Predictors of Premature Clopidogrel Discontinuation within 30 days of Successful Coronary Artery Stenting

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Abstract

Objective: We aimed to determine the prevalence, predictors, and mortality rate of premature clopidogrel discontinuation within 30 days of successful coronary stenting. **Methods:** All consecutive patients who underwent successful coronary stent implantation at our hospital between December 2006 and December 2007 were prospectively included in this study. Patients were interviewed by telephone 30 days after stent implantation. Premature clopidogrel discontinuation was defined as follows: patients who did not continue clopidogrel after discharge were defined as "never used" and patients who received clopidogrel for <20 days or interrupted therapy for at least 5 successive days within the first 30 days were defined as "partially used." **Results:** Follow-up data were available for 381 patients and 58 (15.2%) patients reported premature clopidogrel discontinuation. No mortality and only 1 (0.3%) stent thrombosis occurred in adherent patients, whereas there were 2 (3.4%) mortalities and 6 (10.3%) stent thrombosis in the patients who prematurely discontinued clopidogrel. Those who discontinued clopidogrel therapy were older ($P = 0.02$), more likely to be female ($P = 0.02$), single ($P = 0.03$), of lower economic ($P < 0.05$) and educational status ($P < 0.01$), more likely to have chronic disease ($P = 0.04$), less likely to have undergone previous stenting ($P = 0.01$), and were more likely to be receiving a larger number of drugs ($P < 0.05$). In multivariate analysis, low- or intermediate-economic status, no history of previous stent implantation, and total number of prescribed drugs using were factors independently associated with premature clopidogrel discontinuation. **Conclusion:** This study demonstrates several predictors of premature clopidogrel discontinuation. This data may help clinicians pay particular attention to these patients in an attempt to improve the outcomes of coronary stenting.

Keywords: Clopidogrel, mortality, stent

INTRODUCTION

Despite improvements in coronary stents and interventional techniques, stent thrombosis remains a major problem following percutaneous coronary interventions. Several clinical, anatomic, and procedural factors associated with stent thrombosis have been identified.[1,2] Premature discontinuation of clopidogrel therapy has been reported to be associated with stent thrombosis, cardiac rehospitalization, cardiovascular death, and all-cause mortality.[3-5] Although most of the factors associated with stent thrombosis are not modifiable, premature clopidogrel discontinuation may be reduced by preventative measures.

Several previous studies have reported predictors of premature clopidogrel discontinuation.[6-9] However, recently, Khalili *et al*. reported that the models used to predict nonadherence perform poorly.[10] In this study, we aimed to determine the prevalence, predictors, and mortality rates of premature clopidogrel discontinuation following successful coronary stent implantation.

METHODS

All consecutive patients who underwent successful coronary stent implantation at our hospital between December 2006 and December 2007 were prospectively included in this study. Patients who died because of reasons other than stent thrombosis during the same hospitalization, those who could not provide at least one telephone number for contact, and

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those who refused to participate were excluded from this study. Patients were interviewed by telephone 30 days after stent implantation. Detailed data regarding the adherence to the prescribed medications and rehospitalizations were obtained. Definite and probable stent thrombosis was also determined. Premature clopidogrel discontinuation was defined as follows: patients who did not continue clopidogrel after discharge were defined as "never used" and patients who received clopidogrel for <20 days or interrupted therapy by at least 5 successive days within the first 30 days were defined as "partially used." The study complied with the principles of the Declaration of Helsinki, and the local Ethics Committee approved the study protocol.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (25%–75% percentiles), and categorical variables were expressed as number and percentage (%). The continuous variables were compared across the groups using the Student's *t*-test or the Mann–Whitney U-test. The Kolmogorov–Smirnov test was used to identify normally distributed variables. The categorical variables were compared using the Chi-square or Fisher's exact tests. Forward and backward binary logistic regression analysis was performed to determine the independent predictors of premature clopidogrel discontinuation. The results were presented as odds ratios (OR) and 95% confidence intervals (CI). Analysis of event-free survival was performed using the Kaplan–Meier method and the differences compared using the log-rank test. Event-free survival was defined as the time from enrollment in the study to the first event, which included death or stent thrombosis. All the data were analyzed with SPSS v14.0 for Windows (SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered to be statistically significant.

