figure 8. *Distribution of length of stay (in days) by group, expressed as the percentage of cases at each duration. Cases with a stay of ten days or more are pooled in the "10+" category.*

Put collectively, the component-level analysis makes reconcible the seemingly divergent results in Sections 4.3.2 and 4.3.3. Patients with a coronary reintervention spent less time in a hospital than first-time PCI patients, and incur a lower reimbursement based on DRG which then explains the lower Total Cost M observed in this group. Meanwhile, however, the reintervention process itself seems to be more device-intensive, as indicated by the increased consumption of inpatient materials, and this is the component that drives the higher Total Cost N. In a discussion-oriented perspective, this means that the economic cost of reintervention is not well captured by either of the two cost summaries in isolation: Total Cost M is dominated by the reimbursement scheme (which rewards shorter stays and thereby underestimates the procedural cost of re-PCI), and Total Cost N more faithfully reflects the actual procedural cost of re-PCI. This fact of dissociation between reimbursement and resource consumption is itself a substantive finding.

4.4 Factors Associated with the “Previously Stented” Group

4.4.1 Univariate Analysis of Predictors

Sections 4.3.2 to 4.3.4 discussed in detail the cost difference between the two groups. The previously stated analytic question becomes now: how much does cost differ? To which patient characteristics are associated with belonging to the previous-stent group, and might

therefore be candidate predictors of reintervention? The current section presents the unadjusted (crude) relationship of each candidate predictor with previous-stent group membership, on a one-variable-at-a-time basis. Simple binary logistic regression (giving the crude odds ratio with 95% CI) was used to test each binary predictor and to test age as a continuous predictor whose odds ratio was given per one-year increment. The same six variables that were compared in Section 4.2 at baseline were re-examined here in this regression view with the corresponding p-values being therefore those of the Wald test, which is the natural counterpart of the χ^2 and Mann-Whitney U tests reported in the previous sections. The univariate analysis results are given in Table 9 and visualized in Figure 9.

Predictor (reference category)	Crude OR	95% CI	Wald	p-value
Demographics				
Male sex (vs female)	**1.314**	**1.025 – 1.687**	4.62	**0.032**
Age (per 1-year increase)	**0.976**	**0.967 – 0.985**	27.78	**< 0.001**
Cardiovascular risk factors				
Hypertension (yes vs no)	0.990	0.758 – 1.293	0.005	0.942
Diabetes mellitus (yes vs no)	1.179	0.908 – 1.531	1.53	0.216
Dyslipidaemia (yes vs no)	0.998	0.764 – 1.305	0.000	0.989
Smoking (yes vs no)	0.886	0.674 – 1.163	0.76	0.383

Table 9. *Crude (unadjusted) odds ratios from univariate binary logistic regression, with the previous-stent group as the outcome (event = 1). The Wald statistic and the corresponding two-sided p-value are reported for each predictor. Bold values denote statistically significant associations at $\alpha = 0.05$. For age, the odds ratio is expressed per one-year increase; for binary predictors, the reference category is shown in parentheses.*

In the unadjusted analysis, two of the six candidate predictors were significantly correlated with previous-stent group membership in the unadjusted analysis. The male sex was found to increase the odds of being in the reintervention group by about 31% higher in the male compared to the female patient. Age had a negative relationship with reintervention status with each year of age being associated with a reduction in odds by about 2.4% (OR -0.976, 95% CI -0.967 -0.985, $p < 0.001$). This translates to an odds ratio of about 0.78, i.e. the probability that due to an extra 10 years of age, the odds of falling within the previous-stent group will be decreased by some 22%. This is in line with the descriptive result in Section 4.2 that the patients in the reintervention group were on average four to five years younger as compared to the comparison group.

In contrast, none of the four cardiovascular risk factors showed a statistically significant univariate association with previous-stent group membership. The crude odds ratios of hypertension (0.990), dyslipidaemia (0.998) and smoking (0.886) all fell into the line of no effect with CI that comfortably crossed the line of no effect of 1.0 and p-values well above the traditional 0.05 level. The numerical trend of diabetes mellitus towards higher odds of reintervention (1.179; 95% CI 0.908 1.531; $p = 0.216$) was in line with the higher prevalence (33.3% versus 29.8%) reported in Section 3.2, but the association was not statistically significant. The same set of estimates is presented as a forest plot in Figure 9 where the visual signature of the two significant predictors, the confidence interval that is completely on one side of the odds ratio = 1 reference line is clearly delineated as opposed to that of the non-significant ones, the intervals of which span 1.0.

