Effect of acute coronary syndrome patients' education on adherence to dual antiplatelet therapy

Hassan El-Toukhy [a,*], Abdullah Omar [b], Manal Abou Samra [c]

[a] Dr. Soliman Fakeeh Hospital, Falastin, Al-Hamra'a, Jeddah 21461
[b] Dallah Hospital, An Nakhil, Riyadh 12381
[c] Ghassan Najeeb Pharaon Hospital, Prince Sultan Street, Jeddah 21412

[a,b,c] Saudi Arabia

Purpose: To assess the effect of acute coronary syndrome (ACS) patients' education on their adherence to dual antiplatelet therapy (DAPT) and on lifestyle modifications.

Methods: Patients who were prescribed acetyl salicylic acid and clopidogrel DAPT within 15 days of having an ACS event were enrolled in this study. Patients were randomized into two arms: the first arm received the study intervention, which consisted of education on coronary artery disease and the importance of sustained platelet inhibition, whereas the second arm was the control group. Both arms received education on lifestyle modifications. Patients completed six visits over 1 year. At each visit, pill count was used to assess adherence to DAPT, data on lifestyle modifications were collected, and changes in weight and waist circumference were recorded. Cardiovascular risk factors were recorded at baseline and the occurrence of new events was monitored throughout the study.

Results: There were 153 patients in Arm 1 and 168 in Arm 2. At Month 6, 99.3% of patients in Arm 1 were adherent compared with 94.4% in Arm 2 ($p = 0.016$). At Month 12, 303 (94.4%) patients from the overall population were adherent to DAPT and there was no significant difference between the two arms ($p = 0.443$). In addition, no statistically significant difference was found in mean change in weight (3 kg vs. 2 kg, $p = 0.064$) or mean change in waist circumference (3.5 cm vs. 2.6 cm, $p = 0.071$) between the two arms. There was a significant decrease in the percentage of smokers ($p < 0.001$) and a significant increase in the percentage of physically active patients ($p < 0.001$) within each arm between baseline and Month 12, but the percent change in smokers ($z = 1.72$, $p = 0.085$) and percent change in physically active patients ($z = 0.76$, $p = 0.447$) between the two arms were not significantly different. Fourteen myocardial infarctions and two strokes occurred throughout the study period.

Conclusion: Patient education on DAPT showed short-term effect on adherence to treatment. More effective education methods should be developed to improve long-term DAPT adherence.

P.O. Box 2925 Riyadh – 11461KSA
Tel: +966 1 2520088 ext 40151
Fax: +966 1 2520718
Email: sha@sha.org.sa
URL: www.sha.org.sa

Production and hosting by Elsevier

Introduction

Coronary artery disease (CAD) is one of the leading causes of death worldwide. The latest clinical practice guidelines agree on the usefulness of dual antiplatelet therapy (DAPT) both as part of the treatment of acute coronary syndrome (ACS) and as a measure to prevent recurrence [1,2].

Following recommended frequency and dosage is important to obtain optimal antiplatelet aggregation activity. Nonadherence has been associated with a number of predisposing factors, many of which are modifiable while others are not [3]. Specifically, in DAPT, prior history of nonadherence to medications, lack of pharmacy access, poor physician–patient relationship, low income, and history of other chronic illnesses such as heart failure and chronic obstructive pulmonary disorder have been linked to poor adherence to therapy [4,5]. In addition, premature discontinuation of medication has been correlated with higher morbidity and mortality among patients with CAD [6,7].

A large Canadian registry of postmyocardial infarction patients found antiplatelet agents to have the lowest prescription refill rate, as compared with other cardioprotective agents such as statins, angiotensin-converting enzyme inhibitors, and beta blockers [8]. In addition, the concepts of platelet aggregation and its inhibition are the least understood in the general population, much less so than other ACS medications.

Previous studies have shown that providing patients with clear discharge instructions and education on the nature of the treatment will help in achieving favorable results as they help facilitate adherence to medical regimens [9,10].

The present Adherence–ACS trial is a new approach in the Kingdom of Saudi Arabia for dealing with the issue of adherence, or lack thereof. This study assesses the effects of providing patients with education about CAD and the role of platelets inhibition in the acute setting on the adherence to prescribed medication. The study also assesses the impact of educating patients on lifestyle modifications.

