REPORT

Trends in adherence to secondary prevention medications in post-acute coronary syndrome patients

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Abstract: To evaluate patients' adherence to evidence-based therapies at an average of 2 years after discharge for Acute Coronary Syndrome (ACS) and to identify factors associated with non-adherence. This study was conducted at Hospital Pulau Pinang, Malaysia. A random sample of ACS patients (n=190) who had discharged on a regimen of secondary preventive medications were included and followed up over a three follow-up appointments at 8, 16, and 23 months post discharge. At each appointment, patients were interviewed and given Morisky questioner to complete in order to compare their level of adherence to the prescribed regimens across the three consecutive time periods. Majority of patients reported either medium or low adherence across the three time periods with only small portion reported high adherence. Furthermore, there was a significant downward trend in the level of adherence to cardio protective medications during the study period (p<0.001). This study also identified 6 factors-age, gender, employment status, ACS subtype, number of co morbidities and number of prescription medications per day that may influence Patients' adherence to their medications. Our findings suggest that long-term adherence to secondary prevention therapies among patients with ACS in Malaysia is sub optimal and influenced by many demographic, social as well as clinical factors.

Keywords: Adherence, acute coronary syndrome, secondary prevention medications, Morisky scale.

INTRODUCTION

The treatment and care of patients with known Coronary Artery Disease (CAD), particularly following an acute event, boasts some of the best evidence for increased survival and decreased morbidity (Thompson, 2001). Over the last 20 years, a number of pharmacotherapies namely Antiplatelets, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and lipid-lowering therapy – have been identified to reduce the risk of future cardiac events in patients with acute coronary syndromes (ACS) (Kernis *et al*., 2004; Fox *et al*., 2004; Serruys *et al*., 2002). However, medication usage (and its success) requires the coordination of the behaviors of both the treating physician and the patient, particularly with regards to adherence.

Adherence to recommended medications for the secondary prevention of ACS is a crucial element in the path to the reduction of subsequent disease-related events. Lack of adherence to therapeutic regimens has been recognized as a problem for many years (Jackevicius *et al*., 2002; Cline *et al*., 1999). Studies have shown that adherence among patients with chronic conditions is disappointingly low, dropping most dramatically after the six months of therapy (Osterberg and Blaschke, 2005). Furthermore, numerous reports in the literature had estimated that by 12 months, adherence to cardio protective therapy had dropped to less than 50% across several classes of drugs including statins and ACE-Inhibitors (Ockene *et al*., 2002).

Various kinds of tools have been used to assess patients' adherence to medication, of these, the most convenient, least expensive, and easiest way is self-reporting (Osterberg and Blaschke, 2005; Donnan *et al*., 2002). Morisky scale, also known as Morisky Medication Adherence Scale (MMAS) is one of the most widely used, validated adherence screening tools (Al-Qazaz *et al*., 2010; Shalansky *et al*., 2004). MMAS is composed of 8 questions about past medication use patterns and is thus quick and simple to use during drug history interviews. The Morisky scale would be convenient to use in a busy clinic in an effort to identify patients who are most in need for interventions to improve adherence (Shalansky *et al*., 2004).

The main objectives of the current study were to: (1) evaluate patients' level of adherence to evidence-based therapies at an average of two years after discharge for

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ACS, (2) to document any changes in adherence levels over the study period and (3) to investigate the relationship between patients' non-adherence and various demographic, social, and medical variables.

Subjects and Methods

This cross-sectional study was carried out in the cardiac clinics at Hospital Pulau Pinang (HPP), in Penang, a northern state of Malaysia. HPP is the largest public and tertiary hospital in Penang state. It provides primary and advanced medical health care for all illnesses and accidents, primary and advanced medical healthcare. A random sample of ACS patients (n=190) who had discharged on a regimen of secondary preventive medications were included in this study and followed up over a two-year period (three scheduled follow-up appointments at 8, 16, and 23 months post discharge). The demographic, clinical and drug data were collected at the day of discharge and patients were classified into three groups; those with Unstable Angina (UA), Non-ST-Elevation Myocardial Infarction (NSTEMI) and those with ST-Elevation Myocardial Infarction (STEMI). At each scheduled follow-up appointment, patients were interviewed and given the translated eight-item Morisky Medication Adherence Scale (MMAS) to complete while waiting the medical consultation in the physician's waiting room in order to compare their level of adherence to the prescribed regimens across the three consecutive time periods.

Eligibility criteria included ability to understand and communicate in Malay language. All aspects of the study protocol were approved by the Medical Research and Ethics Committee (MREC) of the ministry of health, Malaysia (Ref: KKM/NIHSEC/08/0804/P-10-174) and from Clinical Research Center (CRC) at HPP. All subjects were fully informed and gave their informed consent before participating in the study.