There are two methodological caveats that it is worth noting before proceeding on to the multivariate model. To start with, univariate odds ratios are not adjusted and any apparent relationship, or lack of relationship, may be confounded by other variables that themselves are correlated with the variable of interest. An illustration is that the protective relationship of age may be partly due to the male preponderance in the reintervention group since the two sociodemographic variables are not independent of each other in cardiovascular cohorts. Separating the independent contribution of each predictor thus requires the multivariate analysis that is found in Section 4.4.2. Second, the fact that there was no significant univariate relationship between the four cardiovascular risk factors, should be interpreted in the light of the coding decision recorded in Section 4.1: blank entries in the source datasheets were operationalized as the absence of the respective factors, which may have artificially weakened otherwise detectable relationships. Combining these considerations, one can

suggest that the univariate findings are to be viewed as a screening step and not as a final answer to the question of what factors predict reintervention.

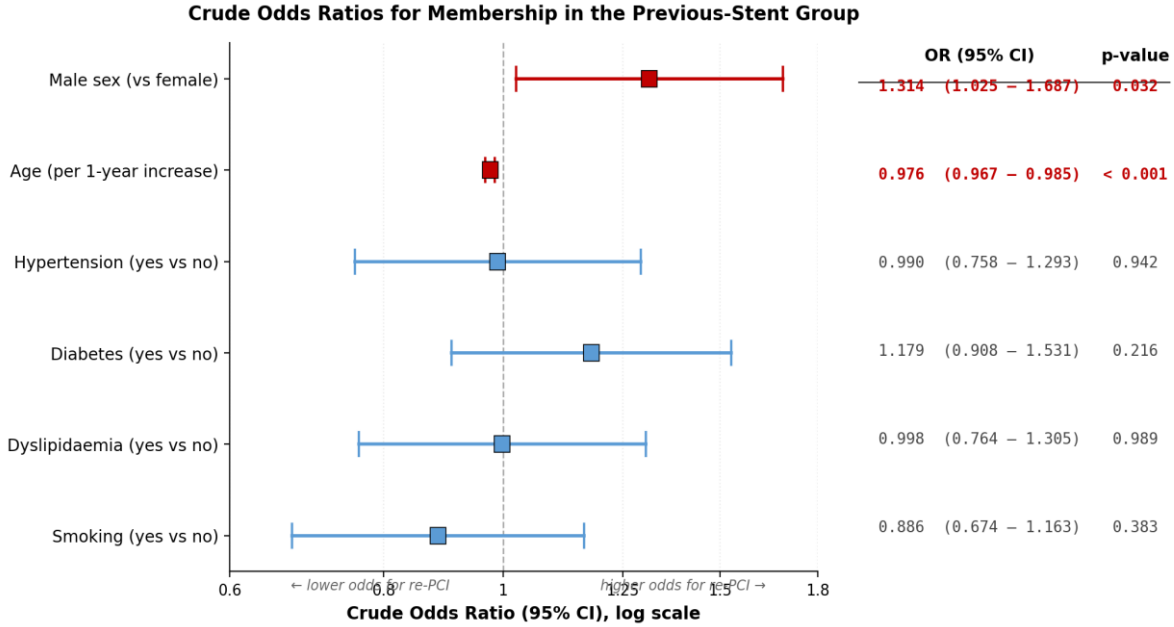

Figure 9. *Forest plot of crude (unadjusted) odds ratios for previous-stent group membership. Each predictor is shown as a square at the point estimate, with horizontal lines indicating the 95% confidence interval; the dashed vertical line marks the line of no effect (OR = 1). Statistically significant predictors at α = 0.05 are highlighted in red. The horizontal axis is plotted on a logarithmic scale so that ratios above and below 1 are visually symmetric.*

4.4.2 Multivariable Analysis, Binary Logistic Regression

A multivariate binary logistic regression model was fitted with the previous-stent group membership as the binary outcome (1 = with previous stent, 0 = without previous stent) and the simultaneous predictors of sex, age (continuous, per one-year increase), hypertension, diabetes mellitus, dyslipidaemia and smoking. Each of the six variables was then inputted into the model in a single step (ENTER method), whereby the adjusted odds ratio of each predictor is conditional on the other predictors also being included in the model. Effect estimates are presented in Table 10, model fit and performance indicators are summarized in Table 11.