Patients and methods

Study population and settings

This study recruited patients from 43 private clinics and hospitals in the Kingdom of Saudi Arabia. Patients aged 21 years or older, presenting for the management of an ACS event (clinically defined and supported by electrocardiography and cardiac enzymes testing), and started on chronic antiplatelets dual therapy of acetyl salicylic acid (ASA) and clopidogrel no later than 15 days after the onset of symptoms were approached by their treating physician at the recruiting site and informed about the study and its objectives. Patients who agreed to participate and signed an informed consent were enrolled in the study.

Patients were excluded if they had a chronic debilitating condition (e.g., AIDS, cancer) or a mental condition (e.g., depression, Alzheimer disease) that precluded them from being responsible for their medical therapy, had a contraindication to the use of antiplatelet therapy (hypersensitivity, etc.), were current users of oral anticoagulants, had chronic renal failure or severe liver impairment, or had a current active bleeding.

The study was approved by the Dr. Soliman Fakeeh Hospital Research and Ethics Committee. The study recruited for a period of 19 months.

Randomization and intervention

Patients enrolled in the study were randomized in a 1:1 ratio into two arms. Patients in Arm 1 were allocated to receive the study intervention and are therefore referred to as the educated arm, whereas patients in Arm 2 did not receive the educational intervention and are referred to as the noneducated arm (control group). The intervention consisted of educating the patients on several aspects of CAD disease. The focus was mainly on atherothrombosis and its different clinical features, the role of platelets in the genesis of events, and the importance of their sustained inhibition. Education was provided by the physician and the educational material was also available in a standardized leaflet form that was kept with the patient. Both arms received education on lifestyle

Abbreviations	
CAD	Coronary Artery Disease
ACS	Acute Coronary Syndrome
DAPT	Dual Anti-Platelet Therapy
COPD	Chronic Obstructive Pulmonary Disorder
MI	Myocardial Infarction
KSA	Kingdom of Saudi Arabia
ASA	Acetyl Salicylic Acid
LDL-C	Low Density Lipoprotein-Cholesterol

Table 1. Baseline characteristics.

	Arm 1 (N = 153)	Arm 2 (N = 168)	p
Demographics			
Age (y), mean ± SD	54.68 ± 8.58	53.31 ± 8.32	0.150
Sex, *n* (%)			
Male	119 (77.8)	142 (84.5)	0.122
Female	34 (22.2)	26 (15.5)	
Nationality, *n* (%)			
Saudi	57 (37.3)	68 (40.5)	0.554
Other	96 (62.7)	100 (59.5)	
Marital status, *n* (%)			
Married	136 (93.2)	152 (93.3)	0.524
Divorced/widowed	7 (4.8)	5 (3.1)	
Single	3 (2.1)	6 (3.7)	
Baseline characteristics			
Height (cm), mean ± SD	170.56 ± 7.15	168.76 ± 7.48	0.036
Weight (kg), mean ± SD	87.91 ± 11.80	84.90 ± 13.51	0.038
BMI (kg/m^2), mean ± SD	30.27 ± 4.05	29.91 ± 4.30	0.461
Waist (cm), mean ± SD	100.34 ± 13.11	99.97 ± 13.76	0.816
SBP (mmHg), mean ± SD	134.50 ± 17.76	134.59 ± 17.98	0.964
DBP (mmHg), mean ± SD	84.05 ± 10.18	83.90 ± 10.67	0.964
Heart rate (bpm), mean ± SD	76.15 ± 9.85	76.27 ± 8.95	0.915
Risk factors			
Left ventricular hypertrophy, *n* (%)	69 (45.1)	53 (31.5)	
Previous heart attack/myocardial infarction, *n* (%)	73 (47.7)	74 (44.0)	
Previous stroke, *n* (%)	12 (7.8)	12 (7.1)	
Peripheral arterial disease, *n* (%)	11 (7.2)	8 (4.8)	
Diabetes mellitus, *n* (%)	81 (52.9)	76 (45.2)	
Abdominal obesity, *n* (%)	79 (51.6)	73 (43.5)	
Family history of premature coronary heart disease, *n* (%)	48 (31.4)	41 (24.4)	
Elevated low-density lipoprotein-cholesterol level, *n* (%)	101 (66)	104 (61.9)	
Lifestyle			
Smoking, *n* (%)			
Never	86 (56.6)	111 (68.1)	0.101
Past smoker	22 (14.5)	19 (11.7)	
Smoker	44 (28.9)	33 (20.2)	
Physical activity, *n* (%)			
Yes	22 (14.4)	24 (14.5)	0.966
No	131 (85.6)	141 (85.5)	

