Improving objective decision making in the TAVI pathway

Assessing the Impact of Next-Day Discharge and Evaluating a Risk Prediction Model

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Preface

Beste lezer,

Het afgelopen jaar heb ik mijn afstudeeronderzoek voor de master Technische Geneeskunde uitgevoerd bij de onderzoeksgroep van Cardiologie in het AmsterdamUMC en voor de onderzoeksgroep Biomedical Signals and Systems voor de Universiteit Twente. Mijn onderzoek richtte zich op het verbeteren van de TAVI-behandelroute door het ontwikkelen van een risicovoorspellingsmodel en het implementeren van fast-track protocollen in combinatie met ambulante monitoring voor de nazorg.

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Aan alle lezers van mijn thesis: dank u wel voor het lezen en ik hoop dat u ervan geniet!

Laura Schepers

Abstract

Introduction: Patients with severe symptomatic aortic valve stenosis undergoing transcatheter aortic valve implantation (TAVI) are subject to various protocols for risk assessment and post-procedural care. This study aimed to enhance the TAVI pathway by developing a risk prediction model and implementing fast-track protocols combined with ambulatory monitoring for post-procedural care.

Methods and Results: The study consisted of 3 studies:

- *Next-Day Discharge:* This study evaluated a next-day discharge protocol in a cohort of 131 TAVI patients, divided into NDD+ (56 patients eligible for next-day discharge) and NDD- (95 patients ineligible). No significant differences were observed in complications, rehospitalizations, mortality, change in NYHA class, or change in quality of life. However, a significant difference in the composite endpoint favored the NDD+ arm, suggesting that next-day discharge is safe and effective.
- *Ambulatory Monitoring:* A review of monitoring systems identified Senselink, Zenicor ECG, and Kardia Mobile-HartWacht as promising options for post-procedural TAVI care.
- *Risk prediction model:* A risk prediction model was developed using the CENTER2 database (24,322 patients) with a logistic regression and feature selection through wrapper-backward elimination using decision trees. The model showed a suboptimal performance, with an AUROC of 0.59 on the validation set, indicating limited predictive accuracy.

Conclusion: The risk prediction model demonstrated limited clinical utility, with an AUROC of 0.59 for 30-day mortality prediction. Despite the lack of improvement in risk assessment, significant advancements were made in streamlining post-procedural care. The next-day discharge study successfully facilitated the discharge of 50% of eligible patients within 24 hours, thereby improving patient comfort by enabling home recovery. No disadvantages of next-day discharge were found, as the only significant statistical difference favored the NDD+ arm. Additionally, various options for ambulatory monitoring have been explored, with the potential implementation of HartWacht allowing for same-day discharge and enhanced patient safety.

Keywords: Transcatheter aortic valve implantation, Next-day Discharge, clinical pathway, length of stay, hospital volume. Ambulatory monitoring, Telemonitoring, Devices, Kardia Mobile, Zenicor ECG, Senselink, Risk score, prediction model.

Abbreviations

Abbreviation	Meaning
AS	Aortic valve Stenosis
SAVR	Surgical Aortic Valve Replacement
TAVI	Transcatheter Aortic Valve Implantation
CCD	Cardiac Conduction Defects
ECG	Electrocardiogram
RBBB	Right Bundle Branch Block
STS	Society of Thoracic Surgeons
AUROC	Area Under the Receiver Operating Characteristic
LV	Left Ventricle
LCC	Left Coronary Cusp
RCC	Right Coronary Cusp
NCC	Non-Coronary Cusp
TTE	Transthoracic Echocardiography
EF	Ejection Fraction
SA node	Sinoatrial node
AV node	Atrioventricular node
AVB	Atrioventricular Block
LBBB	Left Bundle Branch Block
LAHB	Left Anterior Hemiblock
PPI	Permanent Pacemaker Implantation
KNN	K-Nearest Neighbors
RMSE	Root Mean Squared Error
ROS	RandomOverSampler
LASSO	Least Absolute Shrinkage and Selection Operator
LR	Logistic regression
NDD	Next-day discharge
NYHA	New York Heart Association
QoL	Quality of Life
NHR	Netherlands Heart Registration
BMI	Body Mass Index
CVA / TIA	Cerebral Vascular Accident / Transient Ischaemic Attack
MI	Myocardial Infarction
LVEF	Left Ventricular Ejection Fraction
AVA	Aortic Valve Area
NSTEMI	Non-ST-elevation Myocardial Infarction
AF	Atrial Fibrillation
PPG	Photoplethysmography
HR	Heart Rate
MAD	Mean Absolute Deviation
MAPE	Mean Absolute Percentage Error
MACE	Major Adverse Cardiac Events
NaN	Not a Number
CABG	Coronary Artery Bypass Graft
PCI	Percutaneous Coronary Intervention
PVD	Peripheral Vascular Disease
CAD	Coronary Artery Disease
LFLG	Low Flow Low Gradient
DM	Diabetes Mellitus

Contents

1 Introduction

Aortic valve stenosis (AS) is the most common valvular disease in Europe and the United States of America, especially in the elderly population [1]. About 12.4% of elderly people (>75 years) have moderate or severe AS [2][3]. The degree of stenosis varies, and it results in asymptomatic to very severe conditions. Asymptomatic cases of AS can be treated medically with careful patient observation. In more severe aortic stenosis, an aortic valve replacement may be required, either via surgical or percutaneous approach [1][3].

Transcatheter aortic valve implantation

For a long time, surgical aortic valve replacement (SAVR) was the only treatment for severe aortic valve stenosis. Patients with high mortality risk were considered ineligible for SAVR and were treated with medication. Since 2007 transcatheter aortic valve implantation (TAVI) has emerged as an alternative procedure [4]. TAVI is proven to reduce disease burden by improving quality of life and survival in patients with AS for patients with high or intermediate operative risk [5]. One of the most common complications after TAVI is the development of cardiac conduction defects (CDD) or arrhythmias [6]. Post-procedural care, such as neurological evaluation, and administration of postoperative medication is only protocol for the first 4 hours. The need for up to 72-hour stay in the hospital is for continuous monitoring of new-onset CCD for the purposes of pacemaker-dependency identification [7].
Early hospital dismissal enables early resumption of the daily life routine of patients improving patients' comfort and supporting re-establishment of a stable condition. The reduction of length of stay minimizes the proneness of hospital-acquired complications, minimizes the burden of hospital capacity, and is cost-effective. Driven by these advantages and that in most cases new-onset CCDs develop within 24 hours, fast-track protocols aiming for early discharge are currently being developed for the TAVI population [8].

One of the possibilities in these fast-track protocols is to evaluate the additional value of telemonitoring in an elderly population. M.Z.H. Kolk et al. evaluated the patient-reported outcomes of a telemonitoring program, which showed that monitoring did not seem to affect the sense of safety and the health-related quality of life, whereas the perceived physical limitations tended to improve [9]. This introduces the possibility of integrating telemonitoring into fast-track protocols, providing monitoring beyond the hospital setting.

Risk assessment TAVI

The development of prediction models can empower doctors to identify patients who are at an elevated risk of experiencing adverse outcomes related to the procedure. The models serve as a valuable tool for healthcare providers and patients as they offer objective evaluation of the risk of outcomes, like mortality. Ultimately, they aim to reduce undesired subjectivity inherent in clinical decision-making and enhance personalized care [3].
At present, the risk assessment for TAVI relies mostly on the STS and EuroSCORE II [10][11]. These scores are not specifically tailored for TAVI, evidenced by their area under the receiver operating characteristic (AUROC) curve values for TAVI patients of 0.61 and 0.62, respectively. Therefore, in practice, cardiologists don't rely much on the two risk scores as they have a relatively low AUROC for TAVI patients. Ideally, cardiologists would use a risk assessment model generated specifically for TAVI patients for patients selection, risk stratification, and benchmarking [4].
Other risk assessment methodologies, such as machine learning methods, have emerged as powerful tools for refining predictive models. Models that are created and evaluated using machine learning are EuroSCORE II, ACC-TAVI, FRANCE-2, OBSERVANT, German AV, $TAVI_2$-SCORe, TVT-score, CoreValve program, TARIS, and PPO. The risk score that has the best AUROC and is externally validated is the ACC-TAVI score, with an AUROC of 0.64 [4]. These models are not used in practice because of the low AUROC or are not validated in an

external population. According to existing literature, echographic parameters, CT parameters, and frailty represent promising features that have not been previously incorporated into any risk model [3].

2 Research question

The main goal of this study is to improve objective decision making in the TAVI pathway which is done by evaluating:

1. What is the impact of next-day discharge on patient outcomes following TAVI?
2. Which ambulatory monitoring systems are most optimal for implementation at AmsterdamUMC?
3. Can a machine-learning-based model be developed to anticipate 30-day mortality, stroke, MI, and pacemaker implantation following TAVI, with an AUROC comparable to or better than the existing ACC-TAVI model?

To answer research questions 2 and 3, two sub-research questions need to be evaluated.

1. Which ambulatory monitoring systems are commercially available and what are their strengths and weaknesses?
2. How do current developed risk prediction models for TAVI work and what input features do they use?

3 Clinical Background

In this section, a comprehensive exploration of the study's clinical background will be undertaken. The clinical background encompasses the anatomy and function of the aortic valve, the pathophysiology of aortic stenosis (AS), the diagnosis of AS, and possible treatments.

3.1 Aortic valve stenosis

The aortic valve prevents the backflow of oxygenated blood from the left ventricle (LV) to the aorta. Its semilunar shape consists of three collagen-based leaflets or cusps, named left coronary cusp (LCC), right coronary cusp (RCC), and non-coronary cusp (NCC) - corresponding to the coronary arteries. These leaflets connect the aortic root via the aortic annulus, as illustrated in Figure 1 [12][13].

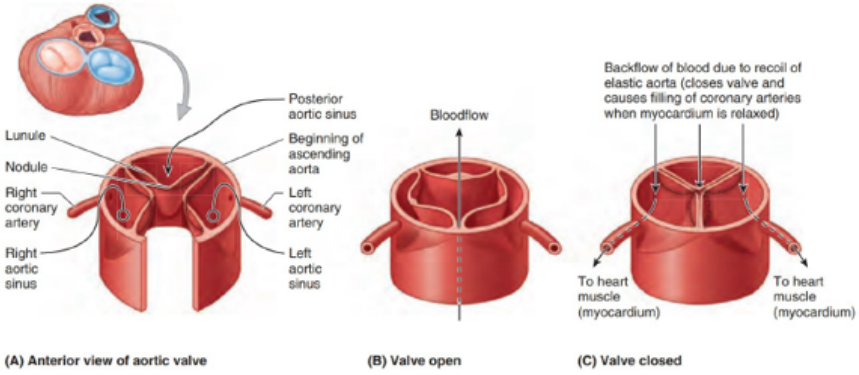


Figure 1: Illustration of the aortic valve. A) The aortic valve has three semilunar-shaped cusps: right coronary cusp, posterior or non-coronary cusp, and left coronary cusp. B) Ejection of blood from the LV forces the cusps apart. C) Closing of the valve due to backflow of blood leads to closure of the valve and filling of the coronary arteries. The cups meet in the center during closure [13]

Aortic stenosis (AS) refers to the narrowing of the aortic valve, obstructing blood flow from the left ventricle to the ascending aorta during systole and possibly causing backflow [13][14]. Possible causes encompass congenital bicuspid valve, idiopathic degenerative sclerosis with calcification, and rheumatic fever. In this study, the focus is on AS in elderly patients caused by the narrowing of the aortic valve because of calcification. Untreated AS may lead to symptoms such as syncope, angina, and exertional dyspnea. Symptoms related to heart failure and arrhythmias may develop, as aortic stenosis can also cause heart failure and arrhythmias caused by calcification in the conduction system [14]. AS is characterized as mild, moderate, severe, and very severe. Aortic stenosis is frequently asymptomatic until individuals have it 10 to 20 years, after which symptoms tend to develop gradually [14].

The diagnosis of aortic stenosis involves clinical suspicion caused by physical examination followed by confirmation through echocardiography, which plays a pivotal role in the accurate quantification necessary for patient management and clinical decision-making.
During auscultation, characteristic crescendo-decrescendo ejection murmur and a systolic ejection click may be present. If there is a delayed closure of the aortic valve, it can result in a single S2 sound. This occurs when the aortic valve closure merges with the pulmonic (P2) component of S2 [15].

Two-dimensional transthoracic echocardiography (TTE) is a primary tool, employed to identify a stenotic aortic valve and its potential causes, quantify left ventricular (LV) hypertrophy and systolic dysfunction, and detect coexisting valvular heart disorders (such as aortic regurgitation and mitral valve disorders) and complications like endocarditis. Additionally, Doppler ECG is utilized to measure the degree of stenosis by assessing jet velocity, transvalvular systolic pressure gradient, and aortic valve area [14][16].

The severity of AS is characterized as follows [14]:

- Mild: peak aortic jet velocity > 2.5-2.9 m/s or mean gradient 10-20 mmHg, or valve area 1.5-2.0 cm^2.
- Moderate: peak aortic jet velocity > 3-4 m/s or mean gradient 20-40 mmHg, or valve area 1.0-1.5 cm^2.
- Severe: peak aortic jet velocity > 4 m/s or mean gradient > 40 mmHg, or valve area < 1.0 cm^2.
- Very severe: peak aortic jet velocity > 5 m/s or mean gradient >60 mmHg.

3.2 Transoartic valve implantation

The management of aortic stenosis involves a careful balance between intervention benefits and associated risks, with decisions guided by symptoms and specific echocardiographic criteria. Periodic clinical evaluations, including ECG and exercise testing, aid in determining the optimal time for valve replacement. Valve replacement is recommended when aortic stenosis is severe and accompanied by symptoms, reduced effort tolerance, or other critical indicators such as a fall in blood pressure $\geq$ 10 mmHg below baseline or LV ejection fraction (EF) <50%. The benefits of interventions do not outweigh the risks if the patients do not reach these criteria [14].

Various interventions exist, including medicinal approaches, balloon valvotomy, SAVR, or TAVI [14]. This study focuses on the TAVI procedure.
TAVI is a less invasive alternative than SAVR and involves the percutaneous implantation of valves through an artery. The new valve is inserted through an artery, mostly the femoral artery, in a collapsed configuration to the aortic valve site and is then deployed to replace the stenotic aortic valve. Different routes of TAVI admission, including transfemoral, transaortic, transapical, and transsubclavic, are considered based on factors like CT scans for vessel and valve diameter, ultrasound for quantifying stenosis severity, and blood and ECG assessments [14][17].

The choice between SAVR and TAVI considers factors such as age, suitability for the transfemoral approach, and life expectancy. Guidelines recommend SAVR for patients < 65 years, while TAVI is favored for those > 75 years or with a life expectancy of < 10 years. For patients aged 65 to 80 years, the decision is based on individual characteristics [14].
Patients with a life expectancy of < 1 year are not recommended for intervention. TAVI presents advantages such as lower short-term mortality, reduced risk of stroke, major bleeding, and atrial fibrillation compared to SAVR. However, it is associated with increased vascular complications, paravalvular regurgitation, the need for pacemaker implantation, and early repeat valve intervention [14].

Possible complications of TAVI include severe bleeding requiring intervention, hematomas, conduction disorders in the heart necessitating permanent pacemaker placement, stroke or heart attack, damage to blood vessels, poor functioning of the new valve, and the need for new interventions due to misplaced valves. The incidence of these complications varies, with mortality around TAVI at 0.7% and within 30 days at 2.6% [19].
Conduction disorders are not uncommon after cardiac surgery. Figure 2 displays the heart's conduction system. The electrical impulse originates in the sinoatrial node (SA node), which serves as the heart's pacemaker. The signal then travels to the atrioventricular node (AV node), where the signal is momentarily delayed allowing the atria to empty the block before the contraction ends. Subsequently, the electrical signal moves to the bundle of His, which splits into the left and right bundle branches, and then proceeds to the Purkinje fibers, prompting the ventricles to contract. One of the main complications that arise post-TAVI is conduction disorders, which include complete atrioventricular block (AVB), left bundle branch block

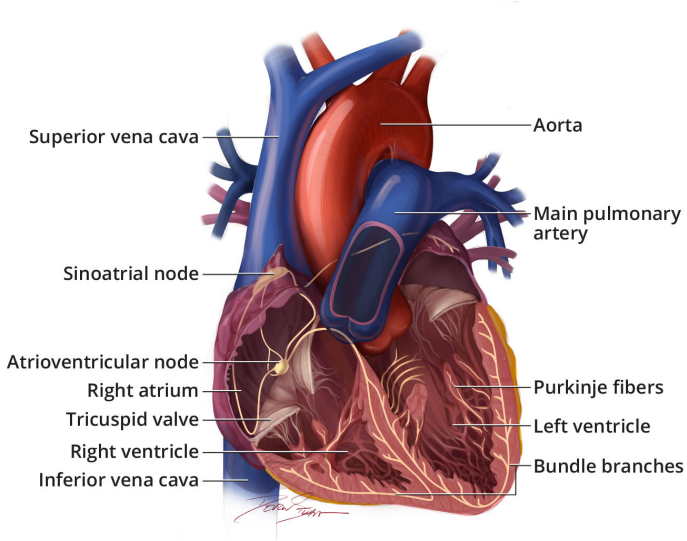


Figure 2: The conduction system of the heart showing the signal starting in the sinoatrial node, progressing to the atrioventricular node to the Bundle of His to the bundle branches ending in the Purkinje fibers.[18]

(LBBB), left anterior hemiblock (LAHB), and right bundle branch block (RBBB). The incidence of post-procedural conduction disturbances varies among studies, with rates of 20% in complete AVB, 7% to 83% in LBBB, 2% in RBBB, and 2% in LAHB. Notably, 37.7% of new LBBB cases were resolved before hospital discharge, with an additional 57% resolving within the 6-12-month follow-up period [20].

Aortic valve stenosis has been linked to prolonged atrioventricular (AV) conduction times and higher degrees of AV conduction disorders. Surgical trauma during open-heart surgery can result in complications, such as complete AV block and new left bundle branch block.
Similarly, TAVI, a less invasive alternative to surgery, poses a risk of damaging the conduction system. Incidences of atrioventricular block, new-onset LBBB, and the need for permanent pacemaker implantation (PPI) are notable concerns during TAVI.
The susceptibility to AV block in TAVI is partly device-specific, with varying incidences reported in different valve types. However, TAVI is a complex procedure involving the manipulation of guide wires and catheter systems in the left ventricular outflow tract, potentially causing conduction system injury beyond the valve itself.
Conduction disturbances in TAVI patients occur early in the procedure, with more than half happening before valve implantation. QRS widening is observed in nearly 50% of patients, often after device implantation or during aortic valve preparation.
Studies highlight a significant increase in the frequency of LBBB after TAVI, suggesting direct injury during valve implantation. New-onset LBBB is common, with varying clinical significance. Mortality data are conflicting, with some studies linking persistent LBBB to an increased risk of all-cause mortality, pacemaker insertion, and syncopal events [21].

