

## Prediction of Coronary Artery Restenosis in Patients Undergoing Angioplasty

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### ABSTRACT

**BACKGROUND AND OBJECTIVE:** Coronary artery restenosis following angioplasty may lead to major unwanted cardiac events. This is one of the most important concerns of cardiologists. This study was performed to evaluate the predictors of coronary artery restenosis in patients undergoing angioplasty.

**METHODS:** In this cohort study, all 2159 patients who referred to Madani Hospital in Khorramabad, Iran for angioplasty between 2004 and 2015 were followed up regarding the incidence of coronary artery restenosis for one or two years (at least 50% stenosis in the place of the previous angioplasty) depending on the type of stent, and clinical variables related to the lesion and procedure were recorded in an information form. Then, agents for predicting coronary artery restenosis were identified based on CART (Classification and Regression Tree).

**FINDINGS:** Cumulative incidence of coronary artery restenosis was 12.9% (279 patients) in subcategories: non-drug-eluting stent (25.8%, 114 patients), comorbidity of diabetes and hyperlipidemia (under the subcategory of drug-eluting stents, 19%, 32 patients), multiple drug-eluting stents (under the subcategory of non-diabetic patients, 14.6%, 25 patients), comorbidity of hyperlipidemia and drug abuse (under the subcategory of non-diabetic group who use one drug-eluting stent, 12.8%, 16 patients).

**CONCLUSION:** According to the results of this study, stent type, history of diabetes, number of stents, hyperlipidemia and drug abuse are among the most important predictors of coronary artery restenosis.

**KEYWORDS:** Coronary Artery Restenosis, Coronary Angioplasty, Coronary Stent, Data Mining, Classification Tree.

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## Introduction

One of the most important concerns of cardiologists is the coronary artery restenosis following angioplasty. Its incidence varies depending on the type of stent during the six months after the angioplasty; it varies between 3% and 20% in drug-eluting types and about 16% to 44% in non-drug-eluting types (1). Some studies suggest that coronary artery restenosis can lead to major unwanted cardiac events, including the need for revascularization on the target vessel through repeat coronary angioplasty and open-heart surgery, myocardial infarction, or even deaths due to cardiovascular diseases (2-4).

According to previous studies, many factors contributed to the occurrence of coronary artery restenosis, and the important risk factors include demographic and clinical properties (age, male gender, smoking, diabetes mellitus, history of hypertension, history of hyperlipidemia, history of chronic renal failure, history of unstable angina and history of myocardial infarction) as well as variables related to the lesion and procedure (location of the lesion, length of the lesion, stented vessel diameter, number of affected vessels, number of stented vessels, stent length and stent size) (5 – 11). Previous studies show that there are some contradictions between their results. The major causes of these contradictions are the use of different statistical communities, different definitions of dependent variable, and particularly the use of various statistical methods in data analysis. The statistical methods used in previous studies were mainly descriptive statistics or Chi-square test (12-14), logistic regression model (15-21), negative binomial regression model (22), generalized estimator equation model (23), and Cox regression model (24-29).

In none of the previous studies, data mining techniques such as decision tree have been used. Classification tree as a non-parametric and powerful tool in data mining has shown an acceptable accuracy in predicting qualitative medical outcomes. The most important advantage of this method is the high perceptual capability due to the tree structure (30). Given the importance of the issue, disagreements between the results of similar studies, lack of a similar study in the statistical population of western Iran and the fact that powerful data mining techniques were not used in any of the previous studies to analyze coronary artery restenosis data, the present study was conducted to predict the occurrence of coronary artery restenosis in Khorramabad based on classification tree technique.

## Methods

This historic cohort study was approved by the ethics committee of Lorestan University of Medical Sciences and was conducted among all patients who referred to Khorramabad Shahid Madani hospital from 2004 to 2015 for angioplasty and stent insertion.

All of these patients were followed up according to the information in the clinical file and using census, from the beginning of stent placement until one year later (for non-drug-eluting stents) or until two years later (for drug-eluting stents) in terms of coronary artery restenosis. In the first stage, using the files in the medical records of the hospital, patients' information was recorded in a researcher-made information form, whose formal and content validity was confirmed based on the review of the literature and the opinion of four faculty members of Lorestan University of Medical Sciences. Demographic variables (age group, gender, place of residence, level of education, income satisfaction, smoking and drug abuse), clinical records (history of diabetes, history of hypertension, history of hyperlipidemia, history of chronic renal failure, history of carotid stenosis, history of unstable angina, history of myocardial infarction and history of hospitalization in CCU), variables related to lesion and procedure (physician code, number of involved vessels, location of the lesion, stent type, stent number, stent brand, stent size, stent length, balloon inflation pressures and post-dilatation after the stent), and finally the patient's condition in terms of coronary artery restenosis were recorded in the corresponding form.