Predictor	β (SE)	Wald	Adj. OR	95% CI for Adj. OR	p-value
Male sex (vs female)	0.291 (0.128)	5.13	**1.337**	**1.040 – 1.722**	**0.024**

Predictor	β (SE)	Wald	Adj. OR	95% CI for Adj. OR	p-value
Age (per 1-year increase)	−0.025 (0.005)	28.69	**0.975**	**0.967 – 0.984**	< **0.001**
Hypertension (yes vs no)	−0.007 (0.138)	0.003	0.993	0.757 – 1.302	0.958
Diabetes mellitus (yes vs no)	0.169 (0.135)	1.56	1.185	0.908 – 1.545	0.211
Dyslipidaemia (yes vs no)	−0.046 (0.139)	0.11	0.955	0.727 – 1.253	0.739
Smoking (yes vs no)	−0.139 (0.141)	0.96	0.870	0.660 – 1.149	0.327
Constant (intercept)	*−0.008 (0.282)*	*0.001*	-	-	*0.979*

Table 10. *Multivariable binary logistic regression model for previous-stent group membership. Adjusted odds ratios (Adj. OR) are reported with 95% confidence intervals; β denotes the regression coefficient on the log-odds scale, with its standard error in parentheses. Bold values denote statistical significance at α = 0.05.*

As indicated in Table 10, two predictors maintained an independent relationship with previous-stent group membership, after adjusting each other. Males experienced higher odds of being in reintervention group (Adj.). odds ratio = 1.337; 95% CI 1.040 -1.722; p = 0.024) and age had a negative association with reintervention status, where each year of age decreased the odds by approximately 2.5%. odds ratio = 0.975; 95% CI 0.967 – 0.984; p < 0.001). The adjusted odds ratios of the four cardiovascular risk factors were not significantly different than the line of no effect (all $p \geq 0.21$), which confirmed the lack of an independent association already indicated by the univariate analysis. The numerically positive trend of diabetes mellitus remained following adjustment (Adj.). odds ratio = 1.185; 95% CI 0.908 – 1.545; p = 0.211) but did not reach statistical significance.

An explicit graphic comparison of the crude estimates of Section 4.4.1 and the adjusted estimate of the current analysis is given in Figure 10. The two groups of estimates are very similar in magnitude and direction, indicating that, at least in the limited set of predictors that are considered here, the univariate associations were not confounded significantly. Adjustment did not move any non-significant predictor across the line of no effect, and the

two significant predictors (sex and age) had essentially the same effect size. This consistency between the crude and the adjusted analysis supports the validity of the conclusion that among the variables that can be analyzed using this dataset, the only variables independently related to reintervention status include sex and age.