4 Technical background

In this section, a comprehensive exploration of the study's technical background will be undertaken. The technical background encompasses the (machine learning) models used for preprocessing, feature selection and risk prediction.
Machine learning, a subset of artificial intelligence, employs algorithms that learn from data, discern patterns, and autonomously construct decision analysis models [22]. In healthcare, transparent machine learning models are preferred, as they allow for comprehensible explanations of their predictions. The models can be used for preprocessing, feature selection, and the risk prediction itself.

4.1 Data preparation

K-nearest neighbors

K-Nearest Neighbors (KNN) is a supervised learning method utilized for the imputation of missing values. It operates on the principle of identifying clusters within data points and assigning a class to unclassified points based on the classes of their nearest neighbors. The algorithm accommodates both linear and non-linear data patterns [23]. The value of 'k', determining the number of nearest neighbors, was selected through cross-validation to optimize performance on the dataset.

The KNN algorithm classifies unknown samples based on their distance to the K-nearest samples in the training set [23]. The algorithm in this model employs the Euclidean distance:

$$D(p,q) = \sqrt{(p_1 - q_1)^2 + (p_2 - q_2)^2 + ... + p_n - q_n)^2} \tag{1}$$

where:

- $D(p,q)$ is the distance between points p and q,
- $p_1, p_2, \ldots, p_n$ and $q_1, q_2, \ldots, q_n$ and are the coordinates of the points p and q in the n-dimensional space [24].

In categorical features, class labels are assigned through a majority voting process. The class that appears most frequently among the nearest neighbors determines the predicted class for the target data point. An illustrative example of KNN's application to categorical features is presented in Figure 3. For continuous features, the class label is determined by computing the average of the target values of the nearest neighbors. This calculated average value serves as the predicted output for the target data point [25].

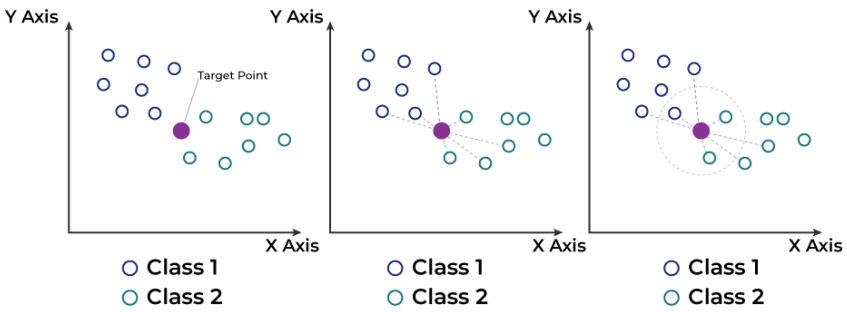


Figure 3: K-Nearest Neighbors diagram for categorical features where the majority vote determines the class of the target point. In this case, the target point will be assigned to class 2 [26].

Iterative Imputer

The IterativeImputer is a multivariate imputation method that estimates each missing value in a feature using the other features in the dataset. Each feature with missing values is modeled in a round-robin fashion, where each missing entry is treated as a function of the other features. In a study by O. Altukhova et al., various imputation methods were evaluated, and both the

IterativeImputer and Fast-KNN exhibited the smallest root mean squared error (RMSE) [27]. This result underscores the efficacy of the IterativeImputer in handling missing data.
A critical aspect of this risk prediction model is its ability to account for the relationships between features when imputing missing values, a capability inherent to the IterativeImputer. Specifically, the IterativeImputer employs Bayesian Ridge regression to predict missing values, ensuring that the interdependencies among features are appropriately leveraged during the imputation process [27].

Mathematically, the objective of the Iterative Imputer can be expressed as follows:

$$\hat{\mathbf{X}} = \arg\min_{\mathbf{X}} \sum_{j=1}^{p} \left[\sum_{i \in \mathcal{O}_j} (x_{ij} - f_j(\mathbf{X}_{-j,i}))^2 + \sum_{i \in \mathcal{M}_j} (x_{ij} - f_j(\mathbf{X}_{-j,i}))^2 \right] \tag{2}$$

where:

- $\mathbf{X}$ complete dataset including the missing data,
- $\hat{\mathbf{X}}$ is the imputed dataset,
- p the number of features,
- $\mathcal{O}_j$ are the indexes of observed values in column j ,
- $\mathcal{M}_j$ are the indexes of missing values in column j ,
- f_j the regression function that is trained on the observed values in column j and the other columns ($\mathbf{X}_{-j}$).

RandomOverSampler
RandomOverSampler (ROS) is a resampling method that randomly selects minority examples, replicates them, and adds them to the original dataset so that the minority set becomes a comparable size to the majority set. In the study of J. Liu et al. the ROS outperforms other oversampling techniques. An explanation is that it maintains the characteristics of the original data [28].

Mathematically, the objective of ROS can be expressed as follows:

$\hat{\mathbf{X}}, \hat{\mathbf{y}} = (\mathbf{X}, \mathbf{y}) \cup \bigcup_{c \in \mathcal{C}} (\mathbf{X}_c^{\text{new}}, \mathbf{y}_c^{\text{new}})$, where $\mathbf{X}_c^{\text{new}}, \mathbf{y}_c^{\text{new}}$ are random duplicates so $|\mathbf{X}_c^{\text{new}}| = n_{\max} - n_c$

where:

- $\mathbf{X}$ is the original dataset,
- $\mathbf{y}$ are corresponding labels,
- $\mathcal{C}$ is the unique class labels,
- $n_{\max}$ is the maximum number of observations in one class,
- $\mathbf{X}_c$ and $\mathbf{y}_c$ are the data and labels of class c,
- $\mathbf{X}_c^{\text{new}}$ and $\mathbf{y}_c^{\text{new}}$ are the random selected duplicates of class c, so that every class has $n_{\max}$ observations.

4.2 Feature selection methods

LASSO regression
Least Absolute Shrinkage and Selection Operator (LASSO) regression is a technique within linear regression that can be used for feature selection. Rather than solely focusing on predicting the target variable, LASSO regression actively identifies and selects the most influential features for the model [29].

In LASSO regression, the model minimizes the residual sum of squares, just like ordinary least squares regression, but with an additional penalty term. This penalty term, denoted by

λ (lambda), is multiplied by the sum of the absolute values of the coefficients. As a result, LASSO regression simultaneously minimizes the error between observed and predicted values (residual sum of squares) and the sum of the absolute values of the coefficients [29].

The key feature of LASSO regression is its ability to enforce sparsity in the coefficient estimates. By setting certain coefficients to precisely zero, LASSO conducts variable selection, effectively eliminating irrelevant predictors from the model. This property makes LASSO particularly useful when dealing with high-dimensional data where the number of predictors exceeds the number of observations [29].

Mathematically, the objective function of LASSO regression is expressed as:

$$\beta^{LASSO} = \underset{\beta_0,\beta_1,\ldots,\beta_p}{\arg\min} \sum_{i=1}^{n}(y_i - \beta_0 - \sum_{j=1}^{p}\beta_j x_{ij})^2 + \lambda \sum_{j=1}^{p}|\beta_j| \tag{3}$$

where:

- y_i represents the dependent variable for observation i,
- β_0 is the intercept term,
- β_j are the regression coefficients corresponding to predictor variables x_j.
- x_{ij} denotes the value of the j-th predictor variable for observation i.
- The regularization parameter λ controls the strength of the penalty applied to the sum of the absolute values of the coefficients.

Overall, LASSO regression strikes a balance between prediction accuracy and model interpretability by shrinking coefficient estimates and performing variable selection. It proves particularly effective when dealing with correlated predictors, as it tends to select one predictor from a group of highly correlated variables while shrinking others to zero. This property results in simpler and more interpretable models, making LASSO regression a valuable tool in statistical modeling and machine learning applications [29].

Wrapper -backward elimination
The wrapper method backward elimination employs a learning algorithm to evaluate the goodness of the selected features, where a specific classifier is trained for each feature subset. The wrapper method backward elimination initially employs a comprehensive model containing all variables. Subsequently, variables are systematically eliminated from the model, one by one, until only those with a significant impact on the outcome remain. The variable with the lowest test statistic or the highest p-value exceeding a predetermined cutoff value is iteratively removed from the model. This process continues until all remaining variables demonstrate statistical significance at the cutoff value [30].

Wrapper methods such as backward elimination are often computationally intensive. However, they yield promising subsets of features tailored to specific classification algorithms. These methods systematically explore feature space to identify the most informative variables for predictive modeling tasks [31].

4.3 Machine learning models in healthcare

Logistic regression
Logistic regression (LR) estimates the probability of an event occurring based on a given data set of independent variables. The logistic regression will take the covariance among variables into account which are subjected to confounding effects [32][33]. LR uses a log odds ratio and an iterative maximum likelihood method to fit the final model, making it suitable for non-normally distributed data or situations with unequal covariance matrices. Logistic regression assumes independence among variables, which is not always met [34].
The logistic regression model is defined by the sigmoid function:

$$p(x) = \frac{1}{1 + e^{-(\beta_0+\beta_1 x_1+\ldots+\beta_p x_p)}} \tag{4}$$

where:

- $p(x)$ is the probability of the outcome x belonging to the positive class,
- $\beta_0, \beta_1, \ldots, \beta_p$ are the regression coefficients,
- $x_1, x_2, \ldots, x_p$ are the predictor variables,
- e is the base of the natural logarithm.

XGBoost
XGBoost is a decision-tree-based supervised learning technique. Decision trees do not have a single equation but consist of a series of if-else conditions. Each node in the tree represents a decision based on the specific features [35]. XGBoost uses a set of weak prediction models (e.g., decision trees) to yield predictions and to optimize the loss function while employing regularization parameters to mitigate overfitting concerns [35]. The core objective of XGBoost is to minimize the combined objective function, encompassing the loss function and regularization terms [36]:

$$L^{(t)} = \sum_{i=1}^{n} \ell(y_i, \hat{y}_i^{(t-1)} + f_t(x_i)) + \Omega(f_t) \tag{5}$$

where:

- ℓ is the loss function that represents the error between observed data y_i and predicted data $\hat{y}_i$,
- f_t is the model of the t-th tree,
- t is the iteration index during the optimization process

The detail of regularisation term Ω can be expressed as:

$$\Omega(f) = \gamma T + \frac{1}{2}\lambda ||w_j||^2 \tag{6}$$

where:

- T indicates the total number of tree leaves,
- γ and λ are penalty coefficients,
- w_j is a vector containing each leaf's score.

During the training process, parameter tuning is imperative. While some parameters like γ in Eq. 6 are determined during training, others such as learning rate (η), maximum tree depth (max_depth), and minimum child weight (min_child_weight) must be defined before the training process can begin. Optimal hyperparameters, which may be found by hyperparameter tuning, are required. Among the prevalent methods for hyperparameter optimization—grid search, random search, and Bayesian optimization—we opt for grid search in this study due to its simplicity.

Random Forest
A random forest is an aggregate learning approach for classification and regression analysis [35]. It is a collection of classification and regression trees trained on datasets of the same size as a training set, called bootstraps, created from a random resampling on the training itself. Once a tree is constructed, a random order set of bootstraps is used as a test set. Random forest is prone to over-fitting, compared to conventional decision trees by averaging predicted values from individual trees [37].

4.4 Cross-validation

K-fold cross-validation
Cross-validation is a robust statistical method used to evaluate and compare learning algorithms by partitioning data into training and validation segments. This technique ensures

that each data point has the opportunity to be used for validation in successive rounds, thus providing a comprehensive assessment of the model's performance. The most common form of cross-validation is k-fold cross-validation [38].

In k-fold cross-validation, the dataset is divided into k equally sized segments, known as folds. The process involves k iterations of training and validation. In each iteration, a different fold is held out for validation, while the remaining $k - 1$ folds are used for training the model. This method ensures that each fold is used exactly once for validation [38].

Formally, the k-fold cross-validation procedure can be described as follows:

$$CV(k) = \frac{1}{k} \sum_{i=1}^{k} e_i \tag{7}$$

where:

- $CV(k)$ represents the cross-validation error for k folds,
- e_i is the error for the i-th fold

During each iteration, the learning algorithm uses $k - 1$ folds to train the model and subsequently makes predictions on the held-out validation fold. The performance of the learning algorithm on each fold is measured using a pre-determined metric such as accuracy. After completing the process, k samples of the performance metric are obtained for each algorithm. These samples can be averaged to obtain an aggregate measure or used in statistical hypothesis tests to compare the effectiveness of different algorithms [38].

5 Next-day discharge

5.1 Abstract

Introduction: Implementing fast-track protocols can potentially enhance hospital capacity, reduce costs, decrease the risk of hospital-acquired complications, and improve patient comfort. The aim of this study was to study the impact of next-day discharge on patient outcomes following Transcatheter Aortic Valve Implantation (TAVI).

Methods and Results: Patients were selected pre-TAVI for eligibility of next-day discharge, including 158 patients. After the procedure patients who were still eligible for discharge after 24 hours were in the NDD+ arm (56 patients), patients not eligible anymore were in NDD- arm (95 patients). The primary endpoint defined as the composite endpoint showed a significant difference (3.6% vs 17.0%, p=0.018). Other endpoints were late complications (1.8% vs 8.5%, p=0.15), rehospitalizations (1.8% vs 6.4%, p=0.26), and mortality (0%, vs 2.1%, p=0.53). Secondary endpoints were the change in NYHA class (-1.0 vs -1.0, p=0.46) and the change in Quality of Life by EQ-5D-Y (-1.0vs. -1.0, p=0.39).

Conclusion: Next-day discharge following TAVI is a viable alternative to the traditional 72-hour discharge protocol. The benefits of next-day discharge included reduced hospital stays, increased hospital capacity, cost savings, and fewer hospital-acquired complications. Patients had also reported a positive experience with earlier return to their home environment. However, due to the small sample size, these findings should be interpreted with caution.

Keywords: Transcatheter aortic valve implantation, Next-day Discharge, clinical pathway, length of stay, hospital volume.

5.2 Introduction

Transcatheter aortic valve implantation (TAVI) is commonly utilized in high and intermediate-risk patients with severe aortic valve stenosis. One of the benefits of this percutaneous approach is the faster post-procedural recovery. Protocols for post-procedural care and duration of hospital stay vary across institutions [39]. Until August 2023, AmsterdamUMC followed a protocol of monitoring patients for 72 hours post-TAVI.
Different trials, such as the FAST TAVI trial, Vancouver 3M trial, and the Tasmanian Experience, have demonstrated positive outcomes with a 24-hour monitoring period for selected patients who meet specific criteria [40][41][42]. The primary purpose of post-TAVI monitoring is to detect new-onset cardiac conduction disorders (CCDs), conduct neurological evaluations, and manage postoperative medication. The neurological evaluation and the management of postoperative medication are completed 4 hours after the procedure [7], which allows patients to mobilize after 4 hours.
Notably, 60-80% of new-onset CCDs after TAVI develop during the procedure or within 24 hours after the procedure [3]. Monitoring CCDs is crucial for monitoring a total atrioventricular (AV) block possibly causing collapse. Patients who develop a total AV-block are indicated for permanent pacemaker implantation (PPI) [43]. Some patients are at higher risk for needing a PPI, for example, a pre-existing right bundle branch block (RBBB). RBBB is a risk factor for developing a complete AV-block and therefore needing a permanent pacemaker [44]. At AmsterdamUMC, 8.3% of the patients are indicated for a PPI over the last 5 years (2018-2023) [19].

Implementing fast-track protocols can potentially enhance hospital capacity, reduce costs, decrease the risk of hospital-acquired complications, and improve patient comfort. Consequently, AmsterdamUMC aims to study the impact of next-day discharge on patient outcomes following TAVI.

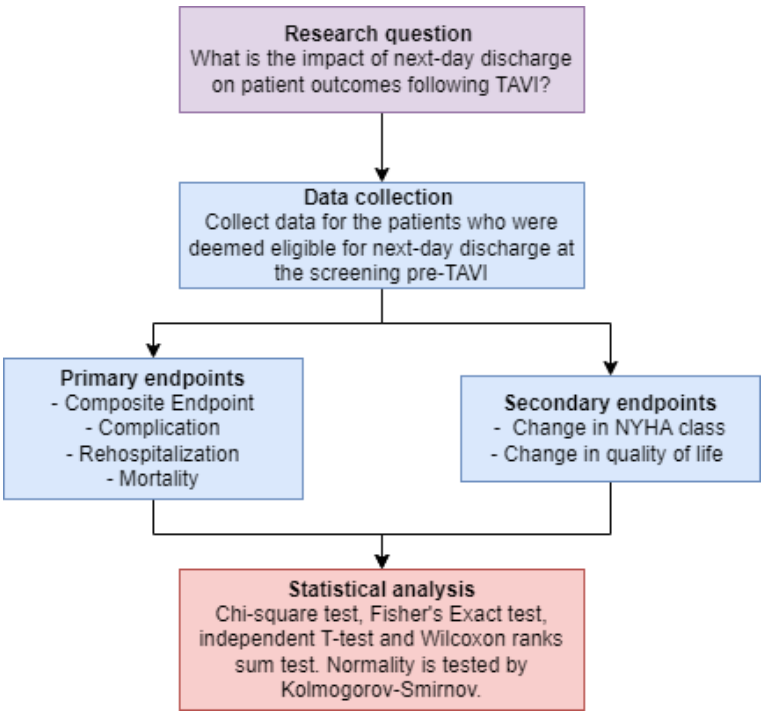


Figure 4: Flowchart of the performed method to analyze next-day discharge. Colors indicate different steps in the method distinguishing the research question, data collection & analysis, and statistical analysis.

5.3 Methods

In Figure 4, an overview of the method to analyze next-day discharge is displayed in a flowchart. The first step in answering the research question regarding next-day discharge was collecting the data. Data was collected from August 2023 to May 2024, with the follow

up extending to June 2024. The primary endpoints were 30-day mortality, rehospitalization, complication, and the composite endpoint. Secondary endpoints were change in NYHA class and change in quality of life (QoL). Statistical analysis consisted of the Chi-square test, Fisher's Exact Test, independent T-test, or Wilcoxon rank sum test. Normality was tested by Kolmogorov-Smirnov.