BMI = body mass index; BPM = beats per minute; DBP = diastolic blood pressure; SBP = systolic blood pressure; SD = standard deviation.

changes (i.e., smoking cessation, weight loss, and physical activity).

Patients with protocol violations and those without an evaluable outcome were excluded from the final analysis.

Study end points

The primary end point was the percentage of patients achieving adherence with prescribed DAPT throughout the study in the two arms. The secondary end point was changes in patients' lifestyle between baseline and Month 12 and included changes in weight, waist circumference, smoking status, and physical activity status.

Measurements

Patients were followed up for a period of 1 year from randomization, and data on end points were collected over six visits (baseline, Month 1, Month 3, Month 6, Month 9, and Month 12).

In this study, adherence was defined as taking more than 80% of DAPT for the duration prescribed by the physician, and was assessed at each visit after randomization using the pill count of both ASA and clopidogrel.

Data on lifestyle modifications were also collected at each visit. Changes in weight and waist circumference were recorded for each patient (measured by the treating physician or the physi-

Table 2. Comparison of adherence between the two arms at different time points.

	Arm 1	Arm 2	*p*
Overall adherence			
Eligible *N*	153	168	
n (%)	146 (95.4)	157 (93.5)	0.443
1-mo adherence			
Eligible *N*	152	168	
n (%)	148 (97.4)	162 (96.4)	0.629
3-mo adherence			
Eligible *N*	146	165	
n (%)	142 (97.3)	156 (94.5)	0.233
6-mo adherence			
Eligible *N*	145	162	
n (%)	144 (99.3)	153 (94.4)	**0.016**
9-mo adherence			
Eligible *N*	144	158	
n (%)	141 (97.9)	152 (96.2)	0.382
12-mo adherence			
Eligible *N*	139	152	
n (%)	134 (96.4)	142 (93.4)	0.251

Bold values indicate statistical significance; ie when *p*-value is less than or equal to 0.05.

cian's assistant nurse), and data on smoking and physical activity statuses were subjectively reported by the patient.

Cardiovascular risk factors were recorded at baseline and the occurrence of new events was monitored throughout the study period.

Statistical considerations

Sample size was calculated based on an improvement of 10% in adherence rate in the intervention arm with a type 1 error rate of 5% and power of 80% ($\alpha = 0.05$, $\beta = 0.20$, $\varepsilon = 0.1$). A sample size of 385 patients was needed in the intervention arm. Considering 15% drop-out rate, 443 (rounded to 450) patients needed to be recruited in the intervention arm; thus, 900 patients were required in both the intervention and control arms.

The sample size was recalculated due to difficulty in recruiting, considering an improvement of 15% in adherence rate based on van der Wal et al.'s report [11]. The newly calculated sample size was 133 patients per arm, adjusted to 160 after considering a 20% attrition rate. Thus, the total sample size would be 320 patients.

Statistical analyses were performed using Epi Info (version 3.5.1, CDC, Atlanta, GA, USA). All statistical tests were two sided with a 5% significance level. Quantitative variables were summarized using means and standard deviations, and qualitative variables using frequencies and per-

centages. Comparison of adherence to prescribed DAPT between the two arms was performed using a Chi-square test. Paired *t* test and McNemar test were performed to test for significant change in means and proportions, respectively, between baseline and Month 12 in each arm. Student *t* test and *z* test were used for the comparison of mean change in means and proportions, respectively, between the two arms. Baseline and incident cardiovascular risk factors were described as frequencies.