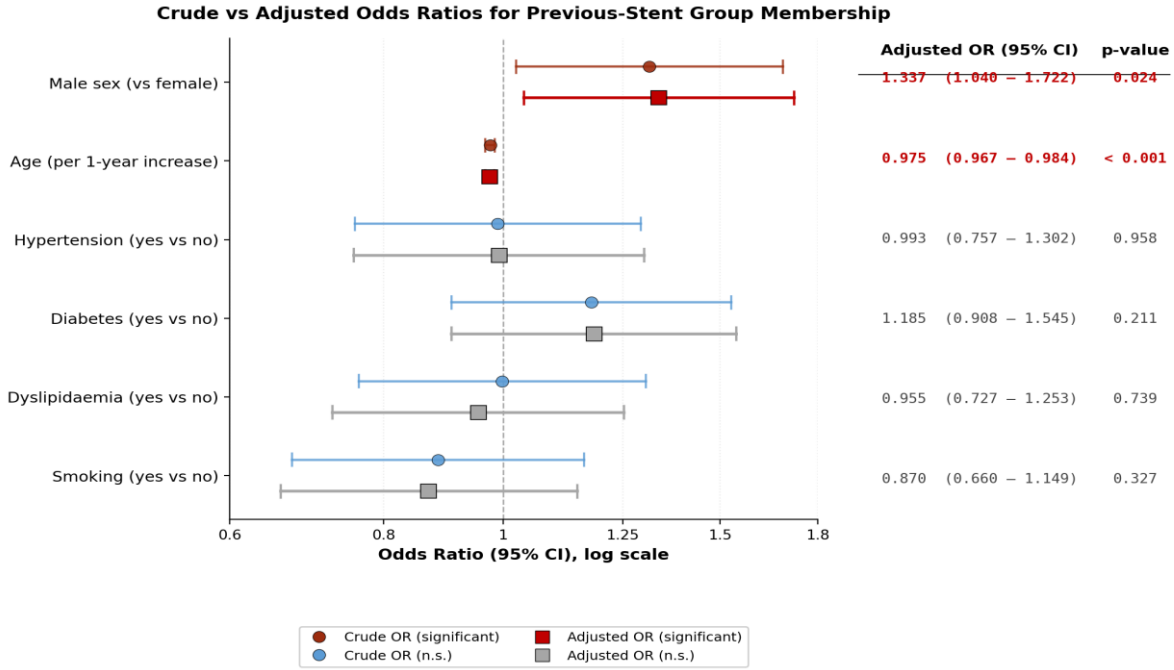

Figure 10. *Forest plot comparing crude (circles) and adjusted (squares) odds ratios for each candidate predictor. Statistically significant predictors at α = 0.05 are highlighted in red; non-significant predictors are shown in lighter colours. The dashed vertical line marks the line with no effect (OR = 1). The horizontal axis is plotted on a logarithmic scale.*

Table 11 summarizes the performance and goodness-of-fit attributes of the multivariate model.

Indicator	Value	Interpretation
Overall model significance		
Omnibus test of model coefficients (likelihood-ratio χ^2)	$\chi^2 = 36.09$; df = 6; $p < 0.001$	*Model significant overall*
Explained variation		
Cox & Snell pseudo-R^2	0.021	*Low explained variation*
Nagelkerke pseudo-R^2	0.034	*≈ 3.4 % of variation explained*

Indicator	Value	Interpretation
Model calibration and discrimination		
Hosmer–Lemeshow goodness-of-fit	$\chi^2 = 15.30$; df = 8; p = 0.053	*Borderline acceptable calibration*
Area under the ROC curve (AUC)	0.602 (95% CI 0.566 – 0.638)	*Poor discrimination*
Maximum variance inflation factor (VIF)	1.013 (range 1.002 – 1.013)	*No multicollinearity*

Table 11. *Model fit and performance indicators for the multivariable logistic regression model. The Hosmer–Lemeshow test, Nagelkerke pseudo-R² and the area under the ROC curve provide complementary information on calibration, explained variation and discrimination, respectively. The variance inflation factor (VIF) is reported as the multicollinearity diagnostic.*

Even though the results of the omnibus likelihood-ratio test show that the model is significantly better than the null, (2 = 36.09; df = 6; p < 0.001), this result should be interpreted in conjunction with the measures of explained variation and discrimination, which are much less promising. The Nagelkerke pseudo-R^2 of 0.034 suggests that the six predictors together are able to explain only about 3.4 percent of the variation in reintervention status, that is, the great majority of the variation remains not explained by the demographic and traditional cardiovascular risk-factor information alone. The Hosmer-Lemeshow test (2 = 15.30; p = 0.053) is slightly above the traditional 0.05 value, which is used to justify borderline acceptable model calibration.

The ability of the model to discriminate among different stimuli was measured in terms of area under the receiver-operating-characteristic curve (AUC), as shown in Figure 11. The AUC of 0.602 (95% CI 0.566 - 0.638) is substantially larger than 0.5 (p < 0.001), which confirms the fact that the model is better than chance, but still way below the traditional threshold of 0.7 that is taken to represent acceptable discrimination.