5.3.1 Study population

Patients were enrolled in the next-day discharge program between Augustus 2023 and May 2024. The follow-up period lasted until June 2024. All patients undergoing transfemoral TAVI over 18 years of age in the AmsterdamUMC were included. Patients were excluded if they had a pre-existing right bundle branch block, it was not an elective procedure, or if no informal caregiver could be present the first night after discharge. The included patients were divided into two groups based on next-day discharge criteria. The criteria were that when patients did not have an increase in PQ-time for 20 ms or more and did not have an eventful procedure limiting patients from mobilizing, they could go with next-day discharge (NDD+ arm). Patients not meeting these requirements were not discharged after 24 hours (NDD- arm). The criteria changed from December 2023. Prior to this modification, criteria included the exclusion of patients with permanent atrial fibrillation (AF) and those with any new-onset conduction disturbances (CCDs) following TAVI or any eventful procedures. After December 2023, these criteria were adjusted or removed. Consequently, there is a subset of patients who met the exclusion criteria between August 2023 and November 2023 but would have been eligible for next-day discharge had the procedure been performed after December 2023. These patients remain in the NDD- group. The different next-day discharge criteria for the two time frames are detailed in Table 1.

Table 1: Next-day discharge criteria in the two phases of the study.

Old next-day discharge criteria	New next-day discharge criteria
Pre-existent RBBB	Pre-existent RBBB
Permanent atrial fibrillation	
Urgent procedure	Urgent procedure
Eventful procedure	Eventful procedure limiting patients from mobilizing
New-onset CCDs post-TAVI	Increase in PQ-time $\geq$ 20 ms
No informal caregiver	No informal caregiver

The old and new next-day discharge criteria are depicted. The old criteria were used from August 2023 to November 2023. From December 2023 the new criteria were used. The differences in criteria were the deletion of permanent AF, and other CCDs besides the increase in PQ-time $\geq$ 20 ms and eventful procedures not preventing patients from mobilizing.
RBBB: Right Bundle Branch Block, AF: Atrial Fibrillation, CCDs: Cardiac Conduction Disorders.

5.3.2 Study design and setting

This was a single-center, retrospective analysis obtained from a prospective TAVI registry. Data was collected for patients who were discharged after 24 hours and was compared to patients who were not discharged after 24 hours.

5.3.3 Data collection and study endpoints

Patient information was registered 30 days after the TAVI procedure to compare the outcomes of next-day discharge to standard care. The primary endpoints are the composite endpoint, late complications (>24 hours after TAVI), rehospitalization, and mortality. Late complications are categorized as permanent pacemaker implantation, stroke with residual symptoms, vascular complications, conduction disorders, and others. Normally, complications after the first 72 hours are considered late, however, the NDD+ group is discharged after 24 hours, necessitating consideration of complications or rehospitalizations occurring between 24 and 72 hours [45]. To ensure a balanced comparison, late complications in the NDD- group are also classified

based on the >24 hours criterion. QoL was measured by EQ-5D-Y, described in Appendix 9.1. Scores go from 5 to 15, with higher scores indicating a poorer quality of life.

5.3.4 Data analysis

Descriptive statistics are reported as mean ± SD for normally distributed continuous variables, or as median and 25th – 75th percentile (IQR) otherwise. Normality of distribution was tested by means of Kolmogorov-Smirnov test. Absolute and relative frequencies are reported for categorical variables. Continuous variables were analyzed with the student's t-test or Wilcoxon rank sum test depending on variable distribution. Differences in proportions were compared by applying the Chi^2-test or Fisher's exact test. For all analyses, a 2-sided $p < 0.05$ was considered statistically significant.

5.4 Results

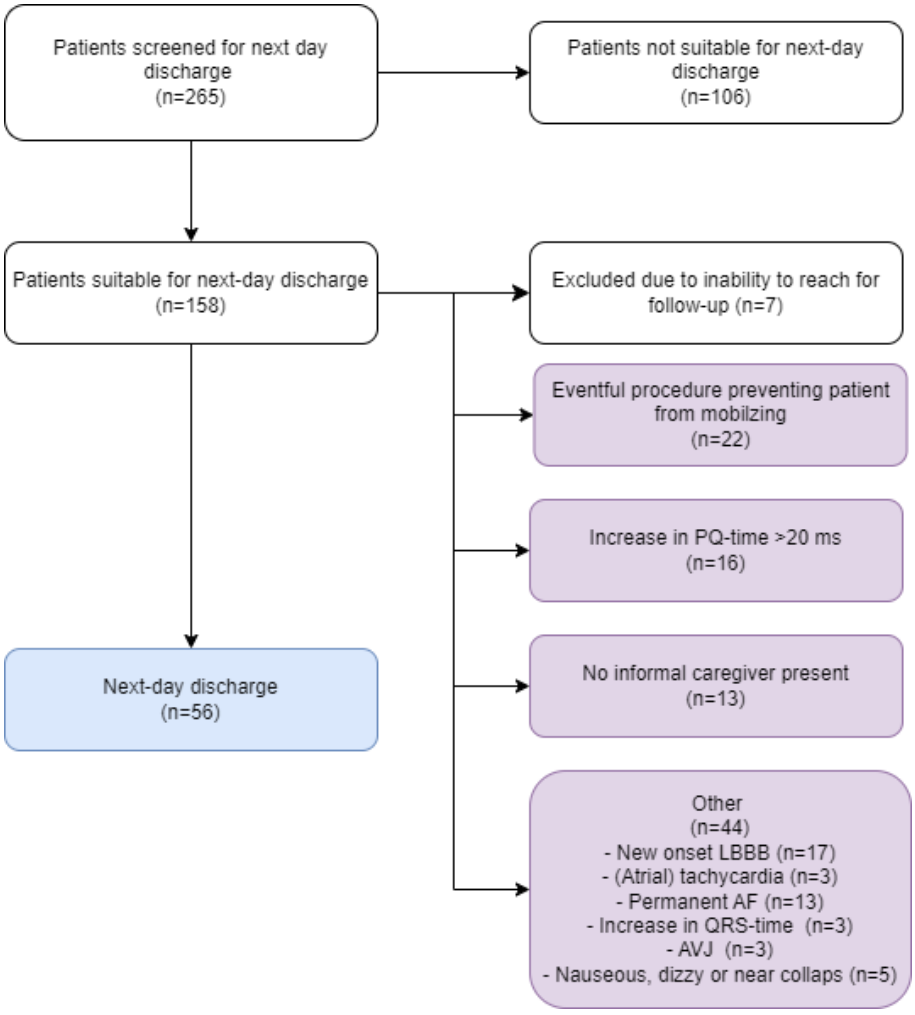


Figure 5: A flowchart of the inclusions of patients in both time periods for the NDD+ arm and NDD- arm. The blue color represents the NDD+ arm, and the purple color represents the NDD- arm. The white color represents the excluded patients.

A total of 265 patients underwent TAVI procedures at AmsterdamUMC between August 2023 and May 2024. Of these, 158 patients (60%) met the pre-TAVI criteria for next-day discharge (NDD) at the screening before the procedure. Patients suitable for NDD were divided into the NDD+ and NDD- arms. The NDD+ arm comprised 56 patients (35% of the patients that were deemed suitable pre-TAVI), 7 patients (4% of the patients that were deemed suitable pre-TAVI) were excluded due to inability to reach for follow-up while the remaining 95 patients (60% of the patients that were deemed suitable pre-TAVI) were categorized into the NDD- arm. Figure 5 displays the inclusions of this study. The factors contributing to a patient's failure to meet

the criteria for NDD despite initially qualifying, are illustrated. The blue color represents the NDD+ group, and the purple color represents the NDD- group. Patients without an informal caregiver present or with 'Other' reasons besides the 'collapse' should have been eligible for Next-Day Discharge. However, the majority of these patients were included based on outdated criteria or due to the untimely provision of information regarding the informal caregiver. If these patients had been discharged the next-day and all patients were available for follow-up, the NDD+ group would have contained twice as many patients causing the NDD+ arm to have comprised 67% of the total patients that met the pre-TAVI criteria.

5.4.1 Demographic characteristics

Baseline characteristics are listed in Table 2 and were broadly comparable across the NDD+ and NDD- arms. The demographic features demonstrated significant differences in the female gender, the QoL, and the presence of a permanent pacemaker pre-TAVI and (respectively 32.1% vs 62.1%, p=<0.001, and 6.0 vs. 6.0, p=0.048, and 24.4% vs 5.3 %, p=0.003). ECG and echographic parameters were comparable across the two groups.

Table 2: Demographic characteristics of patients selected for NDD pre-procedural (n=131)

Features	NDD+ arm (N=56)	NDD- arm (N=95)	p-value
Clinical			
Age (years)	80 (76.2 - 81.3)	82 (80.0-82.4)	0.27
Female gender	18 (32.1%)	59 (62.1%)	<0.001
BMI (kg/m2)	25.7 (25.1-27.7)	25 (25.2-27.3)	0.40
NYHA class	2.0 (1.9-2.3)	2.0 (2.1-2.4)	0.21
QoL	6.0 (6.1-6.7)	6.0 (6.4-6.8)	0.048
Frailty	3.0 (2.2-3.4)	3.0 (2.9-3.8)	0.10
Diabetes	8 (14.3%)	18 (18.9%)	0.45
Prior CVA/TIA	9 (16.1%)	16 (16.8%)	0.88
Prior MI	8 (14.3%)	11 (11.6%)	0.65
Peripheral artery disease	3 (5.4%)	4 (4.2%)	1.0
Permanent pacemaker	12 (21.4%)	5 (5.3%)	0.003
eGFR (mL/min)	62.5 ± 15.5	60.3 ± 17.8	0.45
Syncope	4 (7.1%)	4 (4.2%)	0.47
Baseline ECG			
AV-Block (1st, 2nd, total)	9 (16.1%)	12 (12.6%)	0.57
LBBB	3 (5.4%)	5 (5.3%)	1.0
Permanent AF	10 (17.9%)	25 (26.3%)	0.22
Baseline TTE			
LVEF <50%	12 (21.4%)	24 (25.3%)	0.57
Aortic valve regurgitation	22 (39.3%)	36 (37.9%)	0.94
AV mean PG (mmHg)	39.2 ± 14.4	40.6 ± 15.7	0.59
AVA (cm2/m2)	0.81 ± 0.16	0.76 ± 0.20	0.12

Statistical difference between demographic features that are described by mean + std for normally distributed continuous variables, median (IQR) for not normally distributed variables, and n (%) for frequencies for the NDD+ arm and the NDD- arm.
BMI: Body Mass index, NYHA: New York Heart Association, CVA: Cerebro Vascular Accident, TIA: Transient Ischemic Attack, ECG: electrocardiogram, AV: atrioventricular, AF: Atrial Fibrillation, AV mean PG: Aortic Valve mean Pressure gradient, AVA: Aortic Valve Area.

Figure 6 illustrates the reasons why women and men were selected for the NDD- group,

providing insight into the statistical difference in the demographic characteristics between both groups. Notably, more than twice as many females experienced eventful procedures that impeded their mobilization, and six times as many females exhibited an increase in PQ-time of more than 20 ms. These two factors largely explain why the NDD- group has a significantly higher proportion of females compared to males.

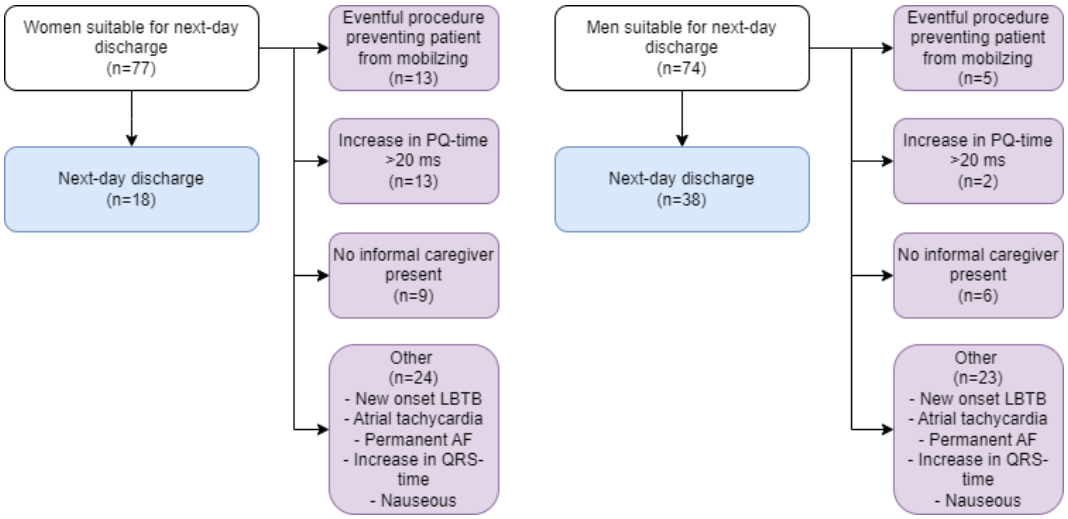


Figure 6: Reasons for the inclusion of women and men in the NDD- group.

5.4.2 Impact new criteria on patient inclusions

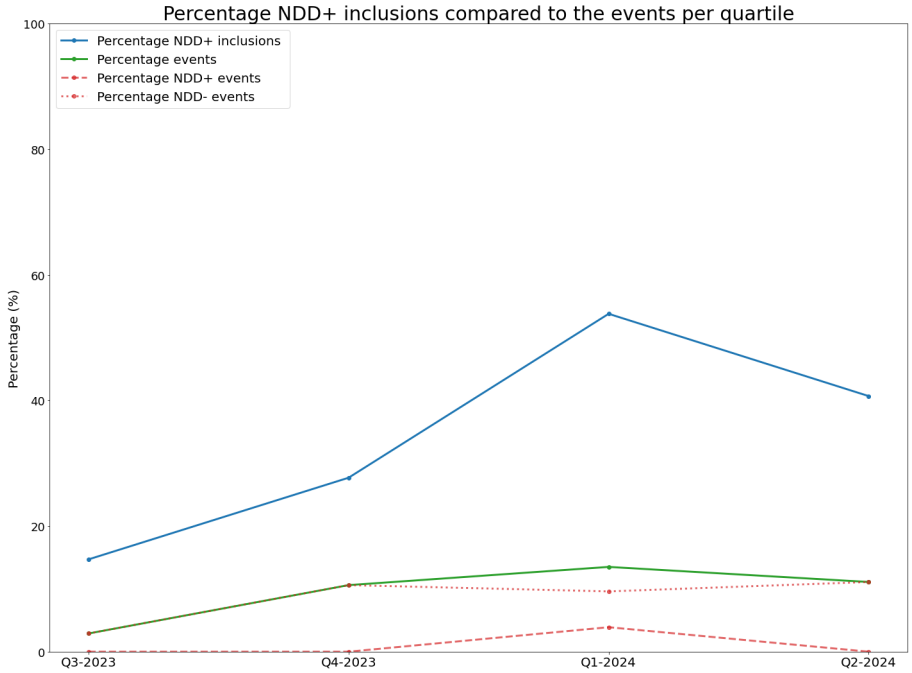


Figure 7: The percentage of the inclusions in the NDD+ arm compared to the percentage of events in each quartile. The blue line represents the percentage of inclusions in the NDD+ arm. The green line represents the percentage of events in that quartile, where the red dotted line represents the NDD- arm and the red striped line represents the NDD+ arm.

Figure 7 illustrates the percentage of inclusions compared to the percentage of events per quartile. The blue line depicts the distribution of the NDD+ inclusions across quartiles. Following the implementation of new criteria in December 2023, there is an evident rise in the percentage of inclusions in the NDD+ arm. Subsequently, although the percentage of NDD+ inclusions decreases slightly beyond this initial quartile, it remains elevated compared to the old criteria.

The green line represents the incidence of events per quartile. Notably, a slight increase is observed in Q1-2024 aligning precisely with the increase in NDD+ inclusions. However, upon examining the events within the NDD+ arm, it becomes apparent that these events predominantly occur in the NDD- arm. Thus, there appears to be no direct correlation between the increase in the size of the NDD+ group and the occurrence of events.

Figure 8 depicts the temporal distribution of the events following TAVI. It shows that 3 events took place in the first two days after the first 24 hours. The other events occurred after the old discharge limit of 72 hours. Of the three events that took place in the first 72 hours, two took place during hospital stay in the NDD- arm: One new-onset atrial fibrillation, and one groin bleeding. One rehospitalization was necessary in the NDD+ arm on day two caused by a total AV-block and a collapse.

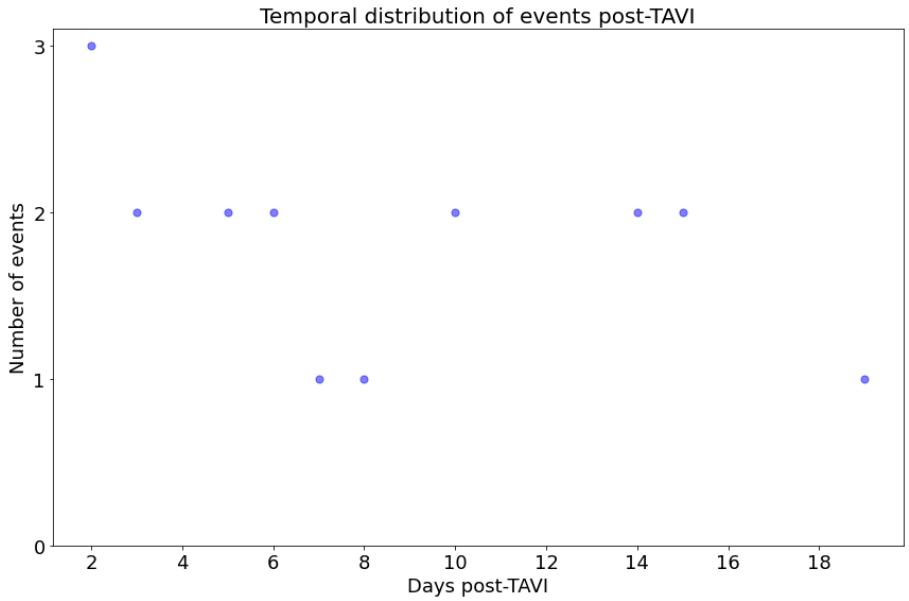


Figure 8: The number of events that took place on days post-TAVI. Three events took place in the first 72 hours after the procedure. The days are counted as the days after the first 24 hours.