Instruments and tools

Morisky scale, also known as Morisky Medication Adherence Scale (MMAS) (Morisky *et al*., 2008) was used for the assessment of ACS patients' adherence to the prescribed regimens after hospital discharge. The MMAS was translated into the Malay language and tested for validity and reliability (Cronbach's $\alpha = 0.675$) (Al-Qazaz *et al*., 2010). MMAS consists of 8 items with a dichotomous response (yes/no) for items 1-7 and a 5 point Likert response for the last item. The total score ranges from 0 to 8 with a higher total score indicating higher medication adherence. The total score for each patient is the summation of the scores in each item. The MMAS showed a good predictive power and was significantly associated with drug pharmacy refill as it showed a 75% concordance (Krousel-Wood *et al*., 2009). The validated Malaysian MMAS scale has an internal consistency of 0.675 (Cronbach's alpha value) with a significant test-retest reliability of 0.816. The MMAS sensitivity and specificity, with positive and negative predictive values were 77.61, 45.37, 46.84 and 76.56%, respectively.

In order to use Morisky Medication Adherence Scale Bahasa Melayu (MMAS-BM) version in this study, a prior written permission was obtained from the corresponding licensor.

STATISTICAL ANALYSIS

Descriptive statistics were used to describe demographic and clinical characteristics of the patients and their medication adherence scores. Percentages and frequencies were used for the categorical variables, while means and standard deviations were calculated for the continuous variables. The characteristics of the whole sample and of the adherent groups were presented. The Chi square (χ^2) test was employed for categorical variables, while analysis of variance (ANOVA) was used to evaluate the differences between the adherent groups. A one-way between groups analysis of variance was conducted to explore the impact of age, gender, race, employment status, ACS subtypes, number of co morbidities and number of prescription medications per day on levels of adherence, as measured by Morisky scale. Bonferroni post hoc procedure (Hinton *et al*., 2004) was applied if differences were found by using the ANOVA test. A one-way repeated measures analysis of variance (ANOVA) was conducted to compare MMAS scores across the three consecutive time periods. All analyses were performed using SPSS statistical software version18 (SPSS Inc., Chicago, IL). The significance level was set at *p*-value less than 0.05.

RESULTS

Study population

A total number of 190 ACS patients were initially enrolled in this study upon discharge. All of those patients were able to attend the first follow-up appointment. At the second appointment, only 4 patients failed to attend, while only 151 (79.5%) patients attended the third appointment. Among the 39 patients who did not complete the follow-up study, 2 had died, 18 were transferred to another center, 13 did not attend the clinics, and 6 patients were informed by their physician that they do not need any more follow-up at cardiac clinics. All patients who managed to attend the follow-up appointments were interviewed and successfully completed the adherence questionnaire (MMAS).

Patients' characteristics

The mean age of our study population was 59 years (range 32-84 years), with 27.9% of patients aged over 65 years. Majority of patients were males (69.5%) and most of them were Chinese (38.9%). Patients with unstable

angina (UA) accounted for 58.4 % of the admissions whereas 21.1 % and 20.5 % of the patients were admitted for NSTEMI and STEMI respectively.

Adherence levels at the three time periods

In general, the majority of patients reported either medium or low adherence across the three consecutive time periods with only small portion reported high adherence. Furthermore, there was a significant downward trend in the level of adherence to cardio protective medications during the study period (fig. 1).

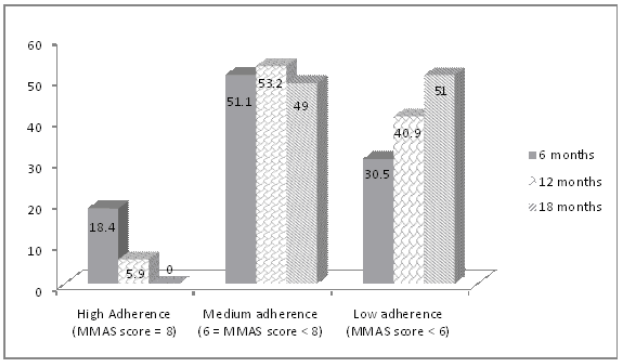

Fig. 1: Level of adherence to the prescribed regimens across the three consecutive time period