Coronary artery restenosis after angioplasty and stent insertion was diagnosed by two cardiologists from Shahid Madani Hospital in Khorramabad, using exercise and re-angiography tests, based on "the presence of at least 50% stenosis of the vessel lumen diameter at the site of previous angioplasty" (31). To observe ethical considerations, all data collection steps were performed without mentioning the patients' names and based on the permission of the Deputy of Research and Technology of Lorestan University of Medical Sciences.

To compare the incidence of coronary artery restenosis regarding independent variables, Chi-square test or Fischer's exact test were used. Independent variables that had  $p < 0.25$  in single-variable analysis entered the classification tree (32). Classification tree is a decision tree that consists of three main components, including root, internal node, and leaf, and based on this process, it first selects an independent variable as root

and is divided into several internal or parent nodes. Each internal node is also divided into other nodes, like the root, to eventually assign a category of dependent variable (leaf node or child) to each node. In a specific model of classification tree called the CART, the appropriate size (depth) of the tree is determined using the cost-complexity pruning technique (33, 34).

In this study, the CART classification algorithm was used to draw the classification tree and the "cross-validation" method was used to validate the tree. In addition, to increase the predictive accuracy of the decision tree, unequal characterization was used. To determine the tree's predictive value, the index of area under the ROC curve, sensitivity, specificity and correct prediction were used. Normalized impact factor was used to choose the most important predictive variables of coronary artery restenosis. Statistical analysis of this

study was performed using SPSS software version 22 and  $p < 0.05$  was considered significant.

## Results

Of 2159 cases of angioplasty in this study, the incidence of coronary artery restenosis was 12.9% (279 patients). There was a significant correlation between the incidence of coronary artery restenosis and drug abuse ( $p=0.025$ ); it was higher in patients with history of drug abuse compared to other people (15.8% [83 patients] versus 12.0% [196 patients]). The history of diabetes was also significantly associated with coronary artery restenosis ( $p < 0.001$ ), which was clearly higher in diabetic subjects compared to non-diabetic subjects (18.2% [106 patients] versus 11.0% [173 patients]) (Tables 1 and 2).

**Table 1. Single-variable evaluation of demographic and clinical factors affecting the incidence of coronary artery restenosis in patients who referred to Khorramabad Shahid Madani hospital for angioplasty from 2004 to 2015**

| Variable                               | Category name                     | All cases * | Cases of coronary artery restenosis * | P-value ** |
|----------------------------------------|-----------------------------------|-------------|---------------------------------------|------------|
| RCA lesion location                    | Yes                               | 585(27.1)   | 78 (13.3)                             | 0.719      |
|                                        | No                                | 1574(72.9)  | 201 (12.8)                            |            |
| LCX lesion location                    | Yes                               | 440(20.4)   | 64 (14.5)                             | 0.265      |
|                                        | No                                | 1719(79.6)  | 215 (12.5)                            |            |
| LAD lesion location                    | Yes                               | 1275(59.1)  | 168 (13.2)                            | 0.696      |
|                                        | No                                | 884 (40.9)  | 111 (12.6)                            |            |
| OM lesion location                     | Yes                               | 131 (6.1)   | 22 (16.8)                             | 0.179      |
|                                        | No                                | 2028(93.9)  | 257 (12.7)                            |            |
| Lesion location of other areas ***     | Yes                               | 56 (2.6)    | 14 (25.0)                             | 0.013      |
|                                        | No                                | 2103(97.4)  | 265 (12.6)                            |            |
| Number of vessels involved             | 1 vessel                          | 1811(83.9)  | 207 (11.4)                            | < 0.001    |
|                                        | 2 or more vessels                 | 348(16.1)   | 72 (20.7)                             |            |
| Physician/operator code                | Code 1                            | 1850(85.7)  | 238 (12.9)                            | 0.855      |
|                                        | Code 2                            | 309(14.3)   | 41 (13.3)                             |            |
| Stent type                             | Only drug-eluting                 | 1717(79.5)  | 165 (9.6)                             | < 0.001    |
|                                        | Only non-drug-eluting             | 233 (10.8)  | 65 (27.9)                             |            |
|                                        | Non-drug-eluting and drug-eluting | 209 (9.7)   | 49 (23.4)                             |            |
| Number of stents                       | 1 stent                           | 1650(76.4)  | 173 (10.5)                            | < 0.001    |
|                                        | 2 stents or more                  | 509 (23.6)  | 106 (20.8)                            |            |
| Average stent length (mm)              | < 15                              | 245 (3.11)  | 42 (1.17)                             | 0.023      |
|                                        | 15 – 24                           | 1409(3.65)  | 186 (2.13)                            |            |
|                                        | ≥ 25                              | 505 (4.23)  | 51 (1.10)                             |            |
| Average stent size (mm)                | < 2.75                            | 1402(9.64)  | 198 (1.14)                            | 0.026      |
|                                        | ≥ 2.75                            | 757 (1.35)  | 81 (7.10)                             |            |
| Balloon inflation pressure (mm / Hg)   | < 16                              | 863 (0.40)  | 119 (9.13)                            | 0.327      |
|                                        | ≥ 16                              | 1296(0.60)  | 160 (3.12)                            |            |
| Post-dilatation after stent deployment | Yes                               | 1057(49.0)  | 129 (12.2)                            | 0.336      |
|                                        | No                                | 1102(51.0)  | 150 (13.6)                            |            |

