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Full title **DERIVATION AND VALIDATION OF A CHRONIC TOTAL CORONARY OCCLUSION INTERVENTION PROCEDURAL SUCCESS SCORE FROM THE 20,000-PATIENT EUROCTO REGISTRY: THE EUROCTO (CASTLE) SCORE**

Short title EuroCTO (CASTLE) Score

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Abbreviations CTO = Chronic Total Occlusion; AUC = Area Under the Curve; PCI = Percutaneous Coronary Intervention; TIMI = Thrombolysis in Myocardial Infarction; IVUS = Intravascular Ultrasound; CART = Controlled Antegrade and Retrograde Tracking and Dissection; OR = Odds Ratio; CABG = Coronary Artery Bypass Grafting; ROC = Receiver- Operating Characteristic; MI = Myocardial Infarction

ABSTRACT

Background

Interventional treatment of chronic total coronary occlusions (CTOs) is a developing subspecialty. Predictors of technical success or failure have been derived from datasets of modest size. A robust scoring tool could facilitate case selection and inform decision making.

Methods

We analysed data from the EuroCTO Registry. This prospective database was set up in 2008 and includes >20,000 cases submitted by CTO expert operators (>50 cases/yr). Derivation (n=14,882) and Validation (n=5,745) datasets were created to develop a risk score for predicting technical failure.

Results

There were 14,882 patients in the derivation dataset (with 2356 (15.5%) failures) and 5,745 in the validation dataset (with 703 (12.2%) failures). 20.2% of cases were done retrogradely and dissection re-entry was performed in 9.3% of cases. We identified six predictors of technical failure – **C**ABG history, **A**ge (≥70yrs), **S**tump anatomy (blunt or invisible), **T**ortuosity degree (severe or unseen), **L**ength of occlusion (≥20 mm) and **E**xtent of calcification (severe). Collectively these form the CASTLE score. When each parameter was assigned a value of 1, technical failure was seen to increase from 8% with a CASTLE score of 0-1, to 35% with a score ≥4. The area under the curve (AUC) was similar in both the derivation (AUC = 0.66) and validation sets (AUC = 0.68).

Conclusions

The EuroCTO (CASTLE) score is derived from the largest database of CTO cases to date and offers a useful tool for predicting procedural outcome.

CONDENSED ABSTRACT

Interventional treatment of chronic total occlusions (CTO) is a developing subspecialty. We examined data from the EuroCTO Registry of 20,000 prospectively-entered cases from dedicated CTO operators. Derivation and Validation datasets were created and subjected to analysis. A simple integer scoring system was created to predict procedural outcome. The simple score suggests that the following factors are of greatest importance: **C**ABG history; **A**ge; **S**tump anatomy; **T**ortuosity degree; **L**ength of occlusion and **E**xtent of calcification (CASTLE). Technical failure rates range from 8% (CASTLE score 0-1) to 35% (CASTLE score ≥4).

INTRODUCTION

Chronic total occlusions (CTO) are present in approximately one-fifth of patients undergoing coronary angiography[1]. Historically, these lesions have often been managed either with medical therapy or with coronary artery bypass grafting in suitable candidates because of their complexity and low interventional success rates. Percutaneous coronary intervention (PCI) of CTOs has become more widely accepted in the last decade, with increasing success rates related to operator experience, guidewire technology and microcatheter sophistication[2]. Despite these improvements, procedural success rates remain lower than those achieved with non-occlusive lesions.[3] . A simple and accurate scoring tool to grade the difficulty of cases would be valuable for appropriate case selection and planning. Attempts have been made to classify procedures according to their likelihood of success based on patient, lesion and procedural features[4,5]. These however have been derived from a relatively modest number of patients, and consequently their predictive ability has not been uniformly consistent[6]. Additionally, some have focussed purely on the antegrade approach, to the exclusion of retrograde possibilities[7]. Using the EuroCTO registry, we analysed the factors influencing technical success and we derived and validated a simple model to predict successful percutaneous treatment of CTOs.

METHODS

Patient population

The EuroCTO club is a collaborative effort amongst high volume CTO operators in Europe aimed at sharing experiences and outcomes data. Since 2008, patient characteristics and procedural data have been prospectively recorded in a dedicated registry (www.ercto.org) by individual members. In this database multiple variables are recorded for every patient regarding preprocedural demographic and anatomical characteristics, procedural details and postprocedural outcomes. The data for this analysis relate to patients in whom CTO recanalization was attempted between 2008 and 2016 in 55 European centres. The aim of the analysis was to develop a scoring system to predict the likelihood of success of CTO PCI.