Primary Endpoints

Table 3 outlines the incidence of primary endpoints between the NDD+ and NDD- arms. In the NDD+ arm, 2 patients had a composite endpoint, compared to 16 in the NDD- arm showing a significant difference (3.6% vs 17.0%, p=0.018). Late complications arose 1 time in the NDD+ arm, and 9 times in the NDD- arm (1.8% vs 8.5%, p=0.15). The complication in the NDD+ arm was a pacemaker implantation. The complications in the NDD- arm consisted of four pacemaker implantations, one non-ST-elevation myocardial infarction (NSTEMI), two major bleedings, and one new-onset atrial fibrillation (AF). One rehospitalization was reported in the NDD+ arm, while in the NDD- arm 6 rehospitalizations were reported (1.8% vs 6.4%, p=0.26). The reported rehospitalization in the NDD+ arm was a patient admitted for observation in the Emergency Cardiac Care, because of dizziness, headache, and seeing light flashes. The rehospitalizations in the NDD- arm consisted of one for a pre-existent rhythm disorder, one for positional dizziness, one for pericardial effusion combined with atrial fibrillation, one for hypoglycemia after not being able to eat well after a peri-procedural stroke, one for cardiac monitoring and one for a fever following TAVI. Two cases of mortality were reported in the NDD- arm (0.0% vs 2.1 %, p=0.53). One was attributed to a neurological cause involving a pre-existing subdural hematoma. The other was attributed to ventricular fibrillation due to a bad LVEF. The only significant difference between the two arms was in the composite endpoint.

Table 3: Comparison of Primary Endpoints between NDD+ and NDD- arms.

Endpoint	NDD+ arm (N=56) n (%)	NDD- arm (N=95) n (%)	P-value
Composite endpoint	2 (3.6%)	16 (17.0%)	0.018
Late complications	1 (1.8%)	8 (8.5%)	0.15
Stroke with residual symptoms	*0 (0.0%)*	*0 (0.0%)*	*1.0*
Permanent pacemaker implantation (PPI)	*1 (1.8%)*	*4 (4.3%)*	*0.65*
Vascular complications	*0 (0.0%)*	*3 (3.2%)*	*0.29*
Conduction/rhythm disorders	*0 (0.0%)*	*1 (1.1%)*	*1.0*
Rehospitalization	1 (1.8%)	6 (6.4%)	0.26
Mortality	0 (0.0%)	2 (2.1%)	0.53

Secondary Endpoints

Table 4 outlines the secondary endpoints. Both endpoints are not normally distributed. The median change of NYHA class of NDD+ and NDD- arms are -1.0 with respectively the interquartile range of -0.88 to -0.48 vs. -0.96 to -0.67. The median change in quality of life of both NDD+ and NDD- arms was -1.0, with respectively the interquartile range of -1.09 to -0.64 and -0.87 to -0.45. Neither secondary endpoint showed statistically significant differences.

Table 4: Comparison of Secondary Endpoints >24 hours post-TAVI between NDD+ arm and NDD- arm

Endpoint	NDD+ arm (N=56) Median (IQR)	NDD- arm (N=95) Median (IQR)	P-value
Change in NYHA class	-1.0 (-0.90 - -0.51)	-1.0 (-0.95 - -0.68)	0.46
Change in quality of life	-1.0 (-1.2 - -0.68)	-1.0 (-0.87 - -0.47)	0.39

5.5 Discussion

This study aimed to evaluate the effects of the next-day discharge following TAVI compared to extended hospital stay. The findings indicate a statistically significant difference in the composite endpoint of the primary endpoints, and no statistical advantages to the 72-hour protocol, suggesting that extended in-hospital monitoring may not be necessary. Similar results have been reported in previous studies, where early discharge protocols did not lead to increased complications or re-admissions [41][42]. Next-day discharge has been associated with several benefits, including reduced hospital stays, increased capacity, cost savings, and fewer hospital-acquired complications. Additionally, patients also have reported a positive experience with faster return to their home environment. Nonetheless, the small sample sizes in both patient groups necessitate a cautious interpretation of these results.

Only the composite endpoints show significant differences in favor of the NDD+ arm, the other endpoints are not significant. Besides the significant difference in composite endpoints, Figure 7 shows that the easing of criteria did not increase the number of events, indicating the current criteria to be safe. Furthermore, only 3 of the 18 events (17%) occurred between 24- and 72 hours post-procedure. All these outcomes indicate that current next-day discharge criteria can be considered safe.

The statistical difference in baseline demographic regarding the permanent pacemaker can be explained by that patients who have a permanent pacemaker before the procedure, can be sent with discharge safely after 4 hours. The significant difference in QoL can be explained by the inherent bias in the NDD- arm, which will be further explained in the limitations. There was a significant difference between the female gender of both arms, which could not be directly

explained. The reason the groups differed was that females had twice as many periprocedural complications and four times as often a delay in PQ-time, as can be found in Figure 6. According to C. Ziou et al., previous retrospective studies have shown that women experience higher in-hospital mortality rates and a greater likelihood of perioperative complications than men, although women tend to have better long-term survival rates [46].
According to J.M Ravoux et al. the female gender is associated with a 14.9% less chance on a PPI after TAVI than males. The increase in PQ time is not directly related to PPI, however, an increase in PQ time does indicate an AV conduction disorder. The reason why four times as many females had an increase in PQ-time can not be explained by literature [47].

A critical limitation of this study is the current sample size, which is significantly small. With a small sample size achieved, the statistical power to detect the meaningful differences between the next-day discharge and 72-hour protocol is limited.
Efforts are underway to extend the data collection across multiple healthcare centers in the Netherlands, including collaborations with ErasmusMC and St. Antonius Hospital Nieuwegein. These collaborations will facilitate the rapid accumulation of patient data, augmenting sample sizes, and improving the statistical power of our analysis. Additionally, the inclusion of diverse patient populations from these centers will enhance the generalizability of our findings.

Another limitation is the inherent bias in the NDD- arm, which consists of patients generally in poorer health compared to those eligible for next-day discharge. This group includes patients with prolonged PQ intervals or those who underwent more complicated procedures. Although the bias was mitigated by considering only complications occurring after 24 hours, this approach does not entirely eliminate the inherent bias.

Despite these limitations, preliminary trends suggest potential advantages associated with next-day discharge following TAVI. Specifically, the next-day discharge arm exhibited a lower incidence of complications, rehospitalization, and mortality compared to the NDD- arm. Notably, two patients in the NDD- arm acquired pneumonia during their stay, highlighting the increased risk of hospital-acquired complications with longer hospital stays. These observed trends suggest that next-day discharge could be a safe and effective effective post-procedural management strategy. This is also confirmed by studies performed in Vancouver and Tasmania [41][42]. Both of the studies proved next-day discharge to be safe.

Patients have also reported a positive experience with faster return to their home environment and recovery there. However, some patients expressed insecurity and desire for an additional check-up one week after discharge to ensure everything progressed well. An ambulatory monitoring device could be a potential solution to address this concern, as discussed in section 5.6.

5.6 Further research

As our study progresses, additional data collection and analysis will be essential to draw definitive conclusions. A comprehensive analysis of patient outcomes, including one-year follow-up data, will provide deeper insights into the comparative effectiveness of next-day discharge versus traditional discharge protocols. Furthermore, subgroup analyses based on patient characteristics such as age, comorbidities, and procedural complexities will help identify individuals who may derive the greatest benefit from next-day discharge strategies. Additionally, ongoing evaluation of healthcare resource utilization and cost-effectiveness will inform healthcare decision-making and resource allocation in the context of TAVI procedures.

Implementing ambulatory monitoring techniques at AmsterdamUMC can enhance the safety of patients in their home environment post-discharge. The successful integration of such monitoring systems could pave the way for same-day discharge following TAVI procedures. An overview of potential ambulatory monitoring systems suitable for implementation at

AmsterdamUMC is provided in section 6.

5.7 Conclusion

In conclusion, this study suggests that next-day discharge following TAVI is a viable alternative to the traditional 72-hour discharge protocol, with statistically significant composite endpoints in favor of the NDD+ arm. The benefits of next-day discharge include reduced hospital stays, increased hospital capacity, cost savings, and fewer hospital-acquired complications. Patients have also reported a positive experience with earlier return to their home environment. However, due to the small sample size, these findings should be interpreted with caution. Further research with larger sample sizes and extended follow-up is necessary to confirm these preliminary results and fully establish the safety and efficacy of next-day discharge protocols.

6 Ambulatory monitoring

6.1 Abstract

Introduction: The aim of this overview is to provide insights that aid in the selection of the most suitable monitoring systems for TAVI patients in AmsterdamUMC, considering performance metrics, compatibility with established criteria, and what the associated challenges are for the implementation.
Methods and Results: PubMed and Google Scholar were utilized to include articles for searches on 'Ambulatory Monitoring ECG', 'Telemetry Cardiac Monitoring', 'Home Monitoring Devices cardiology', 'Ambulatory Monitoring Overview', 'Mobile Cardiac Telemetry', 'Handheld ECG', 'Wearable ECG', and 'Patch ECG'. Included articles were classified on the type of monitoring or the number of ECG leads they provided, an ideal scenario was outlined and the performance of the included devices was outlined. Based on the combination of alignment with the ideal situation and the performance of the devices the best devices appeared to be Senselink, Zenicor ECG, and Kardia Mobile- HartWacht. **Conclusion:** Presently, no ambulatory monitoring system comprehensively meets the criteria developed by M. Hermens et al. for an optimal home monitoring platform targeting the detection of CCDs, particularly atrioventricular block [7]. Nonetheless, various potential scenarios have been considered to enhance conformity with these standards. Of notable significance are Kardia Mobile- HartWacht, Senselink, and Zenicor ECG, identified as the foremost contenders for potential integration within AmsterdamUMC's framework for post-transcatheter aortic valve implantation (TAVI) surveillance

Keywords: Transcatheter aortic valve implantation, Ambulatory monitoring, Telemonitoring, Devices, Kardia Mobile, Zenicor ECG, Senselink.

6.2 Introduction

Transcatheter aortic valve implantation (TAVI) is a relatively new therapy for severe aortic valve stenosis. The number of patients undergoing TAVI is rapidly increasing, indicating the need for optimization of patient outcomes and the procedural trajectory [7].

As discussed in Chapter 5, continuous monitoring of patients is essential for identifying conditions such as a total atrioventricular block (AV-block), which can lead to sudden collapse. The occurrence of AV-block, and the requirement for permanent pacemaker implantation (PPI) are significant concerns in the TAVI aftercare. Specifically for the SAPIEN valve, the incidences of AV block range from 5.9% to 6.5%, and PPI is indicated in 8.3% of the patients over the last 5 years in the AmsterdamUMC [21] [48][19].

While next-day discharge offers numerous advantages, such as reduced hospital stay, cost, hospital-acquired complications, and increased hospital capacity, some patients expressed concern about safety in their home environment. Ambulatory monitoring presents a potential solution by facilitating the detection of conduction disorders and enhancing patient safety, allowing for recovery in their home environment [8].

The subsequent sections of this thesis provide a comparative analysis of clinically validated ambulatory monitoring systems. This analysis aims to identify the most suitable monitoring systems for TAVI patients at AmsterdamUMC, in alignment with the overarching goal of improving patient outcomes and optimizing the TAVI procedure.

6.3 Methods

PubMed and Google Scholar were utilized to conduct searches on topics including 'Ambulatory Monitoring ECG', 'Telemetry Cardiac Monitoring', 'Home Monitoring Devices cardiology', 'Ambulatory Monitoring Overview', 'Mobile Cardiac Telemetry', 'Handheld ECG', 'Wearable ECG', and 'Patch ECG'. Subsequently, devices identified through these initial search terms underwent further investigation via searches for the specific device names and 'device name clinical validation' to acquire additional information. Only devices with clinically validated ECG measurements were included in the study. The classification of devices was based on the type of monitoring or the number of ECG leads they provided. Devices were excluded if they were not commercially available on the market, if they were solely clinically validated for detecting QRS complex or RR interval without analysis of the ECG, or if they could only be operated by a physician rather than the patient themselves.

Subsequently, to the selection of the ambulatory monitoring systems, the performance metrics of each device is outlined. Furthermore, the devices are compared to align with the ideal scenario of telemetry created by M. Hermens et al. [7].

M. Hermens et al. created a framework for postprocedural telemonitoring of patients who underwent a TAVI procedure [7]. Figure 9 displays the pathway of the ideal ambulatory monitoring scenario. Patients are equipped with a mobile sensor system that automatically provides continuous registration of the ECG in any ambulant setting. The system should also facilitate continuous registration and analysis of the respiratory rate and type or level of activity. Incorporating a digital application with an interactive interface to allow symptom registration by the patient would be beneficial. Ideally, possible events are categorized as severe, moderate, and mild. The patient should get feedback if an event is happening and what action should be undertaken [7].

Several criteria have been selected from the framework proposed by M. Hermens et al. Additionally, two additional criteria, not included in the aforementioned framework, have been incorporated. These criteria are that the system should be validated for atrioventricular block (AV-block) and the system should be implementable in EPIC. The ambulatory monitoring systems in this review are assessed based on these criteria [7].

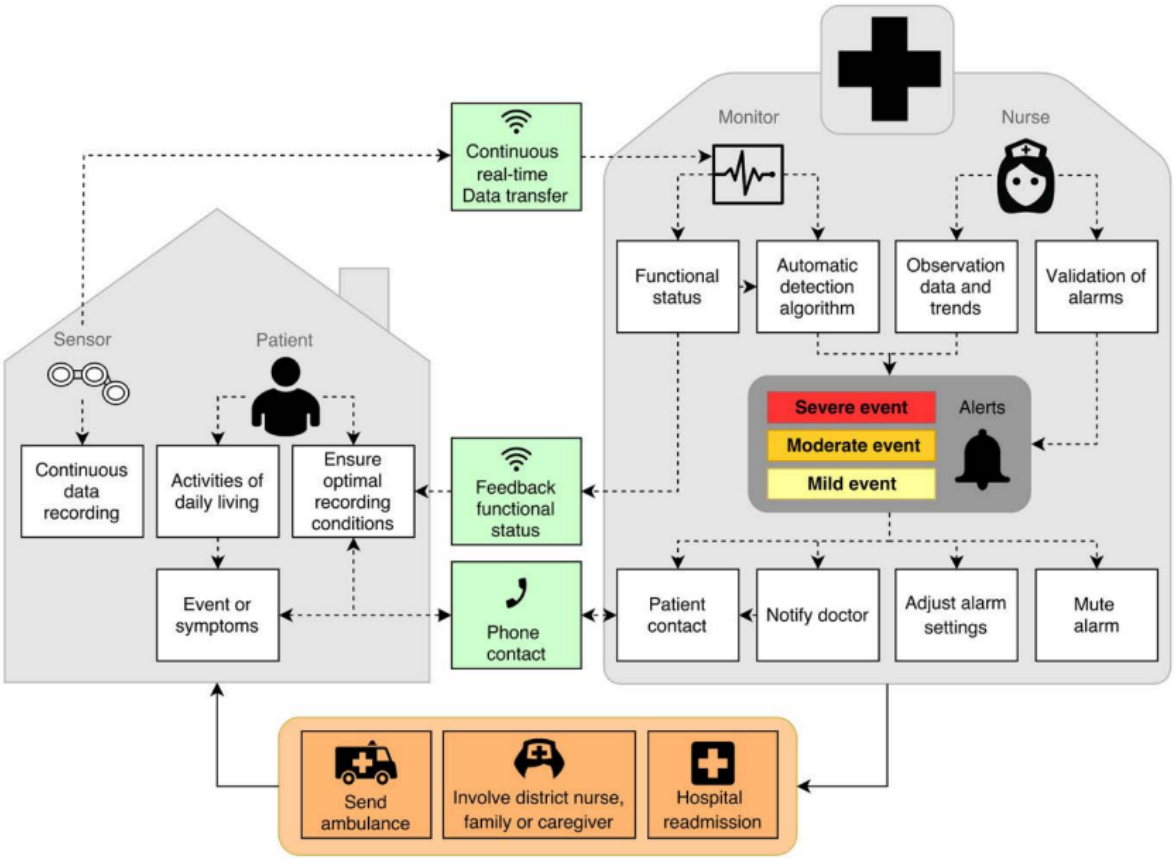


Figure 9: Overview of the ideal telemonitoring scenario based on the framework of M. Hermens et al [7].

1. Continuous monitoring of ECG
2. External specialists evaluate the ECG. Including an increase in PQ-time and width of QRS-complex.
3. Validated for AV-block
4. Enter symptoms
5. Feedback to the patient of the ECG
6. When using an app, this app should be usable on all smartphones
7. User-friendly and comfortable
8. Privacy and security of patient data
9. Invisible under clothes
10. Insurance companies declare the system
11. Legal responsibilities lie with the company
12. Implementable in EPIC (the patient system of AmsterdamUMC)

Devices were categorized based on their performance or alignment. The cumulative scores of performance and alignment were then aggregated to identify the top three devices. It is notable that more than one device could occupy the same ranking position and that criteria related to insurance coverage, compatibility with EPIC implantation, and legal responsibility are not directly assessed in the evaluation table but are considered in the determination of the best-performing systems. Subsequently, the devices occupying the top three positions were evaluated for practical considerations such as legal responsibility, insurance declaration or

cost, and compatibility with EPIC.

6.4 Results

Figure 10 shows that of the 11949 hits, 107 records were assessed for eligibility. Fifty of those records were excluded, leaving 48 records included.

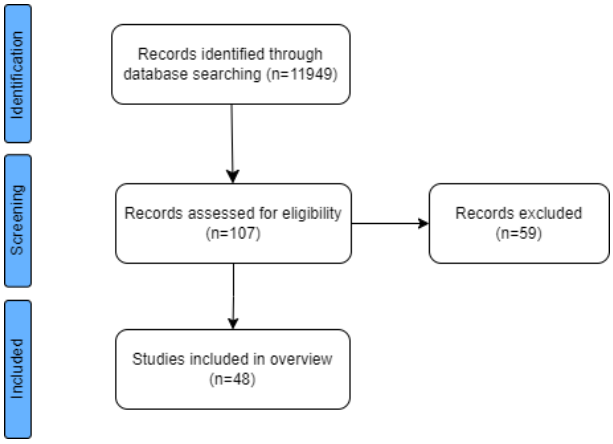


Figure 10: Overview flowchart of included records. Exclusion criteria were if a device was not commercially available, if the device was solely clinically validated for detecting QRS complex or RR interval without analyzing the ECG, or if the device could only be operated by a physician.

A total of sixteen distinct devices were identified from the 48 included records. Among these, Kardia Mobile, Omron, Zenicor ECG, Kardio screen, Nabz Hooshmand-1, and ECG Check are categorized as portable ECG devices featuring electrodes positioned on the fingers and/or chest. Senselink, ZIO XT Patch, and Body Guardian Heart, on the other hand, represent patch holter monitors, offering continuous cardiac electrical activity monitoring capabilities. Withings scanwatch, Fitbit Charge 2, Polar OH, Apple Watch, Garmin, Samsung Gear 2, and Everion are categorized as smartwatches. Details about the types of telemetry each device is (Holter monitor, patch monitor, handheld ECG monitoring device, or smartwatch) are described in Appendix 9.3.