\* All numbers in the columns are based on frequency (%), \*\* Fisher's exact test or Chi-square test were used, \*\*\* Other areas are Diagonal, PDA, PLV, or Ramos Medianos

**Table 2. Single-variable evaluation of lesion and process-related factors affecting the incidence of coronary artery restenosis in patients who referred to Khorramabad Shahid Madani hospital for angioplasty from 2004 to 2015**

| Variable name                          | Category name                     | All cases * | Cases of coronary artery restenosis * | P value ** |
|----------------------------------------|-----------------------------------|-------------|---------------------------------------|------------|
| RCA lesion location                    | Yes                               | 585(27.1)   | 78 (13.3)                             | 0.719      |
|                                        | No                                | 1574(72.9)  | 201 (12.8)                            |            |
| LCX lesion location                    | Yes                               | 440 (20.4)  | 64 (14.5)                             | 0.265      |
|                                        | No                                | 1719(79.6)  | 215 (12.5)                            |            |
| LAD lesion location                    | Yes                               | 1275(59.1)  | 168 (13.2)                            | 0.696      |
|                                        | No                                | 884 (40.9)  | 111 (12.6)                            |            |
| OM lesion location                     | Yes                               | 131 (6.1)   | 22 (16.8)                             | 0.179      |
|                                        | No                                | 2028(93.9)  | 257 (12.7)                            |            |
| Lesion location of other areas ***     | Yes                               | 56 (2.6)    | 14 (25.0)                             | 0.013      |
|                                        | No                                | 2103(97.4)  | 265 (12.6)                            |            |
| Number of vessels involved             | 1 vessel                          | 1811(83.9)  | 207 (11.4)                            | < 0.001    |
|                                        | 2 or more vessels                 | 348 (16.1)  | 72 (20.7)                             |            |
| Physician/operator code                | Code 1                            | 1850(85.7)  | 238 (12.9)                            | 0.855      |
|                                        | Code 2                            | 309 (14.3)  | 41 (13.3)                             |            |
| Stent type                             | Only drug-eluting                 | 1717(79.5)  | 165 (9.6)                             | < 0.001    |
|                                        | Only non-drug-eluting             | 233 (10.8)  | 65 (27.9)                             |            |
|                                        | Non-drug-eluting and drug-eluting | 209 (9.7)   | 49 (23.4)                             |            |
| Number of stents                       | 1 stent                           | 1650(76.4)  | 173 (10.5)                            | < 0.001    |
|                                        | 2 stents or more                  | 509 (23.6)  | 106 (20.8)                            |            |
| Average stent length (mm)              | < 15                              | 245 (3.11)  | 42 (1.17)                             | 0.023      |
|                                        | 15 – 24                           | 1409(3.65)  | 186 (2.13)                            |            |
|                                        | ≥ 25                              | 505 (4.23)  | 51 (1.10)                             |            |
| Average stent size (mm)                | < 2.75                            | 1402(9.64)  | 198 (1.14)                            | 0.026      |
|                                        | ≥ 2.75                            | 757 (1.35)  | 81 (7.10)                             |            |
| Balloon inflation pressure (mm / Hg)   | < 16                              | 863 (0.40)  | 119 (9.13)                            | 0.327      |
|                                        | ≥ 16                              | 1296(0.60)  | 160 (3.12)                            |            |
| Post-dilatation after stent deployment | Yes                               | 1057(49.0)  | 129 (12.2)                            | 0.336      |
|                                        | No                                | 1102(51.0)  | 150 (13.6)                            |            |