Definitions

Coronary CTOs were defined as occlusions of greater than 3 months duration with TIMI (Thrombolysis in Myocardial Infarction) grade 0 intralesional coronary flow[8]. The length of coronary occlusions was estimated from angiographic projections visually with single or dual contrast injections. The degree of calcification was visually estimated on fluoroscopy - moderate calcification was considered to be present if half of the total CTO segment had visible residues; extension of calcification to >50% of the segment was considered to be severe. The CTO was defined as straight if the pre-occlusive segment contained a bend of <70 degrees. Moderate tortuosity was defined as a segment containing either 2 bends > 70 degrees or 1 bend >90 degrees. A severely tortuous CTO vessel contained either 2 or more pre-occlusive bends of >90 degrees or at least 1 bend of >120 degrees. The morphology of the vessel stump was classified as tapered, blunt or unseen depending on its appearance on fluoroscopy. The angiographic assessment of collateral connections was made according to the Werner classification[9]. Opacification beyond the occlusion was classified into either none, faint or good. Good distal visibility was defined as distal opacification comparable to the proximal segment. Technical success was defined as a residual stenosis of<10% at the end of the procedure with TIMI 3 antegrade flow.

Statistical methods

Predictive model development

The aim was to develop an accurate predictive model from a large number of potential risk factors in order to provide robust prediction of success or failure of CTO PCI. Potential predictive factors strongly associated with the failure of the procedure were selected from candidate variables with univariate logistic regression analysis. These variables included patient characteristics and medical history, baseline measurements and lesion characteristics. Given the large number of patients and outcomes important independent clinical predictors were identified using a stepwise approach with $p < 0.01$ as the inclusion criterion. Using multiple imputed data to account for missing values, patients' demographic data and medical history variables were first entered into the logistic regression model. Baseline measurements and lesion characteristics were then added to the model and evaluated using the pre-set p value of < 0.01 for variable retention. In the final stage variables initially excluded were sequentially re-entered into the model and were re-assessed using the pre-set inclusion criteria.

Multiple imputations

There were no missing values for the outcome of the CTO procedure but data were missing for potential predictor variables (<10% for each variable). In order to adjust for these missing data, multiple imputation techniques with chained equations were used, assuming missingness is at random, with 20 imputations using all covariates showing an association ($p<0.01$) including the outcome variable of technical success, smoking status, gender, CTO location and collateral circulation[10]. The variables included in the final model were also imputed on the validation set using the same multiple imputation techniques.

Risk score analyses

The 2008-2014 cohort was available initially to develop the risk score. The 2015-2016 cohort was used for the validation of the model when these data became available and also to help establish whether success rates had improved over time. The coefficients in the final logistic model can be used to develop a detailed risk score to predict the probability of failure for each patient. However, the aim of our analysis was to develop and present a simplified, easy to use risk score for predicting failure. The multivariable predictive model was converted into a simple risk score by allocating a 0/1 score for each variable in the model depending on the value of that variable for each individual. For each risk factor the category with the lowest predicted risk (i.e. the most beneficial group) was allocated a score of 0 together with any categories with a coefficient <0.20 in the model. A score of 1 was assigned to categories where the coefficient was ≥0.20 from the multivariable logistic regression model (which equates to an odds ratio of 1.22). The total risk score for each individual in the cohort was then computed by adding up the assigned scores for each factor. The distribution of the patients' total risk scores was split into four risk groups for comparison of observed and predicted probabilities of failure to ensure a reasonable number of events in each risk group. On the validation set the same scoring systems were applied as on the derivation set in order to classify the patients into different levels of risk categories.

Model performance

The model performance was inspected on the imputed data with the Hosmer-Lemeshow statistic comparing the observed and predicted probabilities of the patients in groups defined by their predicted probabilities and with the area under curve (AUC) quantifying the ability of the model to discriminate patients at high risk from patients at low risk. Overall model performance on the validation set was assessed with the Brier score[11].