RESULTS

We prospectively enrolled 398 consecutive patients in this study. Among these, 13 (3.2%) patients were lost to follow-up. A total of 6 (1.5%) patients died within 30 days and data on clopidogrel maintenance could not be obtained from 4 of these. Therefore, 30-day follow-up data were available for 381 patients. Among the 381 patients, 278 (73%) were men and 103 (27%) were women. Mean age was 57.8 ± 10.6 years. Overall, 58 (15.2%) patients reported premature clopidogrel discontinuation, while 323 (84.8%) reported adherence to clopidogrel therapy [Figure 1]. No patient reported that they prematurley discontinued clopidogrel due to allergy, operation, or bleeding. The baseline characteristics of the patients are summarized in Table 1. Those who discontinued clopidogrel therapy were older ($P = 0.02$), more likely to be female ($P = 0.02$) and single ($P = 0.03$), had lower economic ($P < 0.05$) and educational statuses ($P < 0.01$), were more likely to have chronic disease ($P = 0.04$) and using larger number of drugs ($P < 0.05$), and less likely to have undergone previous stenting ($P = 0.01$). The mortality, stent thrombosis, and nonadherence to other
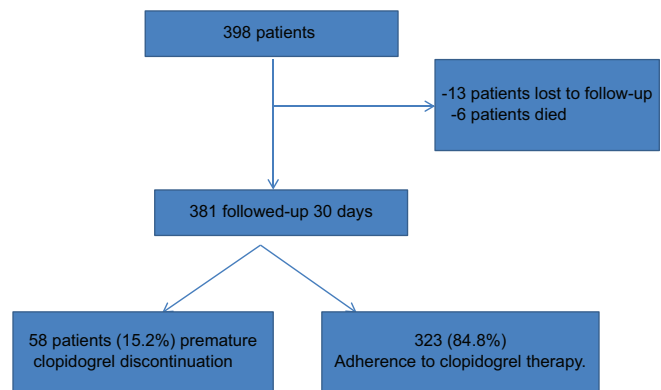

Figure 1: Flowchart of the study

cardiac drugs rates were significantly higher in patients who prematurely discontinued clopidogrel therapy within 30 days [Table 2]. Kaplan–Meier analysis showed that event-free survival within 30 days was higher in patients who adhered to clopidogrel therapy (log rank < 0.001) [Figure 2]. In multivariate analysis, low- and intermediate-economic status (OR: 7.299; 95% CI: 2.642–20.167; $P < 0.05$ and OR: 3.784; 95% CI: 1.352–10.593; $P = 0.0011$, respectively), no history of previous stent implantation (OR: 4.755; 95% CI: 1.339–16.896; $P = 0.016$), and total number of prescribed drugs (OR: 1.940; 95% CI: 1.437–2.619; $P < 0.05$) were factors independently associated with premature clopidogrel discontinuation [Table 3]. On the other hand, age, sex, education status, marital status, living alone, and having chronic disease were not associated with premature clopidogrel discontinuation.

In the subgroup analysis, the patients who had never used clopidogrel were slightly younger than the adherent patients, but the difference was not statistically significant (53.5 ± 10.3 vs. 57.10 ± 10.3, $P = 0.4$). Conversely, the patients who had partially used clopidogrel were significantly older than the adherent patients (65.9 ± 9.8 vs. 57.10 ± 10.3, $P < 0.005$).

DISCUSSION

In this study, we found that approximately 1 in 7 patients prematurely discontinued clopidogrel therapy within 30 days of coronary stent implantation. This prevalence is similar to previously reported rates.[6,11,12] Except for one patient with stent thrombosis, all stent thrombosis and mortalities occurred among patients who prematurely discontinued clopidogrel therapy. A clear association between premature clopidogrel discontinuation and mortality/morbidity was apparent in concordance with previous reports.[4,13-15] We found that a lower economic status is the strongest predictor of premature clopidogrel discontinuation. The majority of the patients had health insurance. However, patients have to pay a partial contribution toward the costs of their prescribed medications and doctor's examination in Turkey. Even this minor contribution could have negative effects on economically disadvantaged patients' ability to start and

Table 1: Baseline characteristics of the patients

Characteristics	No premature discontinuation (*n*=323)	Premature discontinuation (*n*=58)	P
Age (years), mean±SD	57.10±10.3	61.8±11.5	0.02
Sex, male, *n* (%)	243 (75.2)	35 (60.3)	0.02
Married	266 (82.4)	38 (65.5)	0.03
Lifestyle, living alone, *n* (%)	26 (8.0)	10 (17.2)	0.28
Education, *n* (%)			
Illiterate	63 (19.5)	25 (43.1)	<0.05
Complete primary school	181 (56.0)	30 (51.7)	
Complete high school	56 (17.3)	28 (3.4)	
Complete university	23 (7.1)	1 (1.7)	
Economic status			
Low (%)	80 (24.8)	32 (55.2)	<0.05
Intermediate (%)	123 (38.1)	21 (36.2)	
High (%)	120 (37.2)	5 (8.6)	
No health insurance, *n* (%)	18 (5.6)	4 (6.9)	0.69
Heart failure, *n* (%)	52 (16.1)	9 (15.5)	0.09
Hypertension, *n* (%)	260 (80.5)	48 (82.8)	0.88
Diabetes mellitus, *n* (%)	68 (21.1)	11 (19.0)	0.86
Chronic kidney disease, *n* (%)	12 (3.7)	3 (5.2)	0.71
Chronic disease, *n* (%)	42 (13.0)	14 (24.1)	0.04
History of coronary stent, *n* (%)	56 (17.3)	3 (5.2)	0.01
Admission diagnosis, *n* (%)			
STEMI	111 (34.4)	21 (36.2)	>0.05
NSTEM	126 (39.0)	30 (51.7)	
SAP	86 (26.6)	7 (10.1)	
Total number of medicines, mean±SD	5.2±0.9	6.1±1	<0.05