6.4.1 Evaluation performance

Table 5 provides an overview of the performance metrics for each device included in the study. The asterisk (*) denotes that the performance metrics represent a weighted average based on data extracted from various sources. The two asterisks (**) denote different values for firstly PR-interval and secondly QRS-duration. The 'Detection' column is intended to indicate whether a system has been validated for AF or AV-block detection. Among the evaluated devices, Nabz Hoosmand-1 demonstrates the highest sensitivity for both PR-interval and QRS duration, indicating its ability to accurately detect true positive cases. Conversely, Omron exhibits the highest specificity, suggesting its proficiency in identifying true negative cases. Notably, certain devices, predominantly wearable watches, were not assessed for sensitivity and specificity. Instead, their performance was evaluated based on other metrics such as Mean Absolute Deviation (MAD), Mean Absolute Percentage Error (MAPE), and correlation with a reference measurement method considered to be accurate, such as a 12-lead ECG. The Cohen's kappa and the diagnostic yield are displayed for ZIO XT Patch iRhythm.

Table 5: Summary of device performance.

Device Name	Detection	Sensitivity (%)	Specificity (%)	MAD (bpm)-MAPE (%)	Correlation (r=)	Other
Kardia Mobile [49]	AF	85.5*	95.5			
Omron [49]	AV	79	99			
Zenicor ECG [49]	AF	94.7*	92.7*			
Withings Scanwatch [50]	AF	79.7*	89.1*			
Fitbit Charge 2 [51]	AF	66	79		0.807	
Polar OH1 [51]	AF				0.957	
Apple Watch [52]	AF	85	75			
Garmin [52]	AF			2.0<x<5.1 3.1<x<5.4		
Samsung Gear 2 [52]	AF	85	75			
Everion [53]	AF			1.5 - 5.9	0.53	
Senselink [54]	AV				0.988	
Kardio Screen [55]	AV	92	93		0.76/0.82**	
ZIO XT Patch iRhythm [56] [57] [58]	AV				0.99 (AF)	κ=0.36, γ=63.2%
Nabz Hooshmand-1 [59]	AV	100/98**	0.40/0.85**			
ECG Check [60]	AF	74	97			
Body Guardian system [61]	AF	96.3				

* weighted number.
** respectively for PR-interval and QRS duration.

6.4.2 Evaluation alignment with criteria

The criteria for selecting the optimal device are detailed in Section **??**.

The evaluated criteria, along with their corresponding numbers, are as follows:

1. Continuous monitoring of ECG
2. External specialists evaluate the ECG. Including increase in PQ-time and width of QRS-complex.
3. Validated for AV-block
4. Enter symptoms
5. Feedback to the patient of the ECG
6. When using an app, this app should be usable on all smartphones
7. User friendly and comfortable
8. Privacy and security of patient data
9. Invisible under clothes

Each criterion is numerically labeled according to the specifications outlined in Table 6, where device adherence is indicated by 'yes' or 'no' responses. Table 6 demonstrates that not all devices offer continuous monitoring; however, those lacking this feature allow for 30-second ECG recordings when symptoms occur. ECG evaluations are primarily algorithm-based, with exceptions such as the Kardia Mobile, which involves evaluation by HartWacht specialists, and Zenicor, which offers access to external specialists. Few devices are specifically validated for AV-block detection, including Omron, Senselink, Kardio Screen, and Nabz Hooshmand-1. Symptom input is supported by five devices: Omron, Kardia Mobile, Senselink, ZIO XT

Patch, and ECG Check. Feedback to patients regarding ECG results is provided by Kardia Mobile, Omron, Zenicor ECG, and ECG Check. Additionally, all smartphone applications are user-friendly and compatible with smartphones, besides from Samsung Gear 2 and Apple Watch. Devices ensure the privacy and security of patient data, and all are discreet when worn under clothing or not directly attached to the body.

Table 6: Overview of devices and them meeting the requirements described in Methods.

Device name	Requirements								
	1	2	3	4	5	6	7	8	9
Kardia Mobile [62]	No	Yes*	No	Yes	Yes	Yes	Yes	Yes	Yes
Omron [63]	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Zenicor ECG [64] [65]	No	Yes*	No	Yes	Yes	Yes	Yes	Yes	Yes
Withings Scanwatch [66]	No	No	No	No	No	Yes	Yes	Yes	Yes
Fitbit Charge 2 [67]	No	No	No	No	No	Yes	Yes	Yes	Yes
Polar OH1 [68]	No	No	No	No	No	Yes	Yes	Yes	Yes
Apple Watch [69]	No	No	No	No	No	No	Yes	Yes	Yes
Garmin [70]	No	No	No	No	No	Yes	Yes	Yes	Yes
Samsung Gear 2 [71]	No	No	No	No	No	No	Yes	Yes	Yes
Everion [53]	No	No	No	No	No	Yes	Yes	Yes	Yes
Senselink [72]	Yes	Yes**	Yes	Yes	No	-	Yes	Yes	Yes
Kardio Screen [73]	Yes	Yes**	Yes	No	No	Yes	Yes	Yes	Yes
ZIO XT Patch iRhythm [74]	Yes	No	No	Yes	No	-	Yes	Yes	Yes
Nabz Hooshmand-1 [75]	No	Yes**	Yes	No	No	Yes	Yes	Yes	Yes
ECG Check [76]	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Body Guardian heart [77]	Yes	No	No	No	No	Yes	Yes	Yes	Yes

* external specialists do review the ECG, but not specifically on conduction times.
** the ECG is reviewed by an algorithm specifically for conduction times.

6.4.3 Ranking of systems

Performance-Based Ranking of Systems

The performance-based ranking of the systems primarily considers if the system is validated for AF or AV-block. Next it evaluates the sensitivity and specificity, supplemented by metrics such as mean absolute difference (MAD), mean absolute percentage error (MAPE), correlation coefficient, AUROC, Cohen's kappa, and diagnostic yield. The ranking of the systems is as follows:

1. Nabz Hooshmand-1, Kardio screen, Senselink, Zenicor ECG, Body Guardian heart
2. Kardia Mobile, Omron, Polar OH1
3. ECG Check, Apple Watch, Samsung gear 2, Withings Scanwatch
4. Everion, Garmin, VitalPatch, Fitbit Charge 2, Zio XT Patch

Alignment-Based Prioritization of Systems with Ideal Criteria

Devices are ranked based on their alignment with the specified criteria, with higher rankings indicating better alignment.

1. Kardia Mobile, Zenicor ECG, Senselink, Kardio screen
2. ZIO XT Patch, Nabz Hooshmand-1, ECG check, Omron, VitalPatch, Body Guardian Heart
3. Withings Scanwatch, Fitbit Charge 2, Polar OH1, Garmin, Everion
4. Apple Watch, Samsung Gear 2

Final ranking of systems

The final ranking is based on adding the category numbers of performance and alignment with criteria. The top 3 devices are Kardio Screen, Senselink, Zenicor ECG, Nabz Hooshmand-1,

Body Guardian heart, Kardia Mobile, and Omron. The final ranking is as follows:
1. Kardio Screen, Senselink, Zenicor (score 2)
2. Nabz Hooshmand-1, Body Guardian heart, Kardia Mobile (score 3)
3. Omron (score 4)
4. Polar OH1, ECG check (score 5)
5. Withings Scanwatch, VitalPatch, Zio XT patch (score 6)
6. Apple watch, Samsung gear 2, Everion, Garmin, Fitbit Charge 2 (score 7)

6.5 Discussion

6.5.1 Clinical implementation and suitability

The top three devices were assessed for their clinical applicability and suitability, with a primary focus on evaluating criteria that have not been previously considered: EPIC implementation, legal responsibility allocated to the manufacturer, and declaration by insurance providers.

Kardio Screen
Kardio Screen utilizes either 6-lead or 12-lead electrodes, requiring precise attachment to the chest by a trained professional. Unlike patches, these electrodes are not designed for prolonged skin adhesion, thus posing challenges in patient usability. The device does not offer continuous ECG monitoring, necessitating cardiologist review and assuming final legal responsibility. However, its algorithm provides real-time user feedback and has been validated for AV-block detection, demonstrating category 1 performance. Insurance companies have yet to endorse this system, and it remains unimplemented in Dutch patient systems.

Senselink
Senselink is a patch-based device offering continuous ECG monitoring interpreted by a validated algorithm for AV-block detection, achieving category 1 performance. Users can mark events via an event button. However, a cardiologist review is required for ECG analysis, with legal responsibility falling on them. While operational in three Dutch medical facilities utilizing the HiX patient system, its integration with EPIC remains unexplored, although the HiX implementation hints at the feasibility. Insurance companies endorse this system.

Zenicor ECG
Zenicor ECG, a handheld device, exhibits category 1 performance and undergoes expert review, with legal responsibility shouldered by the manufacturer. Validated for AV-block detection, it lacks patient symptom reporting capabilities, however ensures events can be indicated. Insurance companies have not endorsed this device, and it remains unimplemented in Dutch patient systems.

Nabz Hoosmand-1
Nabz Hooshmand-1, another handheld device, demonstrates category 1 performance and measures QRS length, PQ interval, and RR interval. Its AV-block detection efficacy has been validated. However, symptoms and events can not be indicated by the patient. Details regarding legal responsibilities are scarce, and insurance companies have not declared their support. This device is not yet integrated into Dutch patient systems.

Body Guardian Heart
The Body Guardian Heart patch places the legal responsibility for ECG interpretation and diagnosis with the physician but lacks validation for AV-block detection. Symptom logging is available via the app, and the device exhibits category 1 performance. However, insurance companies do not endorse this device, and it remains unimplemented in Dutch patient systems.

Kardia Mobile
Kardia Mobile, particularly the HartWacht variant, has been successfully integrated into the EPIC system at AmsterdamUMC, with legal responsibility assumed by HartWacht and corresponding insurance coverage. Symptoms can be logged via an application. However, the

system lacks validation for AV-block detection and exhibits category 2 performance.

Omron
Omron's device, which measures both ECG data and blood pressure concurrently, utilizes sensors and algorithms from Kardia Mobile. Symptoms can be logged via an application. However, Omron lacks validation for AV-block detection, and it demonstrates category 2 performance. Notably, expert ECG review is absent, legal responsibility rests with cardiologists, and insurance companies do not endorse this device.

6.5.2 Comparative Analysis of Ambulatory Monitoring Systems

Kardia Mobile meets the most criteria for legal responsibility, insurance coverage, and implementation in EPIC. Furthermore, experts review the ECGs, taking away workload from the cardiologists, and giving feedback to the patient. Patients can furthermore send in symptoms. Unfortunately, Kardia Mobile - HartWacht is not validated for AV-block and shows category 2 performance.

Senselink meets the criteria of insurance coverage and implementation in a patient system in the Netherlands, but not EPIC. Senselink is validated for AV, shows category 1 performance, and measures continuous ECGs. Patients can not send in symptoms but can press the event button. Unfortunately, cardiologists need to review the ECGs themselves and take legal responsibility for this.

Zenicor ECG is reviewed by experts, who take legal responsibility for this. Subsequently, the device is validated for AV-block and shows a category 1 performance. Patients can not send in symptoms but can trigger an event button. However, this device is not covered by insurance companies and is not implemented in EPIC or another patient system in the Netherlands.

While Kardia Mobile, Senselink, and Zenicor ECG present varying degrees of alignment with the specified criteria, Kardio Screen, Nabz Hooshmand-1, Body Guardian Heart, and Omron fall short of meeting any of the three criteria: legal responsibility, insurance declaration, or EPIC implementation. As a result, these devices are excluded from consideration in future scenarios.

6.5.3 Future scenarios

In conclusion, none of the presented devices align perfectly with the ideal scenario. Nevertheless, Kardia Mobile, Senselink, and Zenicor ECG demonstrate considerable promise. Three prospective scenarios are delineated for evaluation.

The first scenario entails the adoption of Senselink's continuous measurement approach, wherein patients transmit a new ECG every eight hours for specialist review. This methodology offers several advantages, including pre-existing validation for AV-block and other conduction disorders, direct assessment of ECGs by the Cardiologs algorithm, and continuous ECG monitoring. However, its implementation within AmsterdamUMC and EPIC is a time-intensive endeavor, with legal responsibility for timely ECG review and patient feedback resting upon AmsterdamUMC. Additionally, individual setup for each patient within the hospital necessitates the procurement of an adequate number of devices. The setup of each patient and the evaluation of the ECGs by physicians increases the workload.

Alternatively, the integration of Zenicor ECG into EPIC and insurance can be negotiated. However, it is not sure in what time frame this can be fixed.

The third and most promising scenario involves the validation of HartWacht for AV-block detection. Despite the convenience of HartWacht's existing integration into AmsterdamUMC and the streamlined patient setup process, this approach requires the initiation of a validation study, which may be resource-intensive and time-consuming. However, this may be worth the investment, as the other advantages can outweigh this disadvantage. It saves time that experts

review the ECGs, and it the patient gets direct feedback about their ECG. AmsterdamUMC does not need to invest in multiple devices, as HartWacht rents out the devices for a certain time period. The ECG is not monitored continuously, however, an AV-block does not disappear in the time frame of an hour. Therefore, it is not necessary for continuous monitoring, if patients send ECGs regularly.

6.6 Conclusion

Presently, no ambulatory monitoring system comprehensively meets all prescribed criteria for an optimal home monitoring platform targeting the detection of CCDs, particularly atrioventricular block. Nonetheless, various potential scenarios have been considered to enhance conformity with these standards. Of notable significance are Kardia Mobile- HartWacht, Senselink, and Zenicor ECG, identified as the foremost contenders for potential integration within AmsterdamUMC's framework for post-transcatheter aortic valve implantation (TAVI) surveillance.

Senselink necessitates seamless integration into EPIC, engendering deliberations concerning legal obligations and routine scrutiny of patient records by cardiologists. Conversely, although HartWacht is presently integrated and facilitates external specialist evaluation of ECGs, it lacks continuous monitoring capabilities and remains not validated for atrioventricular block detection, despite the prospect of future validation studies. Conversely, Zenicor ECG boasts validation for AV-block detection and undergoes assessment by external specialists, yet it remains unincorporated within EPIC and lacks endorsement by insurance entities.

In light of the aforementioned considerations, this review recommends initiating dialogue with Kardia Mobile- HartWacht to explore avenues for potential validation for AV-block. However, given the divergent strengths and weaknesses exhibited by each device, AmsterdamUMC is urged to engage in internal deliberations to assess the option that best aligns with their specific requirements.

7 Risk prediction model

7.1 Abstract

Introduction: The development of prediction models can empower doctors to identify patients at an elevated risk of experiencing adverse outcomes related to the procedure. Therefore, this study seeks to identify if a machine-learning-based model can be developed to anticipate 30-day mortality, stroke, MI, and pacemaker implantation following TAVI, with an AUROC comparable to or better than the existing ACC-TAVI model.

Methods and Results: The CENTER2 database is used comprising 24322 patients and 74 features that contained less than 50% missing data. Data was preprocessed by K-nearest neighbors and IterativeImputer, after which feature selection was performed using LASSO regression and Wrapper-backward elimination. Wrapper-backward elimination showed a better performance, therefore those features were selected. Logistic regression, XGBoost, and random forest were compared, for which logistic regression performed best with an AUROC of 0.59 on the validation set.

Conclusion: The model demonstrated suboptimal performance across both training-test and validation sets, with an AUROC of 0.59 for predicting 30-day mortality. The suboptimal performance can be explained by the imbalanced dataset and limited predictive value of demographic features of TAVI patients.

Keywords: Transcatheter aortic valve implantation, Risk score, prediction model.

7.2 Introduction

The development of prediction models can empower doctors to identify patients at an elevated risk of experiencing adverse outcomes related to the procedure. Ultimately, they aim to reduce undesired subjectivity inherent in clinical decision-making and enhance personalized care [3]. At present, the risk assessment for Transcatheter Aortic Valve Implantation (TAVI) relies mostly on the Society Thoracic Surgeons score (STS score) and EuroSCORE II. However, it's important to note that these risk assessment tools are not specifically intended nor verified for evaluating mortality risk associated with TAVI procedures [78].

A thorough risk assessment is necessary for predicting the chances of post-operative major adverse cardiac events (MACE) including mortality, the necessity for permanent pacemaker implantation (PPI), major vascular bleeding (MVB), rehospitalization, and stroke within the initial 30-day period [3]. Several risk scores have emerged for specifically the TAVI populations, however, these are not used in practice because of the low area under the receiver operating characteristic (AUROC) curve or because the scores are not externally validated. Ideally, cardiologists would use risk scores for patients' selection, risk stratification, and benchmarking [4]. Therefore, this study seeks to create a machine-learning-based risk prediction model for mortality, stroke, MI, and pacemaker implantation following TAVI, with an AUROC comparable to or better than the existing models.

7.3 Methods

The methodology for developing and evaluating the risk prediction model is outlined in Figure 11.

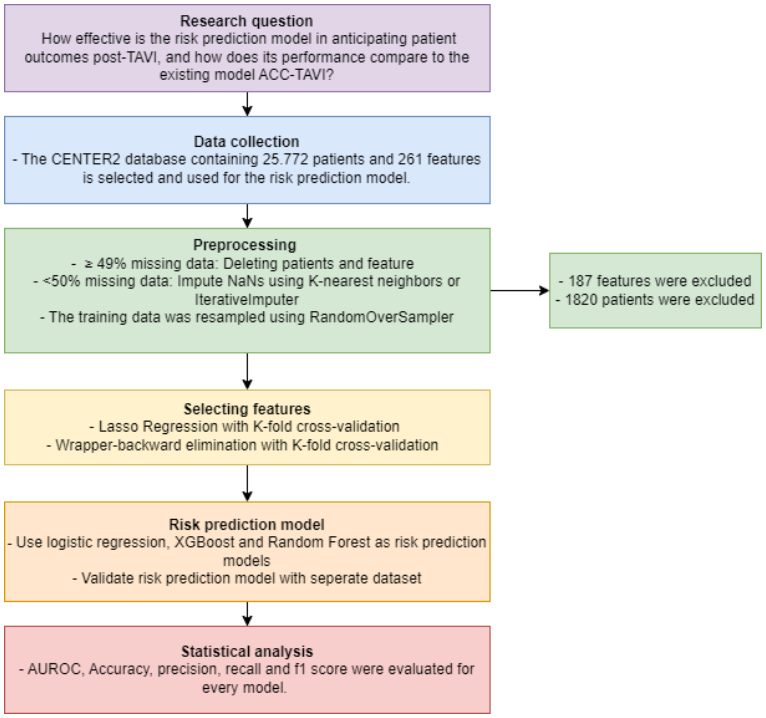


Figure 11: Flowchart of the method used to create and evaluate the risk prediction model. Colors indicate different steps distinguishing the research question, data collection, preprocessing, feature selection, model creation, and statistical analysis.