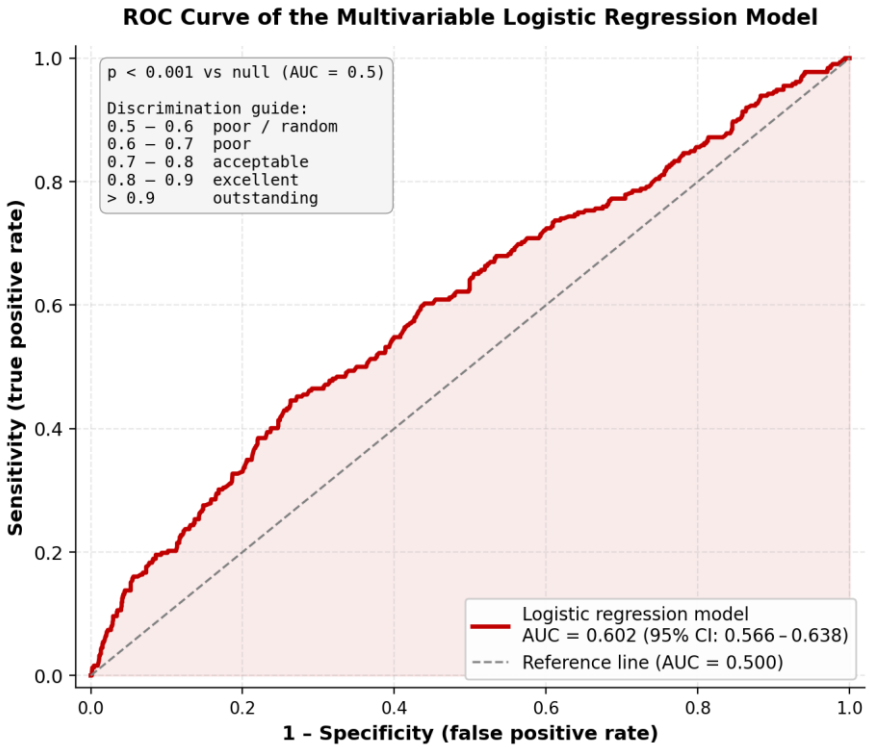

Figure 11. *Receiver-operating-characteristic (ROC) curve for the multivariable logistic regression model. The diagonal reference line corresponds to a non-informative classifier (AUC = 0.500). The shaded area beneath the curve is the model's AUC.*

Lastly, the diagnostics of multicollinearity were checked to make sure that the regression coefficients that have been reported in Table 10 are not volatile. All the VIF were near 1.0 (a range of 1.002 to 1.013), significantly less than the traditional concern level of 5, and they are essentially independent of each other in the regression design. Adjusted estimates of Table 10 are thus not artefacts of redundant covariates and can be read at face value.

Combined, the multivariate analysis confirms that the male sex and (younger) age are independently, although with weak validity, related to the previous-stent group membership. More impressive though is the finding that the model as a whole has a modest calibration and evidently poor discrimination with a Nagelkerke R^2 of barely 3 % and an AUC of just over 0.6. The substantive meaning behind this finding is that the demographic data, as well as traditional cardiovascular risk-factor data, alone are not sufficient to determine the patients who will be in need of a coronary reintervention. Variables not measured in the current dataset, such as anatomical and procedural features of the index intervention, type of stent implanted, completeness of revascularization, or adherence to dual antiplatelet therapy and lipid-lowering treatment are likely to bear the brunt of the predictive information and would be necessary to a clinically useful risk-prediction model.

4.5 Summary of Key Findings

Across the present cohort of 1,736 PCI patients, of whom 312 (18.0%) had a previous coronary stent, the analysis produced four main findings. First, the two groups were largely comparable at baseline: they did not differ in any of the four classical cardiovascular risk factors (hypertension, diabetes, dyslipidaemia, smoking; all $p > 0.20$), but reintervention patients were younger by approximately four years (median 53.5 vs 57.0 years; $p < 0.001$) and more often male (59.9% vs 53.2%; $p = 0.031$). Second, the two cost summaries diverged in opposite directions: Total Cost M was significantly lower in the reintervention group (median €2,518 vs €2,744; $p < 0.001$), whereas Total Cost N was significantly higher (median €1,363 vs €1,109.50; $p = 0.044$), although both effect sizes were small. Third, the component-level analysis explained this apparent paradox: reintervention patients were hospitalized for fewer days, accruing a lower DRG-based reimbursement and lower inpatient drug consumption, but consumed significantly more inpatient materials, pointing to a dissociation between the standardized payment received and the actual procedural resource cost. Fourth, the multivariable logistic regression model identified male sex (Adj. odds ratio = 1.337) and younger age (Adj. odds ratio = 0.975 per year) as the only independent predictors of reintervention status, but it's very low Nagelkerke R^2 (0.034) and AUC of 0.602 indicate that demographic and traditional risk-factor information alone are insufficient to predict which patients will undergo a reintervention.