NSTEMI: Non-ST-segment elevation myocardial infarction, SAP: Stable angina pectoris, STEMI: ST-segment elevation myocardial infarction, SD: Standard deviation

Table 2: Stent thrombosis and mortality within 30 days and discontinuation of other cardiac medicines

	No premature discontinuation (*n*=323)	Premature discontinuation (*n*=58)	P
Stent thrombosis, *n* (%) (definite/probable)	1 (0.3)	6 (10.3)	<0.05
Mortality	0	2 (3.4)	0.01
Discontinuation of other cardiac medicines, *n* (%)	9 (15.5)	5 (1.5)	<0.05
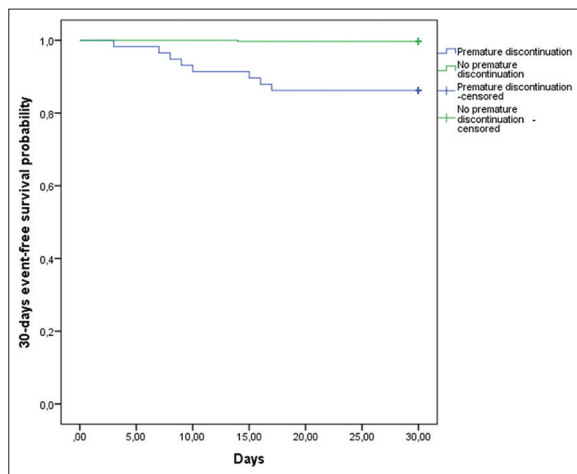
Figure 2: Kaplan–Meier curves for 30-days event-free survival for patients with clopidogrel therapy

maintain treatment without interruptions. Moreover, these patients may experience other unpredictable circumstances that may cause premature clopidogrel discontinuation. Similarly, Khalili *et al.* reported that although clopidogrel was provided at discharge and at nominal cost thereafter, a high rate of nonadherence was observed in a multiethnic, urban, and poor patient population.[10]

No history of previous coronary stenting was another strong predictor of premature clopidogrel discontinuation. This finding shows that patients who did not receive a prior coronary stent were not aware of the hazards of premature clopidogrel discontinuation. On the other hand, this finding also underscores our failure to properly educate patients on the significance of clopidogrel. A short but comprehensive educational session given to patients and their families or providing a printed educational pamphlet on clopidogrel and other medications before discharge may increase adherence to treatment. Using a large number of medications was another significant predictor of premature clopidogrel discontinuation. According to a report by the World Health Organization, approximately 50% of patients do not adhere to the prescribed

Table 3: Predictors of premature clopidogrel discontinuation (backward logistic regression analysis)

Parameter	OR	95% CI	*P*
Low economic status	7.299	2.642-20.167	<0.05
Intermediate economic status	3.784	1.352-10.593	0.011
No previous stent	4.755	1.339-16.896	0.016
Total number of medicines	1.940	1.437-2.619	<0.05
Age	1.029	0.998-1.61	0.068

OR: Odds ratio, CI: Confidence interval

long-term therapies for chronic conditions.[16] In their multicenter study reflecting daily practice in Turkey, Kilic *et al.* had shown that 20.7% of patients with ischemic heart disease do not receive antiplatelet therapy.[17] Poor medication adherence is multifactorial. Broadly, it may be classified as patient-related, physician-related, and health-care system/team building-related factors.[18-20] There are still several efforts that can be made to improve patient health literacy, patient–physician communication, and health-care system-related factors.[21] In a review by Rashid *et al.*, the dominant impact of clinicians on patients' medication adherence was described. The authors claimed that clinicians often unintentionally influence patients' thoughts through their language and lack of accessibility.[22]

In our study, we did not find the patients' education status to be an independent predictor of clopidogrel discontinuation. This result might be due to confounding effects of poor patient–physician communication and health-care system-related problems. Spertus *et al.* found that not completing high school was the only predictor of premature discontinuation of thienopyridine therapy.[5] Age was also not an independent predictor of clopidogrel discontinuation in our study. In the subgroup analysis, while the mean age of patients who had never used clopidogrel after discharge was younger than the adherent patients, the difference was not statistically significant. Younger patients may be in denial about their illness, have a negative attitude toward taking medication, and/or may believe that they have been cured by the interventions.

Study limitations

We conducted a single-center study with a relatively few number of patients. Second, we obtained data by a telephone call and by patient's self-reporting on their adherence. The self-reported adherence data might be unreliable. An additional concern is that 3.2% of patients were lost to follow-up at 30 days and we were unable to obtain data on their adherence or other possible adverse events. Therefore, we may have underestimated the true rates of premature clopidogrel discontinuation. Although our study was not conducted recently, we believe that it still provides relevant and current information.

Conclusion

Improving patients' adherence to their medications is a significant task and an opportunity to decrease stent thrombosis and related morbidity and mortality. Further, studies with more patients are necessary to determine the predictors of premature clopidogrel discontinuation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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