The regression coefficients from the derivation dataset from the logistic model containing the 0-6 patient risk score were applied to compute the predicted risk of failure of PCI for patients in the validation set. To correct for the improvement in success rates in the 2015-2016 cohort compared to the 2008-2014 cohort, an adjustment was made by including the year of operation as a covariate into the model. This allowed for an assessment of the validity of the risk score while presenting better current estimates of actual predicted risks of failure. Risk scores for the validation dataset were calculated in exactly the same way as for the derivation dataset i.e. by allocating a score of 0 or 1 for each of the six variables in the model and summing across variables.

Comparison with J-CTO scoring system

We explored the discriminative capacity of the commonly utilised J-CTO score[4] in our dataset. Score of 1 was first allocated to J-CTO variables of previously failed lesion, blunt/no stump, bending, severe calcification, occlusion length ≥ 20mm. The total risk scores were then obtained on both derivation and validation sets. The discriminative performance of J-CTO scoring system was assessed using ROC curves within both the derivation and validation data sets.

RESULTS

Procedural characteristics

In 76.1% of cases, PCI-CTO was attempted for the first time while 3.7% of cases had had more than two previous failed attempts. Contralateral injection was used in half of the cases. The majority of the cases were done using either 6Fr (42.8%) or 7Fr guide catheters (44.5%). Intravascular imaging with IVUS was performed in 7.4% of cases. The antegrade approach was attempted in 86.1% of cases and was successful in 82.7% of those cases. The single wire technique was commonly successful in recanalization being used in over 75.7% of cases. This was followed by the parallel wire technique (16.8% of successful cases). Dissection re-entry techniques were used in a minority of antegrade cases (2.1%). A retrograde strategy was utilised in 20.2% in our cohort with this approach being used a priori in 13.9%. Touching wire was most commonly used (37.6%) followed by retrograde wire crossing (30.8%), reverse CART

(24.6%) and CART (7.0%). The overall success rate of the retrograde approach (including both upfront and bailout after failed antegrade technique) was 67.3%.

Derivation of the Euro-CTO CASTLE risk analysis tool

Of 14,882 patients in the derivation dataset (2008-14), 2,356 (15.8 %) had unsuccessful CTO PCI. In the validation dataset (2015-2016) there were 5745 patients with 703 (12.2%) who had an unsuccessful CTO PCI. Demographic and clinical variables were explored using the derivation dataset for their association with an unsuccessful CTO procedure (Table 1, SuppTab 1-3).

The derivation dataset had 10,760 patients with no missing values and 4122 patients with at least one missing value for the predictor variables which were imputed as described above. On multivariable analysis of 21 variables associated on univariable analysis, six were identified on the imputed dataset as strong independent predictors of failure of CTO PCI: these were previous **C**ABG, **A**ge, **S**tump anatomy, **T**ortuosity, **L**ength of CTO and **E**xtent of calcification (CASTLE). The estimated odds ratios (ORs) of the association between these variables and the failure of PCI are shown in Table 2. Previous CABG, blunt or no stump, severe tortuosity, high level of calcification, occlusion greater than 20 mm and age above 70 years were all independently associated with an increased risk of failure of the intervention.

To develop an easy to use scoring system able to identify patients at highest risk of CTO PCI failure a robust risk score was developed allocating 0 or 1 for each variable depending on which category a patient was in (Table 2, SuppTab4). The risk score was calculated by the simple addition across all variables.

In order to compare observed and predicted risk for the simple risk score the total scores were grouped into four categories (Figure 2 and Table 3). The total risk scores and risk categories showed good separation of the failure rates across the risk groups. There were 18 unsuccessful PCI procedures in 34 patients with total risk score of 6 (52.9%) compared to 68 unsuccessful procedures in 1129 patients (6.0%) with risk score of 0, an eightfold increase in risk. Overall a good agreement was found between the observed and predicted risks within each group (Table 3, Figure 2), demonstrating good model calibration.

Using the CASTLE model with the identified predictive factors (Table 1) Hosmer-Lemeshow goodness-of-fit test revealed good agreement between the predicted and observed probabilities of failure of PCI (χ^2 with degrees of freedom of 13 = 18.79, p = 0.1 for any imputed data set), demonstrating that the model was well-calibrated. The discriminating ability of the CASTLE model based on the robust scoring defined by the AUC of the total risk scores (AUC = 0.66) was reasonable to distinguish patients at low and high risk.