5. Limitations

The results of the current study are to be viewed in the perspective of a number of methodological and substantive constraints, none of which is lethal to the analysis but each of which qualifies the weakness of the conclusions that can be drawn.

The data were selected based on one tertiary, high-volume PCI centre in Greece. Although this design has the advantage of internal consistency - the same clinical pathways, reimbursement structure, materials supply chain and cost-accounting conventions apply to all the cases in the dataset - it necessarily restricts the generalizability of results. Cost patterns may vary in other centres with lower volumes of procedures, different case mixes, different reimbursement contracts or different organizational structures. The 18%

reintervention rate of the cohort is, as an example, somewhat greater than the approximately 10% figure mentioned in the international literature, perhaps due to the referral profile of the participating centre. The current findings would first have to undergo multi-centre replication before it can be argued that the current findings represent the overall Greek PCI population.

The standard methodological vehicle of the cost-of-care study based on routinely collected data is the retrospective observational design, but it is characterized by the well-known limitation of the fact that the residual confounding cannot be excluded. Patients with a prior stent and patients having a first time PCI may be different on dimensions which were not recorded in the source datasets - such as on functional status, frailty, ejection fraction, prior medical therapy, completeness of revascularization at the index procedure or anatomical complexity of the coronary lesions. Any of these unmeasured variables can confound the association between previous-stent status and the cost outcomes; and the multivariate adjustment that is carried out in Section 4.4.2 only controls the variables that were available and is therefore necessarily incomplete.

The number of candidate predictors that were investigated in the multivariate model was limited to demographic data (age, sex) and the four classical cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking) that were present in the source datasheets. This is a limited set according to current clinical standards. Variables that were widely recognized as important determinants of the risk of reintervention, such as the type of stent implanted at the previous procedure, the nature of the lesions (length, diameter, calcification), the involvement of the bifurcation, completeness of the revascularization, the use of intravascular imaging, adherence to dual antiplatelet therapy and lipid-lowering treatment, were not available in the dataset and could therefore not be included in the analysis. A direct implication of this informational poverty and not an indication that the underlying clinical phenomenon is truly unpredictable is the very low Nagelkerke pseudo-R^2 (0.034) and the modest area under the ROC curve (0.602) reported in Section 4.4.2.

The four binary cardiovascular risk factors were operationalized in such a way that blank entries in the source datasheets were considered as the absence of the respective factors. It is the most parsimonious assumption that can be made given the structure of the data, but it confounds two conceptually different situations: a documented absence of the risk factor on the one hand, and a failure to record the risk factor on the other. Had under-documentation of risk factors been non-trivial in the source system, such a coding convention would have

resulted in underestimation of the actual prevalence of the four risk factors and attenuation of any real association between them and reintervention status. Such observations are in line with this concern as the prevalence of all four risk factors is clustered around 30 per cent - somewhat lower than would be expected in an archetypal Greek cardiovascular cohort.

The two cost summaries utilized in the analysis were constructed based on the categories of cost that were available in accounting system of the participating centre. Total Cost M reflects the perspective of the third-party payer, and Total Cost N reflects the perspective of the providing institution; neither of them incorporates the direct out-of-pocket expenditure borne by the patient or the family of the patient, lost productivity, informal care or the longer-term costs that follow the index hospitalization (such as cardiac rehabilitation, repeat outpatient consultations or further reinterventions that occur beyond the scope of observation). The economic cost of reintervention as reported here must then be seen as a lower limit to the overall cost to society. This was not the scope of the present work to conduct a full societal-perspective economic analysis including the patient and family perspectives.

The final sample size of 1,736 cases is large by the standards of single-centre studies and provides sufficient statistical strength. One consequence of this power, however, is that very small absolute differences become statistically significant - most visibly in the comparison of Total Cost N, where the median between-group difference of approximately €254 became statistically significant ($p = 0.044$) but with an effect size $r = 0.05$ that can best be described as negligible. This mismatch between statistical and practical significance was explicitly stated throughout the Results, but it has to be kept in mind when extrapolating the results to the environment of different magnitude.