\* All numbers in the columns are based on frequency(%). \*\* Fisher's exact test or Chi-square test were used, \*\*\* Other areas are Diagonal, PDA, PLV, or Ramos Medianos

**Results of decision tree:** the area under the ROC, percentage of sensitivity, percentage of features and percentage of correct prediction were 0.703, 70.3%, 61.8% and 62.9%, respectively. In addition, according to the normalized impact factor, the most important predictors of coronary artery restenosis are stent type (100%), history of diabetes (20%), number of stents (10.5%), history of hyperlipidemia (8%), and drug abuse (3.5%).

According to the CART classification tree, the chance of restenosis was higher in the following subcategories, respectively: non-drug-eluting stents

(25.8%, 114 patients), comorbidity of diabetes mellitus and hyperlipidemia (in the subcategory of drug-eluting stents, 19%, 32 patients), the use of multiple drug-eluting stents (in the subcategory of non-diabetic patients, 14.6%, 25 patients), comorbidity of hyperlipidemia and drug abuse (in the subcategory of non-diabetic patients and users of drug-eluting stents, 12.8%, 16 patients) (Fig 1). In addition, the lowest incidence of coronary artery restenosis was observed in patients who used non-drug-eluting stents, non-diabetics and patients without history of drug abuse (5.6%, 45 patients).