The study population comprised patients enrolled in the CENTER2 database. The CENTER2 database is a pooled patient-level database from 10 clinical studies including patients who underwent TAVI between 2007 and 2022, which includes data from 25.772 patients [79]. Participating cities/studies were: Amsterdam, Milan, Rabin, Verona, FRANCE2, BRAZIL, Observant, Padova, BRAVO3, WINTAVI, SPANISH, and RadboudUMC between 2007 and 2022. Eligibility criteria for this study required patients to be over 18 years old and to have

undergone a transfemoral TAVI procedure. Patients were selected for TAVI based on the presence of severe, symptomatic aortic stenosis and the determination by a multidisciplinary heart team that surgical intervention was either contraindicated or posed high risk.

The risk prediction model was developed using a case-control study design. This study compared patients who had adverse outcomes within 30 days following -TAVI - such as mortality, stroke, permanent pacemaker implantation, or myocardial infarction- with those who did not experience these outcomes.

7.3.1 Preprocessing

The percentage of missing data for each feature was individually assessed. Features with more than 50% missing data and patients that had missing feature data for more than 50% of the features were excluded from further analysis. Prior to filling in missing data or resampling, the dataset was partitioned into a training set and a validation set. The validation set is a dataset consisting of 20% of the data. The validation set remained untouched, with no resampling applied. The subsequent preprocessing procedures applied exclusively to the training set.

Missing data

For features with less than 50% missing data, imputation was performed using K-nearest Neighbors (KNN) or Iterative Imputer. The KNN algorithm was employed to impute missing values for both categorical and continuous features, leveraging information from other features. Since KNN cannot handle binary features, the IterativeImputer was utilized for these cases. IterativeImputer is a multivariate imputer that estimates missing values based on all available data, incorporating information from other features. The R^2 metric was used to evaluate the predictive performance of the imputation. This was done by overlaying a mask of missing values on known values and comparing the predicted values to the original values.
The imputation of the validation set was necessary for the evaluation of the logistic regression model. The NaNs were imputed using SingleImputer because this method changes the dataset the least.

Resampling

The CENTER2 dataset exhibits a class imbalance, with 85% of patients classified as alive and 15% as deceased. Machine learning models typically assume a balanced dataset; hence, resampling the training set is necessary to address this issue [80]. Moreover, evaluation metrics such as the AUROC do not function optimally with imbalanced datasets [81].

The data is resampled using the RandomOverSampler (ROS) technique. This method randomly duplicates instances of the minority class until their number equals that of the majority class. ROS increases the likelihood of overfitting, therefore, cross-validation techniques are employed, ensuring the model's robustness and generalizability [82].

7.3.2 Feature selection

To construct an effective risk prediction model, a comprehensive analysis of methodologies from existing models was conducted. This comparative assessment, in Appendix 9.4, included reviewing various feature selection techniques employed in previous risk prediction models and identifying additional methods from pertinent literature. Notably, features such as frailty and echographic parameters were identified as promising based on their recurrent appearance in literature.

Methods for Feature Selection

LASSO regression and the wrapper method-backward elimination were chosen for feature selection. Both methods were implemented using K-fold cross-validation (K=10) and evaluated using performance metrics such as AUROC, accuracy, precision, recall, and F1-score. The feature selection method that demonstrated superior performance was adopted

for subsequent model refinement.

LASSO regression
A K-fold cross-validation with 10 folds was employed. The dataset was then partitioned into training and test sets based on the indices generated by the folds. The categorical features were encoded using the Python Scikit package OneHotEncoder, and the continuous variables were standardized using the Python Scikit package StandardScaler. The best-performing alpha was selected by cross-validation of 5 folds, using the function LASSOCV, in which alphas ranging from 10^{-4} to 10^{4} were tested. The best alpha parameter was used for the LASSO regression. The final LASSO regression was then fitted on training data using the best alpha and used to predict outcomes on the test set. Predictions were binarized using a threshold of 0.5. The AUROC, accuracy, precision, recall, and F1-score were calculated for each fold and features with non-zero coefficients were identified and saved in a data frame. The mean for all performance metrics was computed across the 10 folds, and the frequency of selected features across all folds was summarized.

Wrapper- backward elimination
In Figure 12, a visual representation of wrapper-backward elimination is presented. Every feature combination was evaluated, and the best combination of features was selected.

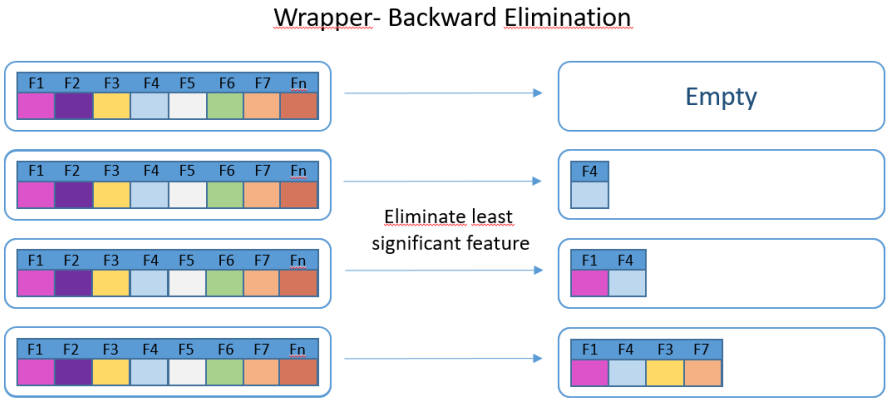


Figure 12: Wrapper-backward elimination. Every combination of features is evaluated, and the best working combination of features is selected. Figure based on [83].

To apply wrapper-based backward elimination effectively, three different models were tested for the SequentialFeatureSelector (SFS). The SFS was employed for feature selection. To determine which model should be used for SFS, the performances of three models were compared. The models tested for SFS were K-nearest neighbors, Gradient Boosting, and Decision Tree. Importantly, these models would not be used in the final prediction of the outcomes to avoid overfitting. The optimized model model was then used for the feature selection.

The selected model was further used to determine the optimal number of features. A K-fold cross-validation with 10 folds was employed. For each number of features, ranging from 1 to the maximum number available, subsets were selected. Cross-validation was performed on each subset using the selected model. The model's accuracy was recorded for each fold, and the average accuracy was calculated for each number of features. The performance scores were plotted against the number of features to visualize the relationship and the optimal number of features was identified as the number with the highest average accuracy across folds.

The optimal number of features was subsequently used as input for the wrapper method. The selected model was used in the wrapper-backward elimination in combination with a 10-fold

cross-validation, where for each fold the dataset was split into training and testing sets. The SFS settings included backward elimination, optimization for R2 score, and 5-fold internal cross-validation. Features that were selected in more than 5 folds, with a maximum of the optimal number of features were chosen for the final model.

Final feature selection
This structured approach to feature selection ensured that the risk prediction model incorporated relevant features while mitigating the 'curse of dimensionality' associated with high-dimensional datasets [84]. By combining advanced statistical techniques with clinical expertise, the model aimed to enhance predictive accuracy and clinical utility. Features that were selected by 5 or more folds were included in the selection.

7.3.3 Risk prediction model
Following feature selection, the selected features were utilized for developing the risk prediction model. A K-fold cross-validation approach with 10 folds was employed to both train and evaluate the model. Each fold partitioned the dataset into distinct training and test sets.
Initially, logistic regression served as the model for training and prediction. Performance metrics were computed for each fold. Subsequently, based on the AUROC score on the validation set, the model yielding the best performance was identified. Predictions on the validation set were binarized, and additional performance metrics were calculated. Mean values of these metrics across the 10 folds summarized the overall performance of the model on both the training and validation datasets.
This process was repeated for XGBoost and random forest classifier models. Comparative analysis of these three models facilitated the assessment of their respective performance.

7.3.4 Statistical analysis
The demographic features were analyzed and depicted for the dataset displaying the mean and standard deviation of continuous variables, and the frequency for the categorical variables. The LASSO regression and wrapper backward elimination were evaluated using the AUROC, accuracy, precision, recall, and F1-score. Features were deemed statistically significant when the feature was selected in ≥ 5 folds. The logistic regression, XGBoost, and random forest were evaluated using the AUROC, accuracy, precision, recall, and F1-score.

7.3.5 Model implementation
The outcome probabilities derived from the best-performing risk prediction model were integrated into an interactive dashboard using HTML. This dashboard enables users to input various features such as the presence of permanent atrial fibrillation, NYHA class, and aortic valve area. Upon selecting these features, the dashboard dynamically computes and displays the corresponding predicted outcome probability.

7.4 Results
The outcomes of the risk prediction model for 30-day mortality are presented in this section. Detailed findings regarding other adverse events such as stroke, permanent pacemaker implantation, or myocardial infarction can be accessed in Appendix 9.5. The conclusive performance metrics for these adverse outcomes derived from the top-performing model are delineated in Tables 12 and 13.

7.4.1 Preprocessing
From an initial cohort comprising 25.772 patients, 1820 individuals were excluded due to excessive missing data. Out of the initial 261 features, 187 were excluded either due to a high proportion of missing values, because they were peri- or post-procedural features, or because there were double features. The demographic features of the 24322 patients were that 13404

(56%) were women, mean (std) age of 81.4(6.7) years. Other baseline characteristics of the dataset are depicted in Table 7

Table 7: Demographic and clinical characteristics of the overall dataset

Variable	Mean ± SD / n (%)
Age (yrs)	81.4 ± 6.7
Female gender	13404 (56.0%)
Length (cm)	160.6 ± 9.6
Weight (kg)	71.3 ± 14.2
BMI (kg/m^2)	27.4 ± 4.9
NYHA	2.4 ± 0.9
DM	7804 (32.6%)
Creatine (µmol/L)	1.17 ± 0.68
eGFR (ml/min/1,73m2)	56.2 ± 25.4
History MI	2994 (12.51%)
History CABG	2062 (8.6%)
History PCI	4855 (20.28%)
History PVD	2853 (11.9%)
History CVA	2424 (10.12%)
Previous surgery	2241 (9.4%)
History Aortic valve intervention	597 (2.5%)
Valve-in-valve	593 (2.5%)
Significant CAD	8796 (36.7%)
Hypertension	19329 (80.7%)
LVEF	56.9 ± 13.1
LFLG	3920 (16.4%)
Baseline AF	6578 (27.47%)
Baseline pacemaker	1193 (5.0%)
Valve size (mm)	26.45 ± 2.7
AVA	0.67 ± 0.2
Mean gradient (mmHg)	49 ± 16.5
Peak gradient (mmHg)	77.8 ± 23.2
Balloon expandable valve	10267 (42.9%)

Patient and clinical characteristics for the dataset in mean ± SD or n (%).
BMI: Body Mass Index, NYHA: New York Heart Association, DM: Diabetes Mellitus, MI: Myocardial Infarction, CABG: Coronary Artery Bypass Graft, PCI: Percutaneous Coronary Intervention, PVD: Peripheral Vascular Disease, CVA:Cerebral Vascular Accident, CAD: Coronary Artery Disease, LVEF: Left Ventricular Ejection Fraction, LFLG: Low Flow Low Gradient, AF: Atrial Fibrillation, AVA: Aortic Valve Area.

Missing data
The continuous and categorical missing data filled in by KNN showed an optimal result of 5 neighbors. The R^2 & MSE were respectively 0.73 & 2391, giving a moderate to good fit between the imputed and observed values.

The R^2 & MSE of the IterativeImputer were respectively 0.65 & 0.05, suggesting a moderate to good performance in capturing the variability of missing data.

7.4.2 Feature selection
LASSO regression
Features selected by LASSO regression consistently across all ten folds included age, length, weight, eGFR, left ventricular ejection fraction (LVEF), aortic valve area (AVA), peak aortic valve gradient (Pgrad), New York Heart Association (NYHA) class, valve size, history of aortic valve intervention, CHADSVASC, early vs new generation valves, gender, diabetes mellitus

(DM), history of myocardial infarction (MI), history of percutaneous coronary intervention (PCI), history of peripheral vascular disease (PVD), history of cerebrovascular accident or transient ischemic attack (CVA or TIA), hypertension, history of previous surgery, baseline pacemaker, baseline atrial fibrillation, and balloon vs self-expandable valves. The feature aortic valve-in-valve (viv) exhibited a non-zero LASSO coefficient in seven out of the ten folds. Since all variables were selected in more than five folds, all features were retained for inclusion in the subsequent analysis.

Wrapper- backward elimination
The performance of the K-nearest neighbors, gradient boosting, and decision tree are depicted in Table 8.

Table 8: The performance metrics of the K-nearest neighbors, Gradient Boosting and Decision Tree.

Evaluation metric	K-nearest neighbors	Gradient Boosting	Decision Tree
Accuracy	0.93	0.69	0.97
Precision	0.91	0.68	0.95
F1-score	0.94	0.69	0.98
Recall	0.97	0.70	1.0
AUROC	0.93	0.69	0.97

The best working model is the DecisionTreeClassifier. The curve for determining the optimal number of features for the random forest is illustrated in Figure 13.

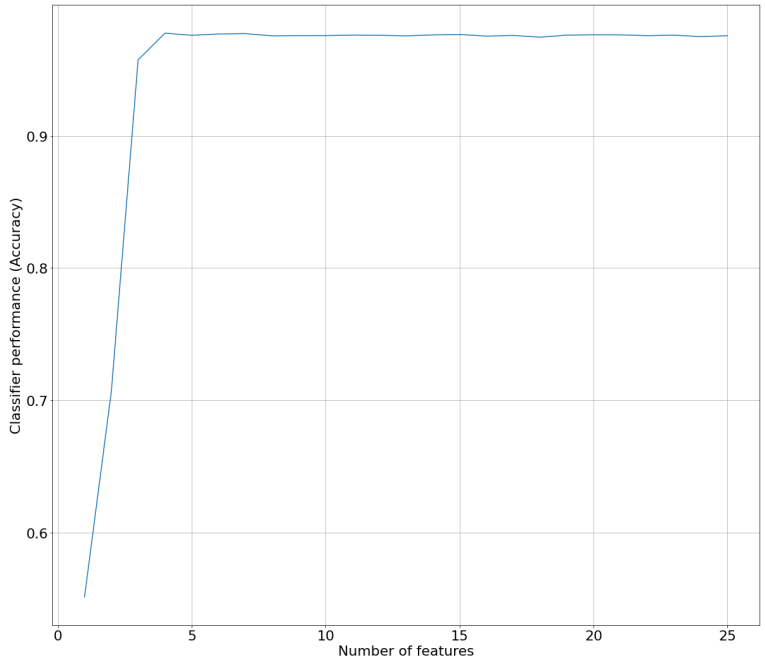


Figure 13: The accuracy of a decision trees wrapper for each number of features. The performance reaches a little peak after including more than 4 features, fully stabilizing at 10 features.

Initially, the accuracy improved rapidly up to four features, after which it stabilized at a high level. At 10 features the graph seemed to be fully stabilized. Therefore, 10 features are included in the wrapper backward selection. Features wrapper selected in 5 or more folds included history of aortic valve intervention, eGFR, age, length, AVA, weight, baseline AF, NYHA class, and LVEF.

Comparison feature selection methods

The results of the evaluation metrics for both LASSO regression and wrapper backward elimination are presented in Table 9. The mean evaluation metrics across all 10 k-folds were calculated, with the range of values across the folds indicated in square brackets. The minimal range of these values suggested a low variability in the performance metrics across the different folds, indicating a high degree of consistency and robustness in the model performance. The wrapper method shows higher results in the evaluation metrics and was therefore chosen as the feature selection method. The features that are selected are history aortic valve intervention, eGFR, age, length, AVA, weight, baseline AF, NYHA class, and LVEF.

Table 9: The mean performance metrics of the 10 folds of LASSO regression and Wrapper backward elimination, where the maximum and minimum values of the folds are represented in the square brackets.

Evaluation metric	LASSO regression	Wrapper backward elimination
Accuracy	0.618 [0.606-0.628]	0.974 [0.971-0.979]
Precision	0.624 [0.595-0.651]	0.950 [0.943-0.960]
F1-score	0.596 [0.593-0.627]	0.975 [0.971-0.976]
Recall	0.609 [0.585-0.612]	1.0 [1.0-1.0]
AUROC	0.618 [0.605-0.629]	0.974 [0.971-0.978]

7.4.3 Risk prediction model

Three risk prediction models - logistic regression, XGBoost, and random forest - were evaluated and compared using input features selected through wrapper-based backward elimination. The performance metrics for the training-test set are summarized in Table 10, where the random forest model exhibits the highest performance, achieving an AUROC of 1.0.

The evaluation of these models on the validation dataset reveals notable differences in their performance compared to the training set as shown in Table 11. The logistic regression model demonstrated the lowest accuracy and precision, followed by XGBoost, with random forest achieving the highest accuracy and precision. Despite RF's superior precision and accuracy, both LR and XGBoost yielded F1-scores approximately three times higher, and LR outperformed both other models in the recall.

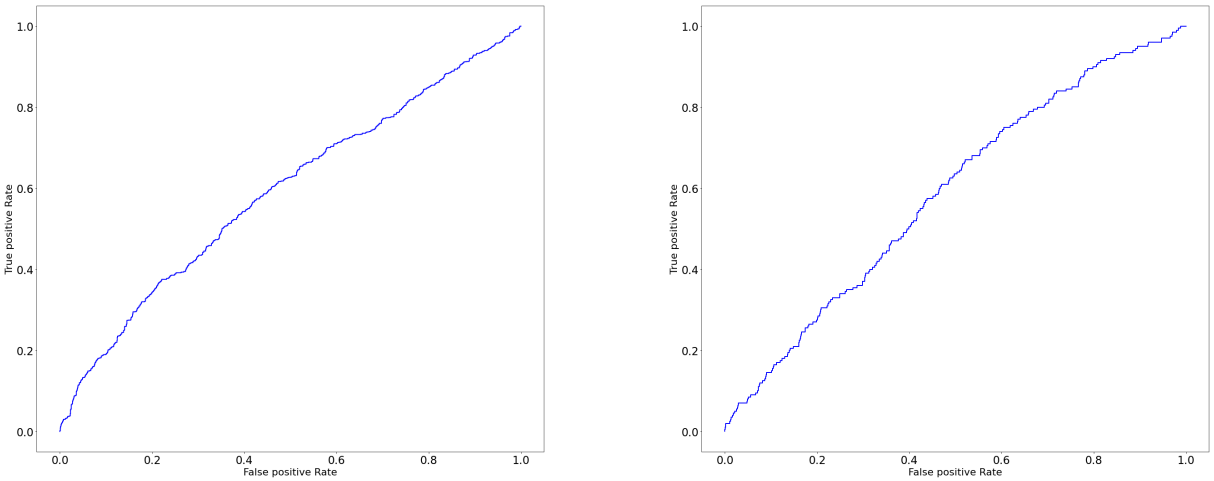
Given the importance of accurately identifying high-risk patients in clinical settings, the logistic regression is considered the most effective, despite its tendency to produce false positives. This trade-off is deemed acceptable due to the model's superior recall, which is crucial for the clinical application. Consequently, logistic regression was selected as the optimal model for this task. The AUROCs for both training-testing and validation datasets are illustrated in Figure 14b.