The study window is about twenty-five months (March 2024 - April 2026) and cross-sectionally treated in this analysis. The reimbursement schedules, materials prices and clinical practice are not constant, and any change in these outside circumstances during the observation window will have introduced some degree of measurement noise with which the present design will have been unable to correct. Moreover, patients whose previous stent was placed in a different facility and whose history was not documented in the local record might have been misclassified into the comparison group, which would have biased the comparison between the two groups towards the null.

6. Conclusions

The main contribution of the current study is that it gives a quantitative characterization of the economic burden of repeat percutaneous coronary intervention in a high-volume, tertiary PCI centre in Greece based on a sample of 1,736 consecutive cases. Four substantive conclusions can be made within the confines of the design.

The first was that the percentage of repeat PCI in the participating centre was 18 per cent, which is higher than the percentage of approximately 10 per cent that is usually reported in the international literature. This observation alone is sufficient justification to continue to pay attention on reintervention as a valuable component of the contemporary PCI workload and it must be verified in multi-centre samples which reflect the Greek setting more broadly.

Second, the economic burden was calculated in the context of the third party payer (Total Cost M), with patients who had a prior stent being identified with a significantly lower cost, though the difference was not very large. By measuring the same burden in the perspective of the providing institution (Total Cost N) the direction of the difference was again reversed previous-stent patients were associated with significantly higher inpatient drug-and-materials cost again with a small effect size. The component-level analysis balanced the two findings into a consistent picture: reintervention patients had shorter inpatient stays and thus received less DRG-based reimbursement and less inpatient drug use, but the procedure itself was more device-intensive and used much more inpatient material. The most consequential finding that comes out of this triangulation is that the standardized reimbursement system is rewarding the shorter length of stay, the lower level of drug consumption in the reintervention episodes, but the higher materials cost that the procedure itself involves. The policy implications of such a dissociation between reimbursement and resource consumption are direct and direct: reimbursement schedules built on the basis of LOS-driven case-mix categories may systematically underprice the procedural intensity of repeat PCI, with the budgetary implications absorbed by the providing institution, rather than by the payer. This observation has the right to be further investigated in the future in the context of the multi-centre level, it may receive a recalibration of the respective DRG weights.

Third, the predictors of reintervention status were searched (univariately and using multivariate logistic regression) and only identified two independent associations: male sex (adjusted odds ratio ≈ 1.34) and younger age (adjusted odds ratio ≈ 0.98 per year). All four

classic cardiovascular risk factors, which were examined, were not independently linked to reintervention status, after adjustment. The overall model accounted for only approximately 3% of the variance in reintervention status (Nagelkerke pseudo-R^2 = 0.034) and was a poor discriminant between groups (AUC = 0.602). This is a substantive result and not a methodological failure: it shows that demographic and traditional risk-factor data, when presented in the form they are found in routine administrative data, are not sufficient to identify which patients will proceed to need a coronary reintervention. Such variables as the most likely to bear the brunt of the predictive information - type of stent implanted, anatomical complexity of the index lesion, completeness of revascularization, and adherence to the dual antiplatelet and lipid-lowering therapy were not available in the current dataset and represent a clear priority in future research in this area.

Fourth, and more generally, the present study demonstrates the methodological usefulness of examining the subject of healthcare cost through more than one prism and at more than one level of aggregation. The two cost summaries employed in this case gave apparently conflicting signals when viewed in isolation, and the interpretation of the two cost summaries became consistent only when supplemented by a component-level disaggregation and by the auxiliary clinical variable of length of stay. This contends the regular reporting of costs outcomes across a number of perspectives and at a variety of levels of granularity in the further economic assessments of PCI in the Greek context.

To conclude, repeat PCI is a clinically and economically significant aspect of modern PCI practice. The average cost per-case in the perspective of the providing institution is slightly higher than that of first-time interventions, and its average reimbursement is slightly less - a combination which implies an under-compensation of procedural intensity by the current reimbursement scheme. Demographic and traditional cardiovascular risk-factor data are not, in themselves, enough data to determine the patients who go on for reintervention. The two practical priorities to which this work aims to make its contribution are improving this predictive capacity and ensuring a fair alignment between reimbursement and actual resource consumption.

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