Validation of Euro-CTO CASTLE risk analysis tool

The distribution of the identified predictive variables by the outcome of the procedure on the validation Euro-CTO data set from years 2015 and 2016 is shown in SuppTab5. The validation dataset had 5258 patients with no missing values and 487 patients with at least one missing value for the predictor. The distribution of the total risk scores of patients in the imputed validation set (Figure 3a) was very similar to that on the derivation set (Figure 1). Although the model seems to overestimate the likelihood of failure of PCI to some extent (Figure 3b, SuppTab6, SuppTab7), this can largely be explained by the improved success rate over time. The overall rate of the observed failure of PCI on the derivation set (15.8 %, 2356/14482) was higher by 3.5 % than that on the validation set (12.2 %, 703/5745). A decreasing trend year on year in the observed annual failure rates from years 2008 to 2016 was also revealed ($p < 0.001$) (Figure 4). Adjusting the CASTLE model for year of operation indeed proved that this improvement in the success of PCI helps to explain small discrepancies between the observed and predicted failure rates computed by the CASTLE algorithm on the validation set (Figure 5, SuppTab8). The overall model performance on the validation set quantified by the Brier-score (Brier score = 0.103 and 0.102 without and with the adjustment of the CASTLE model for year of operation, respectively) was reasonable. The concordance probability measured by the AUC was actually higher on the validation set (AUC = 0.68 for both unadjusted and adjusted models) when compared to the derivation set (AUC = 0.66).

Comparison with J-CTO score

The AUC of J-CTO scoring tool was 0.63 and 0.64 within the training and validation sets respectively. In comparison, our AUC showed a higher discriminatory capacity for both data sets (for the derivation set AUC=0.66; for the validation set AUC=0.68).

DISCUSSION

We present a simple scoring system to predict technical success when performing CTO PCI. Despite technical advances, CTO-PCI remains one of the most difficult areas of interventional cardiology and the one most likely to fail. Therefore being able to predict in advance the likelihood of success will help cardiologists choose wisely, in a number of important ways. Firstly it will help guide interventionalists during their learning phase as CTO operators in terms of case selection; Secondly it will aid Heart Team discussions regarding the likelihood of complete revascularisation with PCI or CABG; Thirdly it will aid comprehensive informed consent for patients regarding the likelihood of CTO PCI success.

A number of scoring systems have been developed over the years to predict successful PCI. Morino et al. publish the J-CTO score in 2011, derived from 400 CTO cases. This study identified five characteristics associated with failure to pass an antegrade guidewire across the occlusion within 30 minutes.[4] The characteristics included a previous failed attempt and did not include previous CABG (widely recognised to be an adverse feature). While procedural failure has been shown to be associated with higher lesion scores in some studies, this relationship has not been observed consistently[6].

Alessandrino et al. published the single-centre CL-score which identified independent predictors of procedural failure in patients undergoing CTO-PCI for the first time.[7] Two clinical variables (history of CABG and previous MI) and four lesion specific characteristics (blunt stump, lesion calcification, non-LAD CTO and lesion length>20mm) were found to be associated with an unsuccessful procedure.

The PROGRESS score developed by Christopoulos et al. estimated the likelihood of success in CTO treated using a hybrid approach[12]. Four lesion characteristics - proximal cap ambiguity, moderate/severe tortuosity, circumflex artery CTO and the absence of retrograde collaterals were found to determine technical success.

Maeremans et al recently published the RECHARGE score[13]. Six factors associated with technical failure were identified: a blunt stump, lesion calcification, in-lesion tortuosity ≥45°, lesion length >20 mm, a diseased distal landing zone and previous bypass graft on the CTO vessel. This score however was derived from 880 patients undergoing a particular approach to CTO treatment using the CrossBoss or Hybrid techniques, used relatively rarely in the

EuroCTO database. However, it is reassuring to see that some negative predictors remain consistent.

The strength of the EuroCTO CASTLE score rests on the large and varied volume of patients from which it is derived and validated. Previous scoring systems have largely been single-institution, based on the antegrade technique alone or based on relatively modest numbers of patients. This study uses patient numbers an order of magnitude greater, with cases undertaken by a large number of different operators across Europe, and should therefore reflect more accurately global practice and offer greater contemporary relevance. Previous scores have provided valuable insight into the predictors of failure. However, some of these are no longer contemporary, and our study demonstrates the importance of adjusting for improved success rates over time in predicting actual failure rates. Despite this change over time, the score performs well both in identifying predictors of procedural failure and demonstrating their persisting relevance.