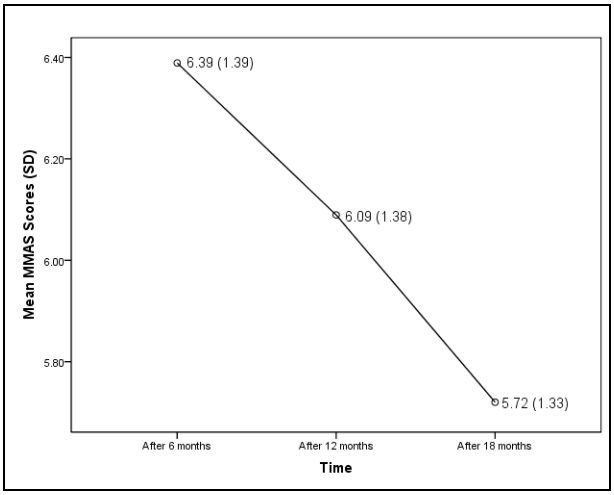

Fig. 2: Changes in MMAS scores over the study period

Repeated measures ANOVA analysis of Adherence

A one-way repeated measures analysis of variance (ANOVA) was conducted to compare MMAS scores across the three consecutive time periods. This analysis was restricted to the cohort who completed the follow-up study (n=151). The means and standard deviations are presented in fig. 2.

There was a significant decrease in MMAS score across the three different time periods, F (2,149)=111.152, $p<$ 0.001; Wilks' Lambda=0.401. The value obtained for multivariate eta squared, which is used to assess the effect size, was 0.599. Using the commonly applied guidelines proposed by (Cohen, 1988) (0.01=small, 0.06=moderate, 0.14=large effect) (Cohen, 1988), this result suggests very large effect size of time on levels of adherence, as measured by MMAS.

Long term adherence to treatment regimens

At the end of the follow-up period, long-term adherence was evaluated by calculating the average of three sets of scores at the three consecutive time periods. This analysis was restricted to the cohort who completed the follow-up study (n=151).

The majority (60.3%) of patients were categorized as medium adherents (i.e., 6≤ average MMAS score <8), while the remaining 39.7% were categorized as low adherents (i.e., average MMAS score <6). None of the patients were categorized as high adherents.

Between adherent groups, significant differences were found in age, employment status, number of co-morbidities and number of prescription medications per day (p<0.05). No significant differences (p>0.05) were found among the groups in terms of gender, race or ACS subtype. The characteristics of the total and adherent groups are shown in table 1.

Factors predicting medication adherence

A one-way between groups analysis of variance was conducted to explore the impact of age, gender, race, employment status, ACS subtype, number of comorbidities, and number of prescription medications per day on levels of adherence, as measured by MMAS.

There was a statistically significant difference in the mean MMAS scores across age groups. Male patients reported higher adherence than females. Employed patients reported higher adherence than unemployed. STEMI patients reported the highest adherent behavior, followed by NSTEMI and UA patients respectively. Patients with multiple co-morbidities (≥3) or those who were prescribed multiple medications (≥5) reported significantly poorer adherence (table 2).

DISCUSSION

Results from this study highlight the difficulty of maintaining consistent long-term adherence to evidence-based secondary prevention therapies after ACS, even when these therapies are initiated upon hospital discharge. Among patients prescribed aspirin, a statin, a beta-blocker, and an ACEI/ARB, as currently recommended by Malaysian guidelines for the care of post-ACS patients (NHAM, 2008, 2011, Kassab *et al.,* 2013), 39.7% of patients reported low adherence and none of them reported high adherence with these medications 2 year after their hospital discharge. This result demonstrates that there is a problem of non-adherence to secondary

Table 2: Characteristic of patients according to the level of adherence

Characteristics	Total N= 151	Adherence level		*p-value*
		Low N = 60	Medium N = 91	
Age, mean (SD)	58.3 (10.7)	62.6 (10.34)	55.5 (10.0)	<0.001[a]
Gender, Male *n* (%)	106 (70.2)	37 (61.7)	69 (75.8)	0.063[b]
Race *n* (%)				0.244[b]
Malay	55 (36.4)	17 (32.8)	38 (41.8)	
Chinese	63 (41.7)	28 (46.7)	35 (38.5)	
Indian	33 (21.9)	15 (25.0)	18 (19.8)	
Employed *n* (%)	81 (53.6)	23 (38.3)	58 (63.7)	0.002[b]
ACS subtype *n* (%)				0.090[b]
UA	88 (58.3)	39 (65.0)	49 (53.8)	
NSTEMI	29 (19.2)	13 (21.7)	16 (17.6)	
STEMI	34 (22.5)	8 (13.3)	26 (28.6)	
Comorbidities, mean (SD)	3.0 (1.5)	3.7 (1.3)	2.6 (1.4)	<0.001[a]
Medications, mean (SD)	6.3 (1.8)	7.1 (1.9)	5.8 (1.5)	<0.001[a]