Results

Study population

From April 24, 2011, to November 19, 2012, 424 patients were enrolled. Mean age of patients included was 54 ± 9 years, and male patients represented more than two-thirds of the sample (83.2%). After randomization, 153 patients in Arm 1 and 168 in Arm 2 remained for analysis. The two arms were comparable for most of the demographic and baseline characteristics. However, mean height and weight were slightly higher in Arm 1 (171 ± 7 cm vs. 169 ± 7 cm; *p* = 0.036 for height and 88 ± 12 kg vs. 85 ± 14 kg; *p* = 0.038 for weight; Table 1).

Dual antiplatelets therapy dose

The mean daily dose of ASA prescribed at baseline was 92 ± 30 mg in Arm 1 and 90 ± 22 mg in Arm 2. The mean daily dose of clopidogrel prescribed in Arms 1 and 2 was 77 ± 13 mg.

Adherence

Adherence to DAPT was defined in this study as taking more than 80% of prescribed therapy (pills) for the duration recommended by the physician. At the end of the study at Month 12, 303 (94.4%) patients met the definition of adherence in the overall population. In Arm 1, of the 153 patients, 146 (95.4%) were adherent to prescribed DAPT throughout the study period as compared with 157 of 168 patients (93.5%) in Arm 2 (*p* = 0.443).

A significant difference was found between Arm 1 and Arm 2 at Month 6 with regard to adherence. As much as 99.3% of patients in Arm 1 achieved adherence compared with 94.4% in Arm 2 (*p* = 0.016). Adherence assessment at different time points is shown in Table 2.

Table 3. Lifestyle modifications between baseline and Month 12 comparisons between the two arms.

	Arm 1			Arm 2			p
	Baseline	Month 12	p	Baseline	Month 12	p	
Weight (kg), mean ± SD	87.91 ± 11.81	85.59 ± 11.45	**<0.001**	84.90 ± 13.51	83.10 ± 12.95	**<0.001**	
Mean change	3.03 ± 4.92			1.97 ± 4.36			0.064
Waist circumference (cm), mean ± SD	100.34 ± 13.11	97.58 ± 11.70	0.816	99.97 ± 13.76	97.66 ± 12.70	0.956	
Mean change	3.51 ± 4.79			2.61 ± 4.00			0.071
Smokers, n (%)	37 (27.2)	14 (10.3)	**<0.001**	28 (18.7)	13 (8.7)	**<0.001**	
Percent change	16.9			10.0			0.085
Physically active, n (%)	20 (14.1)	89 (62.7)	**<0.001**	21 (13.6)	89 (57.8)	**<0.001**	
Percent change	48.6			44.2			0.447

Bold values indicate statistical significance; ie when p-value is less than or equal to 0.05.
SD = standard deviation.

Effect of baseline characteristics on overall adherence

When studying the effect of baseline characteristics on overall adherence, there was no significant difference between the adherent and nonadherent groups in terms of anthropometric measurements or lifestyle factors.

As for demographics, married patients were significantly more adherent than divorced/widowed and single patients ($p = 0.037$). Regarding baseline risk factors and comorbidities, patients with a previous incidence of heart attack/myocardial infarction ($p = 0.021$) and patients with a previous incidence of stroke ($p < 0.001$) were significantly less adherent than those with no previous history of these events (see Table S1 in the supplementary information online).

Lifestyle modifications

The impact of education about lifestyle changes was tested by comparing lifestyle modifications in each arm between baseline and Month 12, whereas the impact of the study intervention (i.e., the material provided only to the intervention arm) was tested by comparing mean changes in lifestyle between the two arms.

Weight and waist circumference

In Arm 1, mean weight at baseline was 88 ± 12 kg and it decreased to reach 86 ± 11 kg at Month 12 ($p < 0.001$). In Arm 2, mean weight at baseline was 85 ± 14 kg and 83 ± 13 kg at Month 12 ($p < 0.001$). When comparing mean change in weight between the two arms, no statistically significant difference was found (3 kg vs. 2 kg, $p = 0.064$).