Our scoring system has a greater discriminative capacity compared to the widely used J-CTO score. The EuroCTO CASTLE score incorporates four factors that are included in the other two main general scoring systems – stump anatomy (J-CTO); tortuosity (J-CTO (in-lesion) and PROGRESS); length of occlusion (J-CTO and PROGRESS) and extent of calcification (J-CTO). Importantly however it also includes two additional variables – previous CABG and Age, both of which are objective and not open to operator interpretation. This enhances the functional integrity of the score. It is also noteworthy that the incidence of previous CABG was lower at 6% to 9% in the previous main scoring systems but was 13% in the EuroCTO Registry. This relatively higher prevalence helps justify why previous CABG merits consideration as an important variable. Although our score is broadly similar to published ones, our study confirms the importance of previously identified predictors of CTO PCI success using contemporary data from a multitude of operators. In order to facilitate usage and uptake, we deliberately simplified the scoring system using a point-based approach. We will also be creating a more precise model using the original coefficients of the model, which will be available in App form.

Study limitations

Our analysis was performed on registry data in the absence of independent verification by core laboratory. Lack of external validation is a limiting factor in our analysis. In addition, while procedural outcome was obtained in all cases, data collection on variables was incomplete. However the amount of missing data did not exceed 10% for any variable. Angiographic data was obtained by visual assessment rather than by quantitative coronary analysis. Thus we cannot eliminate operator-related bias. Data was collected from high volume centres with highly skilled operators at CTO-PCI. Our model may not apply to centres where operator experience is lower. The failure rate for CTO PCI fell gradually during the course of the study, therefore the predictive failure rates are marginally higher than those seen in the final year of the Registry.

CONCLUSIONS

The EuroCTO (CASTLE) prediction score is a multi-centre derived scoring system to predict technical failure in the percutaneous treatment of CTO. Previous CABG, age over 70, a blunt stump, severe tortuosity, length of the occlusion and extent of calcification were strongly associated with unsuccessful CTO-PCI.

FUNDING SOURCES:

None

CLINICAL PERSPECTIVES

WHAT IS KNOWN?

Interventional treatment of chronic total coronary occlusions is a developing subspecialty. Demographic and anatomical criteria which can predict outcome have been derived from relatively modest sample sizes and not been subject to extensive contemporary data analysis

WHAT IS NEW?

We examined data from the EuroCTO Registry of 20,000 prospectively-entered cases from dedicated CTO operators and created a simple integer scoring system to predict technical outcome. The following factors were found to be of greatest importance - **C**ABG history; **A**ge; **S**tump anatomy; **T**ortuosity degree; **L**ength of occlusion and **E**xtent of calcification (CASTLE). Technical failure rates range from 8% (CASTLE score 0-1) to 35% (CASTLE score ⩾4).

WHAT IS NEXT?

The predictive ability of our model needs to be validated in future studies

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FIGURE LEGENDS

Figure 1. Risk scores and predicted probabilities of failure of PCI for patients in the Euro-CTO derivation data set from years 2008 – 2014. The graph represents the distribution of total risk scores of 14882 patients with CTO. The red line shows the predicted surgical failures.

Figure 2. Model calibration in Euro-CTO derivation data set from years 2008 – 2014 (N = 14882). Comparison of the observed and predicted probabilities of failure of PCI across the four risk groups.

Figure 3 Risk scores and calibration of the CASTLE model in the Euro-CTO validation data set from years 2015 and 2016. (a) Distribution of the risk scores of 5745 patients with CTO. (b) Comparison of the observed and predicted probabilities of failure of PCI computed by the EuroCTO CASTLE model across the four risk groups.

Figure 4. Annual failure rates of PCI of CTO from years 2008 to 2016. The decreasing trend year on year in the observed annual failure rates was statistically evaluated with trend test ($p < 0.001$).

Figure 5. Comparison of the observed risk scores and the adjusted predicted risk scores on the Euro-CTO validation data set from years 2015 and 2016 (N = 5745). The CASTLE model was adjusted for the effect of time on failure rate before computing the predicted failure rate of PCI.