Table 10: Results of the three different risk prediction models on the training set with the input features of wrapper backward elimination. The maximum and minimum values of the folds are represented in the square brackets.

Evaluation metric	Logistic Regression	XGBoost	Random Forest
Accuracy	0.56 [0.556-0.575]	0.84 [0.833-0.853]	0.9997 [0.9992-1.0]
Precision	0.57 [0.548-0.589]	0.83 [0.813-0.846]	0.9994 [0.998-1.0]
F1-score	0.54 [0.528-0.555]	0.85 [0.837-0.856]	0.9997 [0.9992-1.0]
Recall	0.51 [0.485-0.542]	0.86 [0.844-0.873]	1.0 [1.0-1.0]
AUROC	0.59 [0.570-0.608]	0.92 [0.917-0.933]	1.0 [1.0- 1.0]

Table 11: Results of the three different risk prediction models on the validation set with the input features of wrapper backward elimination. The maximum and minimum values of the folds are represented in the square brackets.

Evaluation metric	Logistic Regression	XGBoost	Random Forest
Accuracy	0.56 [0.548-0.577]	0.79 [0.778-0.802]	0.96 [0.958-0.959]
Precision	0.053 [0.052-0.054]	0.057 [0.053-0.060]	0.52 [0.33-0.83]
F1-score	0.097 [0.095-0.099]	0.093 [0.087-0.010]	0.036 [0.029-0.049]
Recall	0.57 [0.54-0.59]	0.26 [0.25-0.29]	0.019 [0.015-0.025]
AUROC	0.59 [0.586-0.589]	0.55 [0.544-0.552]	0.59 [0.574-0.595]



(a) Training and test set showing an AUROC of 0.59

(b) Validation set showing an AUROC of 0.59

Figure 14: The area under the receiver operating curve of the training-test set and validation set.

The feature importance of the features in the logistic regression is depicted in Figure 15. Four features contribute most to the outcome as the other features have marginal influence. The most influential features are NYHA class, baseline AF, AVA, and history aortic valve intervention.

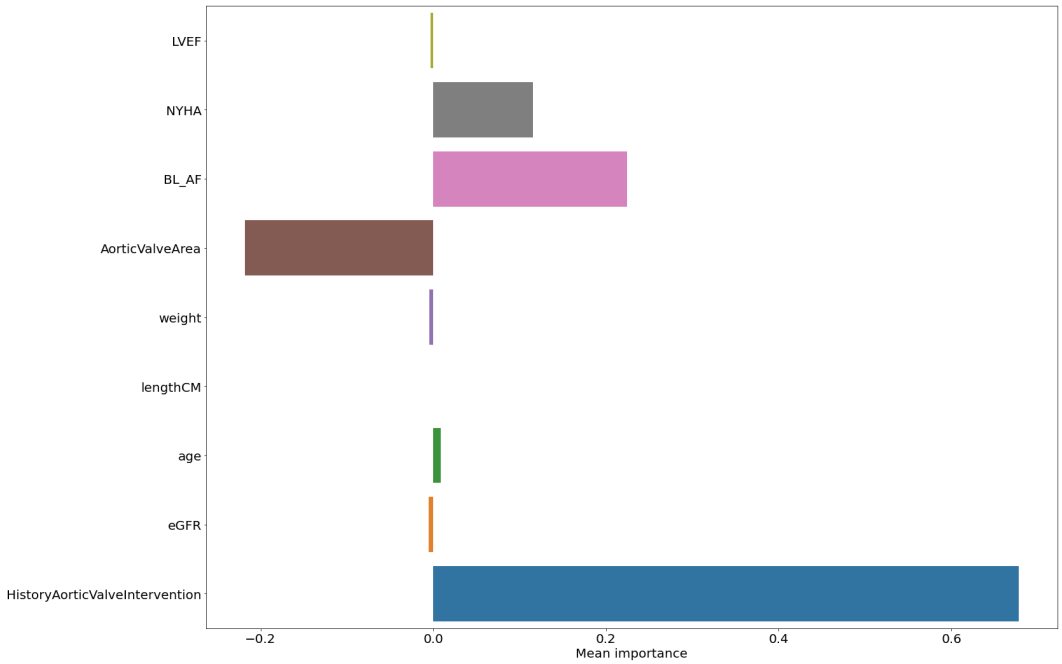


Figure 15: The mean feature importance of selected features in the best working logistic regression model.

7.4.4 Performance metrics adverse events

The performance metrics of the prediction models targeting adverse events - mortality, stroke, permanent pacemaker implantation, and myocardial infarction- for both the test data and validation datasets are presented in Tables 12 and 13. Notably, for PPI prediction, the random forest model demonstrated superior performance compared to LR and XGBoost and thus was selected as the preferred model instead of logistic regression. For the other adverse outcomes, the LR was selected as the prediction model.
The models predicting mortality, stroke, and MI exhibited similar performance levels on the training-testing data. Among these, the model predicting MI emerged as the most effective, achieving the highest metrics. The model's performance in predicting PPI in the training set was near-perfect.

The validation datasets showed consistent patterns with the training datasets for mortality, stroke, and MI, except for deviations observed in precision and F1-score. However, the model's predictive capability for PPI in the validation set was significantly diminished compared to its performance in the training set. For all four outcomes, the AUROCs of the validation datasets ranged between 0.56 and 0.65, indicating performance levels consistent with those observed in previous models.

Table 12: Performance of the random forest classifier on the training set, where input features were selected using the wrapper. The maximum and minimum values of the folds are represented in the square brackets.

Evaluation metric	Death	Stroke	MI	PPI
Accuracy	0.56	0.57	0.60	0.98
Precision	0.57	0.58	0.60	0.96
F1-score	0.54	0.52	0.60	0.98
Recall	0.51	0.48	0.60	0.998
AUROC	0.59	0.59	0.63	0.998

Table 13: Performance of random forest classifier on the validation set, where input features were selected using the wrapper. The maximum and minimum values of the folds are represented in the square brackets.

Evaluation metric	Death	Stroke	MI	PPI
Accuracy	0.56	0.66	0.64	0.84
Precision	0.053	0.032	0.025	0.43
F1-score	0.097	0.061	0.048	0.25
Recall	0.57	0.46	0.63	0.18
AUROC	0.59	0.56	0.65	0.62

7.5 Discussion

This study aimed to develop and evaluate a risk prediction model for anticipating adverse patient outcomes following TAVI with a similar or better AUROC than ACC-TAVI. The model demonstrated suboptimal performance across both training-test and validation sets, with an AUROC of 0.59 for predicting 30-day mortality. The model's performance in predicting 30-day myocardial infarction was marginally better, with an AUROC of 0.65 on the validation set. However, given the suboptimal AUROCs, clinicians cannot reliably identify patients at elevated risk of experiencing adverse outcomes, limiting the model's clinical applicability for risk assessment.

The model's performance on the validation set revealed notably low precision and F1-scores when using logistic regression and XGBoost, and a low F1-score and recall when employing random forest. Given the objective of this prediction model - identifying patients at high risk of adverse outcomes- accurately detecting true high-risk patients is most important, even if it

means accepting a higher rate of false positives. The relatively higher recall of LR compared to RF indicated that LR is more effective in correctly identifying true positives.

The observed decline in precision and F1-score may suggest overfitting within the model. Although cross-validation was employed to mitigate overfitting, and different models were used for feature selection and prediction, a more plausible explanation for the performance drop could be the imbalanced dataset. Despite the large dataset size, the severe imbalance - where 85% of patients survived, and 15% did not - posed significant challenges in training an effective model.
Additionally, a considerable amount of missing data was present. While imputation was performed considering relationships among the features, this process may have introduced noise, potentially affecting the model's performance.

TAVI mortality prediction models, including the newly developed model (AUMC), ACC-TAVI, FRANCE-2, OBSERVANT, TAVI2-score, TVT-score, CoreValve, TARIS, PPO, and German-AV, exhibit varying degrees of predictive accuracy as depicted in Table 14 [3][85]. The AUROC of the newly developed model did not exceed those of the established models. Despite using different datasets and exploring promising features, all these models - including AUMC- struggled to achieve high performance, indicating that demographic features may not be sufficiently predictive for the TAVI population. The homogeneity of TAVI patients, characterized by high age and broad medical histories, may limit the effectiveness of demographic features.

Table 14: Overview of performance for TAVI risk prediction models [86][87][88][15][78][85][89][90][91].

Study name	**AUROC**
AUMC	1.0 (Validation: 0.66)
ACC-TAVI	0.66 (Validation: 0.64)
FRANCE-2	0.59 (Validation: 0.63)
OBSERVANT	0.71 (Validation: 0.58)
$TAVI_2$-score	0.72
TVT-score	0.66
CoreValve	0.75
TARIS	0.71*
PPO	0.622
GERMAN-AV	0.81 (Validation: 0.60)

Literature suggests that incorporating features such as echographic parameters and frailty could enhance model performance [85][87][89]. This study included echographic parameters such as peak gradient and aortic valve area. However, only AVA was implemented in the model. Frailty was temporarily added despite over 50% missing data, which ultimately led to a decline in model performance, necessitating its removal. The results of the model with the addition of frailty are described in Appendix 9.6. This frailty feature had 64% missing data which was filled in with KNN. It could have influenced the performance of the prediction model, however, it is more likely that it is not a promising feature as it does not only not increase the performance, it declines it.

7.6 Future Studies

For future studies CT parameters could be added to the input features, giving information about the calcium score and diameters of the arteria femoralis. Furthermore, a balanced dataset

should be gathered to properly train the model.

7.7 Conclusion

In conclusion, this study highlights the challenges of developing a robust risk prediction model for patient outcomes after TAVI. The model's suboptimal performance on the validation sets for all adverse outcomes was primarily attributable to imbalanced data and the limited predictive value of demographic features. Comparison with established models such as ACC-TAVI, OBSERVANT, and German-AV underscores the marginal improvements achieved, emphasizing the need for more comprehensive feature sets. Although literature suggests that incorporating echographic parameters and frailty could enhance model performance, our findings indicate that these features did not significantly contribute, particularly when frailty data were incomplete.

8 General discussion and future perspectives

The primary goal of this study was to improve the TAVI procedure by creating a more streamlined pathway for post-procedural care and developing a risk prediction model to predict adverse outcomes. This could have helped determine which patients would benefit from TAVI, weighing the advantages against the risks. The three studies—Next-Day Discharge, Ambulatory Monitoring, and Risk Prediction Model—each provided significant insights that contribute to these objectives.

Next-Day discharge

The Next-Day Discharge study demonstrated that the current criteria used by AmsterdamUMC create a safe environment for the next-day discharge of TAVI patients. The study showed no statistically significant increase in complications, readmissions, or mortality compared to the traditional discharge protocol. However, it showed a significant difference in the composite endpoint. Despite the small dataset, the results are promising, indicating benefits such as reduced hospital stays, increased hospital capacity, cost savings, and fewer hospital-acquired complications. Additionally, patients reported positive experiences with earlier return to their home environment. However, to enhance patient safety and comfort, especially for potential same-day discharge, ambulatory monitoring systems were reviewed for their suitability.

Ambulatory monitoring

Presently, no ambulatory monitoring system fully meets the ideal criteria for an optimal home monitoring platform targeting the detection of conduction disorders, particularly atrioventricular block. Nevertheless, the Kardia Mobile-Hartwacht, Senselink, and Zenicor ECG systems meet most requirements and are considered the foremost contenders for integration within AmsterdamUMC's framework created by M. Hermens [7], for post-TAVI surveillance. HartWacht, in particular, appears to be the best fit if it is validated for AV-block. These systems can help patients feel safer at home, potentially enabling same-day discharge.

Risk prediction model

The developed risk prediction model aimed to predict 30-day mortality, stroke, permanent pacemaker implantation, and myocardial infarction. The model demonstrated a suboptimal performance across both testing and validation sets, with an AUROC of 0.59. This indicates that the model does not predict samples accurately, primarily due to imbalanced data and possibly to the limited predictive value of demographic features. Literature suggests that incorporating echographic features and frailty could enhance model performance; however, this was not the case in this study.

General Findings

The three studies collectively enhance objective decision-making in selecting TAVI patients and ensuring their safe discharge from the hospital. Accurate risk estimation is crucial for informing patients and determining whether the benefits of the procedure outweigh the risks. The risk prediction model does not work well enough for clinical implementation and enhance objective decision making. The study of current next-day discharge criteria provide valuable tools for caregivers, giving certain criteria that are proven to be safe. Ambulatory monitoring complements the next-day discharge protocol, offering an additional layer of safety for patients recovering at home.

The conclusions drawn from the next-day discharge study are also limited due to the small sample size. Additionally, the usability and effectiveness of ambulatory monitoring systems need to be validated in clinical settings, particularly for detecting first-degree AV-block.

8.1 Clinical relevance and future directions

Despite the promising findings, the risk prediction model is not yet suitable for clinical practice, as it only predicts correctly about 59% of the time. Other existing models also perform poorly, suggesting that demographic features alone may not hold significant predictive value for TAVI patients. The Next-day discharge and Ambulatory monitoring studies did however have clinical relevance. These studies provide specific tools for healthcare professionals for next-day discharge as well as for the implementation of ambulatory monitoring systems. Further studies in implementing these devices and especially validating the Kardia Mobile- HartWacht for AV-block can enhance post-procedural care. Furthermore, the implementation of Next-Day discharge has already have impact on the hospital capacity, cost reduction, and reduction in hospital-acquired complications.

For future studies more patients could be included for next-day discharge also from multiple centers, to create a multicenter cohort, which gives more generalizable results. Moreover, the PQ-time detection should be validated using Kardia Mobile- Hartwacht. Lastly, CT parameter features could be included in the risk prediction model as well as gathering a more balanced dataset, to try to train the model better.

8.2 Conclusion

The primary aim of this study was to enhance the TAVI procedure by developing a more streamlined post-procedural care pathway and constructing a risk prediction model to predict adverse outcomes. The risk prediction model, however, demonstrated limited clinical utility with an AUROC of 0.59 for 30-day mortality. Nonetheless, significant progress has been made in streamlining post-procedural care. The Next-Day discharge study successfully facilitated the discharge of 50% of eligible patients within 24 hours, thereby improving patient comfort by enabling recovery in a home environment. Additionally, various options for ambulatory monitoring have been explored, with their implementation potentially allowing for same-day discharge and enhancing patient safety.

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9 Appendices

9.1 Quality of Life Questionnaire : EQ-5D-Y

Mobility

1. I have no problems walking about
2. I have some problems walking about
3. I have a lot of problems walking about

Looking after myself

1. I have no problems washing or dressing myself
2. I have some problems washing or dressing myself
3. I have a lot of problems washing or dressing myself

Doing usual activities

1. I have no problems doing my usual activities
2. I have some problems doing my usual activities
3. I have a lot of problems doing my usual activities

Having pain or discomfort

1. I have no pain or discomfort
2. I have some pain or discomfort
3. I have a lot of pain or discomfort

Feeling worried, sad or unhappy

1. I am not worried, sad, unhappy
2. I am a bit worried, sad, unhappy
3. I am very worried, sad, unhappy

9.2 Abstract published in the Netherlands Heart Journal (NHJ) for the NVVC conference

Advancing TAVI Outcomes: Assessing the Impact of Next-Day Discharge

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Purpose:
This study aims to assess the impact of next-day discharge (NDD) on patient outcomes, including mortality, rehospitalization, and complications such as permanent pacemaker implantations (PPIs), following transcatheter aortic valve implantation (TAVI).

Methods:
This prospective cohort study employs a two-arm design to investigate the impact of Next Day Discharge (NDD) compared to a standard 72-hour in-hospital stay following transcatheter aortic valve implantation (TAVI). Primary endpoints include the incidence of complications, rehospitalization rates, and mortality 30 days post-TAVI. Secondary endpoints encompass patient-reported experiences and a cost-effectiveness analysis.
Eligible participants meeting NDD-criteria are allocated to either the NDD-arm or In-Hospitalarm. The NDD-criteria are the absence of pre-existing right bundle branch block (RBBB), a PQtime increase of $\geq$ 20 ms compared to baseline electrocardiogram (ECG), the

presence of an informal caregiver during the first night post-discharge, and the absence of complications during the TAVI procedure. Patients in the NDD-arm are discharged 24 hours post-TAVI upon meeting criteria. Follow-up assessments are conducted 30 days post-TAVI via telephone interviews. The In-Hospital-arm comprises patients meeting NDD-criteria but with a standard 72-hour in-hospital stay.

Results:
Since the start of the study, 57 patients are included. The NDD-arm consists of 23 patients (40.3%). The In-Hospital-arm consists of 34 patients (59.6%). For this study, 74 patients were excluded because they did not meet the NDD criteria, which is 56.5% of the patients undergoing TAVI. The study is ongoing, with enrollment numbers subject to change. Not all included patients can already be included in the analysis of the results. An example of exclusion is that the TAVI procedure is performed within 30 days, or the patient is not reachable. In the NDD-arm, 13 patients can be analyzed, while in the In-Hospital-Arm 16 patients can be analyzed. In the NDD-arm, 4 patients (30.7%) experienced complications following TAVI, while in the In-Hospital arm, 9 patients (56.2%) experienced complications. Complications included hypovolemia, dizziness symptoms, palpitations, stroke, ischemic stroke, and urosepsis. In the NDD-arm 1 patient (7.6%) was rehospitalized, whereas 2 patients (12.5%) in the InHospital-arm were rehospitalized. The reasons were urosepsis and stroke. One patient from the In-Hospital-arm died within 6 months after TAVI due to complications arising from urosepsis.

Conclusion:
The interim findings of this ongoing study suggest a potential advantage in favor of the Next Day Discharge (NDD) arm, characterized by lower incidences of complications, rehospitalization, and mortality post-transcatheter aortic valve implantation (TAVI). However, it is essential to note that the current sample size may limit the robustness of these observations.

Keywords:
Trancatheter aortic valve implantation (TAVI), next-day discharge

9.3 Types of telemetry

Holter monitors

Holter monitors, a prevalent form of telemetry, enable the continuous recording of cardiac electrical activity through electrocardiography (ECG) over a duration typically extending up to 48 hours. Configured in 2-, 3-, or 12-channel formats, these monitors rely on electrodes affixed to the patient's chest, transmitting data to a compact recording device. However, the discomfort caused by the electrodes renders them unsuitable for prolonged wear exceeding 48 hours. While effective in capturing intermittently present arrhythmias, the reliance on patient input for symptom documentation and the absence of real-time data analysis are notable limitations. Additionally, traditional Holter monitors necessitate specialized expertise by a physician for comprehensive data interpretation and analysis [92].