Mean waist circumference was 100 ± 13 cm in Arm 1 at baseline and 98 ± 12 cm at Month 12 ($p < 0.001$), whereas it was 100 ± 14 cm and 98 ± 13 cm in Arm 2 at baseline and month 12,

respectively ($p < 0.001$). The comparison between the two arms in mean waist circumference change showed no statistically significant difference (3.5 cm vs. 2.6 cm, $p = 0.071$; Table 3).

Smoking and physical activity

There was a substantial decrease in the proportion of smokers between baseline and Month 12 in both arms. At baseline, 27.2% of patients in Arm 1 were smokers. The proportion was significantly decreased at the last visit (Month 12) to reach 10.3% ($p < 0.001$); 18.7% were smokers at baseline in Arm 2, whereas only 8.7% were smokers at Month 12 ($p < 0.001$).

The Z test for comparison in percent change in smokers between the two arms yielded an insignificant difference ($z = 1.72$, $p = 0.085$).

When evaluating physical activity in patients, both arms showed an increasing pattern in the proportion of physically active patients. The percentage of physically active patients was 14.1% in Arm 1 at baseline and 62.7% at month 12 ($p < 0.001$). In Arm 2, the proportion of physically active patients increased from 13.6% to 57.8% ($p < 0.001$).

Z test for comparison in percent change in physically active patients between the two arms yielded an insignificant difference ($z = 0.76$, $p = 0.447$). Results are shown in Table 3.

Cardiovascular risk factors and events

Elevated low-density lipoprotein-cholesterol level (63.9%) was the most commonly reported cardiovascular risk factor among the study population at baseline, followed by diabetes mellitus (48.9%), abdominal obesity (47.4%), and history of myocardial infarction (45.8%). Throughout the study period, 14 myocardial infarction and two stroke events occurred.

Discussion

The primary objective of this interventional study was to determine the effect of education about CAD and the role of platelets inhibition in the acute settings on patients' adherence to prescribed clopidogrel–ASA. We found no significant difference in the overall adherence to clopidogrel–ASA between the two arms. Our findings were consistent with a study that concluded that giving discharge instructions about the importance of the adherence to antiplatelet therapy did not affect adherence at 12 months [12]. Another study also showed that lack of understanding of the disease pathophysiology was, according to patients, last on the list of factors affecting adherence, whereas depression, asymptomatic ischemic disease treatment, and lack of patient confidence in the treatment could easily influence patient adherence [13]. By contrast, Garavalia et al. [14] identified a lower education level, immigrant status, and a lack of instructions regarding antiplatelet therapy on discharge from the hospital to be associated with nonadherence. Patients reported nonadherence as being mainly due to a lack of knowledge regarding the treatment and poor communication with health-care professionals [14]. De Servi et al. [13] showed that adherence to medication required medical staff to ensure that the patient and his/her caregiver were correctly and completely informed, upon discharge, about the rationale behind antiplatelet therapy as well as the risks associated with premature clopidogrel–ASA interruption.

Importantly, our findings showed a significant difference in clopidogrel–ASA adherence between the two arms at the 6 months; 99.3% of patients in Arm 1 were adherent, compared with 94.4% in Arm 2. The observed difference could be construed as the result of patient motivation waning between the 3rd and 6th months, leaving only the educational intervention to account for the significant difference seen at Month 6. Consequent visits showing no significant difference between the two arms might suggest that the effect of the intervention wore off.

This is also supported by the decline in adherence observed in other studies after 6 months of therapy start [15–17].

Our study reported an overall nonadherence in 5.6% of the patients at Month 12. This incidence was lower than that reported in other studies [18,19]. Among those, Shroff et al. [19], using pharmacy refill records and a definition of adherence similar to ours, found that 20.3% of patients who had undergone percutaneous coronary intervention were nonadherent to their clopidogrel therapy for the prescribed duration [19]. The substantial difference observed is explained by the difference in design between the two studies. Shroff et al.'s [19] study was retrospective in design, whereas our study was a prospective collection of adherence data. Thus, patients in our study were more likely to adhere to the prescription regardless of whether or not they had received education on platelet aggregation and its inhibition.