[a]One-Way ANOVA test, [b] Chi-square test

Table 2: Factors predicting medication adherence

Characteristics	*n* (%)	Mean score (SD)	F-statistic [a] (df)	*P-value*
Age groups			3.489 (4; 150)	0.009 [b]
≤ 44 years	16	6.9 (0.6)		
45 – 54 years	42	6.4 (1.3)		
55 – 64 years	55	5.9 (1.3)		
65 – 74 years	23	5.8 (1.6)		
75 – 84 years	15	5.4 (1.1)		
Gender			4.348 (1; 150)	0.039
Males	106	6.2 (1.2)		
Females	45	5.7 (1.5)		
Race			0.879 (2; 150)	0.417
Malay	55	6.24 (1.5)		
Chinese	63	6.00 (1.3)		
Indian	33	5.88 (1.2)		
Employment status			6.539 (1; 150)	0.012
Employed	81	6.3 (1.2)		
Unemployed	70	5.8 (1.4)		
ACS subtypes			5.440 (2; 150)	0.005 [b]
UA	88	5.95 (1.1)		
NSTEMI	29	5.68 (1.6)		
STEMI	34	6.68 (1.4)		
Co morbid conditions			13.51 (1; 150)	< 0.001
<3comorbidities	48	6.63 (1.5)		
≥3comorbidities	103	5.80 (1.2)		
Concomitant drugs used			5.115 (1; 150)	0.025
<5 medications	32	6.53 (1.4)		
≥5 medications	119	5.94 (1.3)		

[a]One-Way ANOVA test.
[b]Only mean MMAS score between "patients ≤44 years and patients aged 75-84 years" was significantly different by post-hoc test Bonferroni's procedures.
[c]Mean MMAS scores between "STEMI patients and NSTEMI patients" and also "STEMI and UA patients" pairs were significantly different by post-hoc test Bonferroni's procedures.

prevention medications among patients with ACS in Malaysia. However, caution must be taken before drawing a conclusion about the rate of non-adherence since this study used a relatively small, homogenous sample of patients who received their treatment at a single institution and may not be generalizable to all Malaysian patients.

High rates of medication non-adherence have been demonstrated by previous investigators and the rates of adherence we observed in our study mirror these (Jackevicius *et al*., 2002; Benner *et al*., 2002; Kassab *et al*., 2013). For example, results from the GRACE (Global Registry of Acute Coronary Events) project revealed that 8-20% of patients prescribed medications at discharge were no longer taking them after 6 month (Eagle *et al*., 2002). Newby et al. assessed medication adherence among patients who had undergone cardiac procedures and discharged on a combination of lipid-lowering agents, beta-blockers, and aspirin. They found that only 35% of patients prescribed these drugs were classified as 'consistent' users (Newby *et al*., 2006). Choudhry et al. found that among post-MI patients who were prescribed a statin, a beta-blocker, and an ACEI/ARB, 50% of those patients were adherent with these medications 1 year after their hospital discharge (Choudhry *et al*., 2008). Others have reported that persistence among patients with chronic conditions is dropping most dramatically after the first 6 months of therapy (Osterberg and Blaschke, 2005).

The present study also identified 6 factors-namely age, gender, employment status, ACS subtype, number of comorbidities and number of prescription medications per day-that may influence patients' level of adherence to the prescribed regimens. Non-adherence was found to be higher in older patients. Literature reports regarding the relationship between age and medication adherence are contradictory. For example, Roe et al found reduced compliance with medication use among older patients following an admission for heart failure (Roe *et al*., 2000), whereas Jackavicius *et al* and Benner *et al* identified older age as a predicator of noncompliance with statin treatment. However, Sud et al found no association between age and medication adherence (Sud *et al*., 2005). Another important factor identified was the prevalence of multiple co-morbidities. Poor adherence was higher among patients with three or more co-morbid conditions. This result was expected since patients having multiple co-morbidities may require the use of multiple medications which may lead to treatment regimens that are particularly complex and therefore make patients feel hassled about sticking to their treatment plan and finally lees adherent to their therapy. Similar results were found in previous studies (McLane *et al*., 1995; Wang *et al*., 2002).

CONCLUSION

The present study provides an insight into adherence to key medications following hospitalization for acute coronary syndromes. Results from this study suggest that there is difficulty of maintaining consistent long-term adherence to evidence-based secondary prevention therapies among patients with ACS in Malaysia. Furthermore, this study demonstrates that older patients, female patients, unemployed patients, patients with more comorbid conditions, and those receiving multiple medications are less likely to adhere to their prescribed medications 2 years after hospital discharge.

ACKNOWLEDGMENTS

This work was supported by Research Acculturation Grant Scheme (RAGS), Malaysia (RAGS/2013/UITM/SKK02/2). The authors would like to express their gratitude to Ministry of Higher Education, Malaysia and Universiti Teknologi MARA, Malaysia for financial support for this research.

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