Patch Monitors

In contrast, patch monitors merge Holter monitor characteristics with enhanced patient comfort. Adhering securely to the skin with an adhesive backing, these monitors eliminate cumbersome wires and electrodes. Patients can effortlessly annotate symptoms using a button on the device, improving the correlation between symptoms and recorded events. Notably, patch monitors boast extended monitoring durations, often worn for up to 14 days compared to conventional 48-hour monitors [93].

For instance, the Senselink device, when paired with Cardiologs, operates as a full-disclosure Holter device capable of recording 3-, 5-, or 12-lead ECG data. The recorded data is promptly analyzed by the Cardiologs algorithm and transmitted to a system for direct review, distinguishing it from traditional Holter devices. Patients can trigger an event button sending

an ECG in real-time to a cardiologist. However, contrary to an event recorder, Senselink measures an ECG continuously [72].

The ZIO XT Patch monitor continuously measures a single-lead ECG, automatically analyzing the recorded data using a deep learning algorithm, with the report made available post-recording [74].

Body Guardian heart is a patch monitor continuously measuring a single lead ECG. Events can be separately recorded when feeling symptoms. More leads ECG can be requested. ECGs are not reviewed by an algorithm or expert [77].

Handheld ECG monitoring devices

Handheld electrocardiogram (ECG) devices represent portable instruments that afford patients the capability to record their cardiac activity using their fingers, legs, and/or chest. An illustrative example of such a handheld monitoring device is depicted in Figure 16, featuring the AliveCor Kardia Mobile.

The AliveCor Kardia Mobile serves as a compact, handheld device facilitating the capture of either single-lead or 6-lead ECGs. Operationally, users place one finger from each hand on the device's electrode, as demonstrated in figure 16. For acquiring a 6-lead ECG, the device is positioned on the knee instead of a stable surface. The recorded ECG data is subsequently transmitted to a paired smartphone via a wireless communication protocol utilizing ultrasonic audio. Additional contextual information such as symptoms, activities, or dietary details can be appended to the Notes section for a specific ECG recording. The accompanying smartphone application integrates an algorithm developed by HartWacht, which analyzes the captured ECG data and provides feedback to the patient [62].

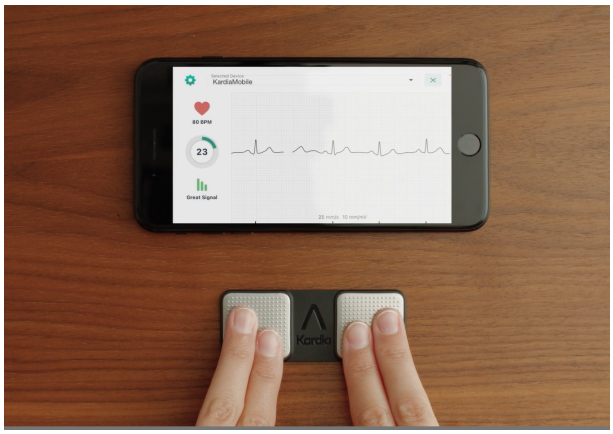

Figure 16: Measurement of ECG by laying two fingers for 30 seconds on the electrodes of the KM [94].

Omron offers another handheld device capable of recording ECGs concurrently with regular blood pressure measurements. This device captures a single-lead ECG, with an embedded detection algorithm identifying atrial fibrillation and presenting results on the device's screen and through a corresponding smartphone application. Blood pressure readings are displayed directly on the device. Omron captures the ECG by placing two fingers on the sensors [63].

The Zenicor ECG device, also handheld, features finger sensors for recording a single-lead ECG. Notably, it includes an onboard display, obviating the need for a smartphone application. Although it does not provide real-time ECG tracing on the device itself, recorded ECG data can be transferred from the device to a centralized database for subsequent review. It boasts a capacity for storing a considerable number of ECG recordings [64][65].

Kardio screen facilitates the recording of 6- and 12-lead ECGs. While the device primarily measures signals from the fingers, limb patches can be affixed to generate 6- and 12-lead recordings. Supporting a broad ECG bandwidth ranging from 0.05 to 75 Hz, this device is

accompanied by a compatible application for measurement assistance. The sensors need to be applied correctly and are not made for long-term attachment. Therefore, it is possible that a caregiver needs to apply the electrodes [73].

The Nabz Hooshmand-1 incorporates electrode leads on both its front and back surfaces, featuring two electrodes for the hand fingers and one electrode for the left leg. This configuration enables the measurement of both 1-lead and 6-lead ECGs [75].

ECG Check operates by positioning two fingers on its surface, registering a 30-second, one-lead ECG, and storing it on the device via Bluetooth. Subsequently, the device's application employs an algorithm to classify the ECG data [76].

SmartWatches
Smartwatch-based electrocardiogram monitoring devices employ integrated sensors and algorithms to capture and analyze the user's ECG signals directly from their wrist. These devices are typically equipped with electrodes within the watch casing or utilize photoplethysmography (PPG) sensors to detect subtle variations in blood volume, which indirectly reflect the heart's electrical activity. Users can initiate ECG recordings through specialized applications or by activating dedicated ECG monitoring functions on their smartwatches. The captured ECG data is subsequently processed either on the device itself or transmitted to a paired smartphone for further interpretation and analysis. This technology offers users the convenience of continuous monitoring of heart rhythm and the detection of irregularities, facilitating real-time cardiovascular health assessment while on the move. Prominent examples of such devices include the Withings Scanwatch, Fitbit Charge 2, Polar OH, Apple Watch, Garmin, Samsung Gear 2, and Everion. Variations in performance among these devices primarily stem from differences in the employed detection algorithms.

For instance, the Withings Scanwatch employs three dry electrodes to record a 30-second single-lead ECG resembling lead I of a traditional 12-lead ECG. The real-time signal captured by the watch is streamed to a smartphone application, where it is stored, exported, and analyzed using a proprietary algorithm [66]. The Fitbit Charge 2 utilizes PurePulse wrist heart rate (HR) technology for HR measurement [67]. The Polar OH1 utilizes six light-emitting diode sensors to record data at one-second intervals, with live transmission via Bluetooth to a smartphone equipped with the Polar Beat application [68]. Similarly, the Apple Watch, Garmin, and Samsung Gear 2 employ a comparable operational framework, albeit with differing classification algorithms. These watches record single-lead ECG data, which can be stored and printed for further examination [69][70][71] . The Everion, a Conformité Européene class IIa-certified wearable sensor worn on the upper arm, measures vital signs—including HR, RR, and SpO2—via PPG and temperature using a negative temperature coefficient thermistor, with data transmitted via Bluetooth to the HealthyChronos application on a bedside tablet [53].

9.4 Input features risk prediction models

Table 15 depicts the number of included patients, the AUROC of the model, the number of input features, and which model it uses for the prediction. All models are used for predicting the 30-day mortality, except for TARIS, this model predicts 1-year mortality. Feature analysis was performed by univariate logistic regression, Fisher's exact test, t-test, and chi^2-test. Suggestions for future studies were to add frailty. $TAVI_2$-score, TVT-score, CoreValve, and TARIS are not externally validated.

Table 16 gives an overview of which input features are included in which risk prediction model.

Table 15: Overview of study details for TAVI risk prediction models[86][87][88][15][78][85][89][90][91].

Study name	Number of Patients	AUROC	Input Features	Risk prediction model
EUROSCORE II	14.799	0.66 (Validation: 0.61)	18	Logistic regression
FRANCE-2	3833	0.59 (Validation: 0.63)	9	Logistic regression
ACC-TAVI	13718	0.66 (Validation: 0.64)	9	Logistic regression
OBSERVANT	1878	0.71 (Validation: 0.58)	7	Logistic regression
GERMAN-AV	11147	0.81 (Validation: 0.60)	15	Logistic regression
$TAVI_2$-score	511	0.72	10	Point system
TVT-score	3491	0.66	7	Logistic regression
CoreValve	3687	0.75	10	Cox regression
TARIS	845	0.71*	8	Cox regression
PPO	2137	0.622	21	Logistic regression

* AUROC of 1-year mortality instead of 30-day mortality

Table 16: Overview of input features for TAVI risk prediction models [86][87][88][15][78][85][89][90][91].

Study name	Input features
EUROSCORE II	Age, gender, chronic lung disease, extracardiac arteriopathy, poor mobility, previous cardiac surgery, active endocarditis, critical preoperative state, renal impairment, diabetes on insulin, CCS angina class 4, LV function, recent MI, pulmonary hypertension, NYHA class, surgery on thoracic aorta, urgency of operation, weight of operation
FRANCE-2	Age, BMI, dialysis, pulmonary oedema, pulmonary hypertension, respiratory insufficiency, critical state, NYHA class, and access site.
ACC-TAVI	Age, chronic lung conditions, dialysis, NYHA class, cardiogenic shock, resuscitation < 1 h, eGFR, urgency, and access site.
OBSERVANT	Diabetes, pulmonary hypertension, critical state, LVEF, NYHA class, previous balloon aortic valvuloplasty, and eGFR
GERMAN-AV	Age, BMI, gender, COPD, dialysis, pulmonary hypertension, critical state, impaired renal function, active endocarditis, LVEF, recent myocardial infarction, NYHA class, no. diseased arterial vessels, no sinus rhythm, previous cardiac surgery, and urgency
$TAVI_2$-score	Age, gender, obstructive long conditions, LVEF, recent myocardial infarction, NYHA class, hypertension, porcelain aorta, aortic valve mean gradient, hemoglobin, hematocrit, and urgency
TVT-score	Age, gender, COPD, dialysis, NYHA class, eGFR, urgency, and access site
CoreValve	Age, home oxygen, preop. mechanic circulation support, and albumin
TARIS	Age, BMI, gender, pulmonary hypertension, active endocarditis, hypertension, eGFR, and hemoglobin
PPO	Age, BMI, gender, chronic lung disease, diabetes, prior peripheral artery disease pulmonary hypertension, hypertension, coronary artery disease, carotid disease, cerebrovascular disease, aortic regurgitation, mitral regurgitation, atrial fibrillation, atrial flutter, ventricular tachycardia/fibrillation, sick sinus syndrome, 2nd degree AV-block, 3rd degree AV-block, hemoglobin, and creatinine

9.5 Results of risk prediction model predicting adverse outcomes

Stroke

Table 17: The mean performance metrics of the 10 folds of Wrapper backward elimination with the range of values across the folds in the square brackets.

Evaluation metric	Wrapper backward elimination
Accuracy	0.98 [0.98-0.99]
Precision	0.98 [0.97-0.98]
F1-score	0.99 [0.98-0.99]]
Recall	1.0 [1.0-1.0]
AUROC	0.99 [0.98-0.99]

Selected features

The selected features used as input for the risk prediction model were: Pgrad, history CVA, LVEF, length, age, eGFR, NYHA, DM, and valve size.

Table 18: Results of risk prediction model for stroke with the input features of Wrapper backward elimination.

Evaluation metric	Logistic Regression	XGBoost	Random Forest
Accuracy	0.57 [0.55-0.58]	0.88 [0.86-0.89]	0.9997 [0.999-1.0]
Precision	0.58 [0.56-0.61]	0.86 [0.85-0.88]	0.999 [0.998-1.0]
F1-score	0.52 [0.51-0.54]	0.88 [0.87-0.90]	0.9997 [0.999-1.0]
Recall	0.48 [0.46-0.50]	0.91 [0.88-0.93]	1.0 [1.0-1.0]
AUROC	0.59 [0.98-0.99]	0.95 [0.94-0.96]	1.0 [1.0-1.0]

Table 19: Results of validating risk prediction model for stroke with the input features of Wrapper backward elimination.

Evaluation metric	Logistic Regression	XGBoost	Random Forest
Accuracy	0.66 [0.65-0.67]	0.88 [0.87-0.89]	0.98 [0.86-0.89]
Precision	0.032 [0.031-0.034]	0.045 [0.033-0.053]	0.0 [0.0-0.0]
F1-score	0.061 [0.057-0.063]	0.073 [0.054-0.086]	0.0 [0.0-0.0]
Recall	0.46 [0.45-0.47]	0.20 [0.14-0.24]	0.0 [0.0-0.0]
AUROC	0.56 [0.56-0.56]	0.57 [0.55-0.59]	0.56 [0.55-0.59]

The logistic regression model showed the best performance on the validation set and is therefore picked as the final prediction model.

Myocardial infarction

Table 20: The mean performance metrics of the 10 folds of Wrapper backward elimination with the range of values across the folds in the square brackets.

Evaluation metric	Wrapper backward elimination
Accuracy	0.99 [0.99-0.99]
Precision	0.99 [0.98-0.99]
F1-score	0.99 [0.99-0.99]
Recall	1.0 [1.0-1.0]
AUROC	0.99 [0.99-0.99]

Selected features
The selected features used as input for the risk prediction model were: NYHA, length, eGFR, history PCI, self-expandable vs balloon expandable valve, Pgrad, weight, CHADSVASC, and LVEF.

Table 21: Results of the risk prediction model for MI with the input features of Wrapper backward elimination.

Evaluation metric	Logistic Regression	XGBoost	Random Forest
Accuracy	0.60 [0.58-61]	0.97 [0.96-0.97]	0.9998 [0.999-1.0]
Precision	0.60 [0.58-0.61]	0.95 [0.95-0.96]	0.9996 [0.999-1.0]
F1-score	0.60 [0.57-0.61]	0.97 [0.96-0.98]	0.9998 [0.999-1.0]
Recall	0.60 [0.56-0.62]	0.99 [0.97-0.99]	1.0 [1.0-1.0]
AUROC	0.63 [0.62-0.64]	0.99 [0.99-0.997]	1.0 [1.0-1.0]

Table 22: Results of validating the risk prediction model for MI with the input features of Wrapper backward elimination.

Evaluation metric	Logistic Regression	XGBoost	Random Forest
Accuracy	0.64 [0.63-0.64]	0.94 [0.93-0.95]	0.98 [98]
Precision	0.025 [0.024-0.026]	0.051 [0.043-0.064]	0.0 [0.0-0.0]
F1-score	0.048 [0.047-0.050]	0.079 [0.069-0.098]	0.0 [0.0-0.0]
Recall	0.63 [0.61-0.66]	0.18 [0.16-0.21]	0.0 [0.0-0.0]
AUROC	0.65 [0.65-0.65]	0.56 [0.54-0.58]	0.59 [0.56-0.63]

The logistic regression model showed the best performance on the validation set and is therefore picked as the final prediction model.

Permanent Pacemaker implantation

Table 23: The mean performance metrics of the 10 folds of Lasso regression and Wrapper backward elimination with the range of values across the folds in the square brackets.

Evaluation metric	Wrapper backward elimination
Accuracy	0.92 [0.92-0.93]
Precision	0.87 [0.86-0.88]
F1-score	0.93 [0.92-0.94]
Recall	0.997 [0.99-0.999]
AUROC	0.92 [0.92-0.93]

Selected features
The selected features used as input for the risk prediction model were: The selected features used as input for the risk prediction model were: weight, balloon vs self-expandable valve, age, Pgrad, baseline pacemaker, eGFR, gender, baseline AF.
(nyha)

Table 24: Results of the risk prediction model for permanent pacemaker implantation with the input features of Wrapper backward elimination.

Evaluation metric	Logistic Regression	XGBoost	Random Forest
Accuracy	0.59 [0.57-0.61]	0.69 [0.67-0.70]	0.98 [0.98-0.98]
Precision	0.58 [0.55-0.60]	0.66 [0.64-0.68]	0.96 [0.96-0.97]
F1-score	0.62 [0.60- 0.64)]	0.71 [0.70-0.72]	0.98 [0.98-0.98]
Recall	0.67 [0.64-0.69]	0.78 [0.76-0.79]	0.998 [0.99-1.0]
AUROC	0.62 [0.60-0.64]	0.77 [0.75-0.78]	0.998 [0.996-0.9996]

Table 25: Results of validating the risk prediction model for permanent pacemaker implantation with the input features of Wrapper backward elimination.

Evaluation metric	Logistic Regression	XGBoost	Random Forest
Accuracy	0.51 [0.51-0.52]	0.58 [0.57-0.59]	0.84 [0.83-0.84]
Precision	0.19 [0.19-0.19]	0.20 [0.20-0.21]	0.43 [0.41-0.45]
F1-score	0.29 [0.29-0.29]	0.30 [0.29-0.31]	0.25 [0.24-0.26]
Recall	0.65 [0.65-0.66]	0.58 [0.56-0.58]	0.18 [0.17-0.18]
AUROC	0.60 [0.60-0.60]	0.61 [0.61-0.62]	0.62 [0.62-0.63]

The random forest model showed the best performance on the validation set and is therefore picked as the final prediction model.

9.6 Results of risk prediction model adding frailty

To effectively compare the difference between frailty and no-frailty in the model, only the variable frailty is added to the model, the other features are the same as the original risk prediction model for 30-day mortality. The missing data is 64% for frailty, this data is filled in using Iterative Imputer

The results of the Random Forest with the input features of the wrapper method including frailty are depicted in Tables 26 and 27.

Table 26: Results of the risk prediction model for 30-day mortality with the input features of Wrapper backward elimination including frailty.

Evaluation metric	Logistic Regression	XGBoost	Random Forest
Accuracy	0.59 [0.58-0.61]	0.86 [0.85-0.87]	0.9998 [0.999-1.0]
Precision	0.59 [0.57-0.62]	0.83 [0.82-0.84]	0.9996 [0.9994-1.0]
F1-score	0.61 [0.59-0.63]	0.86 [0.85-0.88]	0.9998 [0.9994-1.0]
Recall	0.62 [0.61-0.64]	0.90 [0.89-0.92]	1.0[1.0-1.0]
AUROC	0.62 [0.61-0.64]	0.94 [0.93-0.95]	1.0 [1.0-1.0]

Table 27: Results of validating the risk prediction model for 30-day mortality with the input features of Wrapper backward elimination including frailty.

Evaluation metric	Logistic Regression	XGBoost	Random Forest
Accuracy	0.80 [0.80-0.80]	0.93 [0.93-0.93]	0.95 [0.95-0.95]
Precision	0.050 [0.050-0.050]	0.081 [0.063-0.094]	0.97 [0.67-1.0]
F1-score	0.078 [0.078-0.078]	0.059 [0.049-0.071]	0.018 [0.017-0.026]
Recall	0.17 [0.17-0.17]	0.046 [0.039-0.057]	0.0.0092 [0.0.0087-0.013]
AUROC	0.55 [0.55-0.56]	0.48 [0.46-0.50]	0.56 [0.54-0.58]