As for the effect of the study intervention on lifestyle modifications, we found no statistically significant differences between the two arms in any of the lifestyle variables. However, there was a statistically significant decrease in weight and in proportion of smokers as well as a statistically significant increase in the proportion of physically active patients between baseline and Month 12, in each of the two arms. This mirrors the effect of the lifestyle modification education, which was provided at baseline for both arms, but does not support any effect for the study intervention on lifestyle modifications.

This is a success regarding the risk factors of CAD, but we cannot ascertain that such an educational intervention is solely responsible for this result.

Conclusion

Educating patients about CAD and the importance of clopidogrel–ASA in the management of their disease has proven to have a short-term benefit on patients' adherence to treatment. Enhancements should be made by health-care professionals and broad efforts should be drawn by the public health sector to provide more effective education to improve long-term and stringent clopidogrel–ASA adherence.

Authors' contribution

H.E-T developed the concept and design of the study and contributed to the acquisition of data. A.O. contributed to literature search, acquisition of data, and statistical analysis. M.A.S. contributed to the study conception and design as well as data acquisition and interpretation. El-H.E-T, A.O., and M.A.S. contributed to this manuscript's preparation, editing, and review of content and approved the final submitted version.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jsha.2017.02.003.

References

[1] Amsterdam EA, Wenger NK, Brindis RG, Casey Jr DE, Ganiats TG, Holmes Jr DR, et al.. 2014 ACC/AHA guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:e344–426.

[2] Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al.. 2014 ESC/EACTS guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–619.

[3] Yallapragada S, Siddiqui S, Gindi R, Shroff A. Adherence to dual antiplatelet therapy: can we do better? Expert Rev Cardiovasc Ther 2013;11:1417–24.

[4] Ko DT, Chiu M, Guo H, Austin PC, Marquis J-F, Tu JV. Patterns of use of thienopyridine therapy after percutaneous coronary interventions with drug-eluting stents and bare-metal stents. Am Heart J 2009;158:592–8.

[5] Muntner P, Mann DM, Woodward M, Choi JW, Stoler RC, Shimbo D, et al.. Predictors of low clopidogrel adherence following percutaneous coronary intervention. Am J Cardiol 2011;108:822–7.

[6] Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, et al.. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation 2006;113:2803–9.

[7] Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al.. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.

[8] Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. Circulation 2008;117:1028–36.

[9] Phillips CO, Wright SM, Kern DE, Singa RM, Shepperd S, Rubin HR. Comprehensive discharge planning with post discharge support for older patients with congestive heart failure: a meta-analysis. JAMA 2002;91:1358–67.

[10] Koelling TM, Johnson ML, Cody RJ, Aaronson KD. Discharge education improves clinical outcomes in patients with chronic heart failure. Circulation 2005;111:179–85.

[11] van der Wal MH, Jaarsma T, Moser DK, Veeger NJ, van Gilst WH, van Veldhuisen DJ. Compliance in heart failure patients: the importance of knowledge and beliefs. Eur Heart J 2006;27:434–40.

[12] Ferreira-González I, Marsal JR, Ribera A, Permanyer-Miralda G, García-Del Blanco B, Martí G, et al.. Background, incidence, and predictors of antiplatelet therapy discontinuation during the first year after drug-eluting stent implantation. Circulation 2010;122:1017–25.

[13] De Servi S, Roncella A, Reimers B. Causes and clinical implications of premature discontinuation of dual antiplatelet therapy. Curr Opin Cardiol 2011;26:S15–21.

[14] Garavalia L, Ho PM, Garavalia B, Foody JM, Kruse H, Spertus JA. Clinician-patient discord: exploring differences in perspectives for discontinuing clopidogrel. Eur J Cardiovasc Nurs 2011;10:50–5.

[15] Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002;288:462–7.

[16] Cramer J, Rosenheck R, Kirk G, Krol W, Krystal J. Medication compliance feedback and monitoring in a clinical trial: predictors and outcomes. Value Health 2003;6:566–73.

[17] Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. JAMA 2002;288:2880–3.

[18] Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, et al.. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet 2013;382:1714–22.

[19] Shroff A, Ali A, Groo VL. Clopidogrel adherence following percutaneous coronary intervention with a drug-eluting stent in a VA Medical Center. J Pharm Technol 2009;25:164–8.