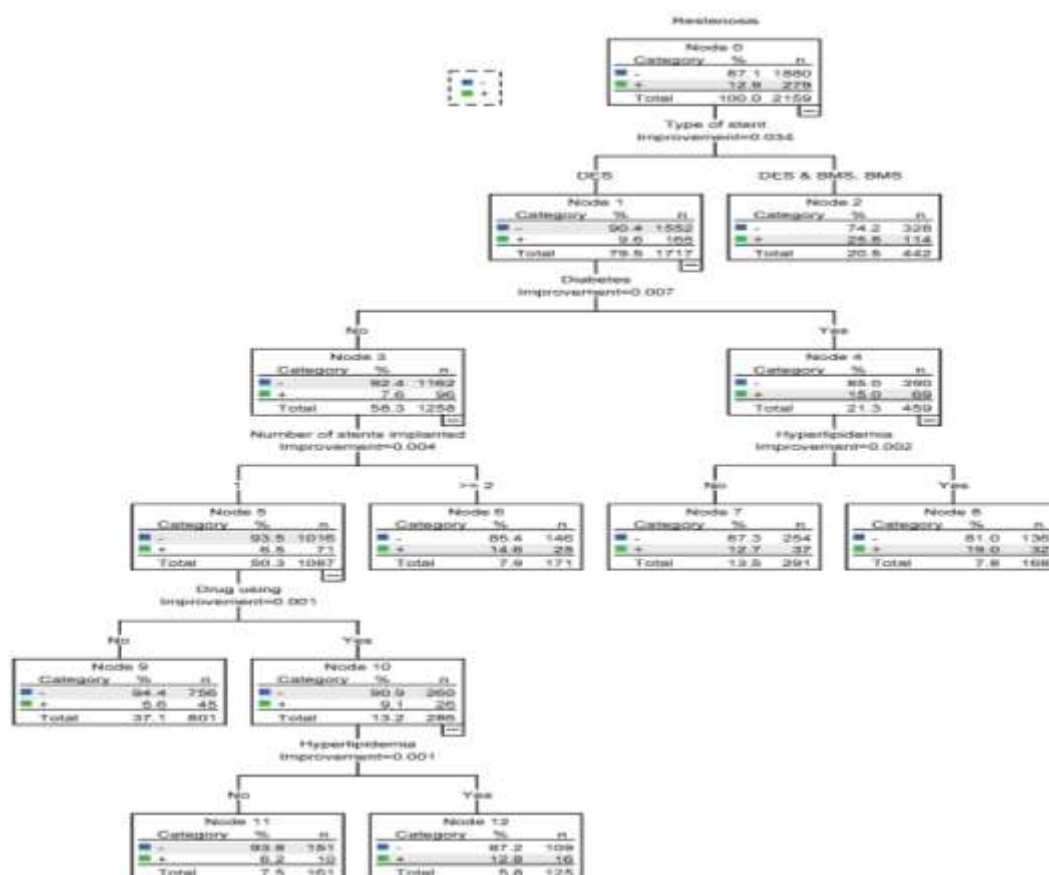


Figure 1. CART classification tree in predicting the incidence of coronary artery restenosis in patients who referred to Khorramabad Shahid Madani hospital for angioplasty from 2004 to 2015 \*

\*: The tree content is set up from top to bottom. Green indicates the risk factor and blue means lack of relevant risk factor. The numbers inside each rectangle (node) are in the form of n (frequency of individuals) and % (percentage of individuals). In addition, in this tree diagram, DES is drug-eluting stent and BMS is non-drug-eluting stent.

## Discussion

In this study, the most important factors for predicting coronary artery restenosis were stent type, diabetes history, number of stents, history of hyperlipidemia and drug abuse. Based on the objective results of the classification tree, the occurrence of coronary artery restenosis in patients who used drug-eluting stents was lower than that of non-drug-eluting stents. This finding is quite consistent with the results of other similar studies (13,14,19,20). In this study, the reverse effect of diabetes has been more pronounced in the subcategory of drug-eluting stents. In most previous studies, the effect of diabetes on coronary artery restenosis has been confirmed, which is also confirmed in the present study (19,22,23,31). However, this relationship was not significant in a small number of studies (20,21), which can be attributed to the lower incidence of diabetes in patients of these studies compared to the present study. In this study, the reverse effect of drug abuse in the subcategories of drug-eluting stents, non-diabetic patients, and patients using only one stent was more obvious. In a number of previous

studies, the effect of drug abuse on the increased risk of coronary artery restenosis has been confirmed, which confirms the results of the present study (21,22), but this relationship was not confirmed in a study by Naserian et al. (16). The reason for this inconsistency can be seen in the different pattern of drug abuse in different cultures and its different prevalence in the studied communities. Based on the results of the present study, the incidence of coronary artery restenosis was clearly higher in patients who used multiple stents (in the subcategory of non-diabetic and diabetic patients).

In many previous studies, such as review articles by Kim et al., Lee et al., Jukema et al., and Hasani et al., similar results were found (3, 11, 13, 35). However, in a small number of studies, the relationship between the number of inserted stents and the occurrence of coronary artery restenosis has not been confirmed (8,20). The possible cause of this inconsistency can be attributed to the effect of other confounding variables, such as the type of stent, the length and size of the stent, and the stented lesion location. The history of hyperlipidemia is considered to be a major risk factor

for coronary artery restenosis. However, its effect was found to be diverse in two different subcategories in this study: first-line, diabetic patients who used drug-eluting stents and second-line, non-diabetic drug users who were embedded with one drug-eluting stents, and this significance is relatively consistent with two recent studies of Ebrahimzadeh, et al. among patients in Zanjan (25, 26). However, in most previous studies, there was no significant relationship between the history of hyperlipidemia and coronary artery restenosis (20,18).

The probable cause of these inconsistencies can be attributed to the fact that some studies used the "the frequency of coronary artery restenosis in a time interval" or "waiting time to the occurrence of the first coronary artery restenosis" as dependent variables (12,18). The most important strengths of this study were the use of a large sample size (2159 people), the use of a wide range of patient-related risk factors, lesion and procedures in statistical modeling and effective use of data mining techniques in statistical analysis of data. The most important limitation of this study could be the retrospective nature of the research, and as a result, the researchers did not have access to some variables related to the lesion such as "length of lesion" and "diameter of the involved vessel". In addition, failure to

accurately record the time of occurrence of coronary artery restenosis in some patients made it impossible to use survival analysis models in analyzing the data in this study.

In this study, the role of predictors such as diabetes mellitus, drug abuse, hyperlipidemia, the use of non-drug-eluting stents and multiple stents were emphasized; therefore, it is recommended that by providing the necessary training by health care staff, the possibility of exposing patients undergoing angioplasty to these risk factors be prevented and more frequent follow-ups be done among the exposed patients.

**Conflict of Interest:** The authors of this article state that there is no conflict of interest.

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