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Factors Associated with Re-hospitalization and Status of Risk Factors among Patients with Stable Coronary Artery Disease Referring for Medical Therapy: An Unmatched Cohort Study

Majid Davari[1], Mende Mensa Sorato[2], Behzad Fatemi[1,*], Soheila Rezaei[2], Parham Sadeghipour[3], Abbas Kebriaeezadeh[1] and Fatemeh Soleymani[1]

[1] Department of Pharmacoeconomics and Pharmaceutical Administration, Tehran University of Medical Sciences, Tehran, Iran
[2] Department of Pharmacoeconomics and Pharmaceutical Administration, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Cardiovascular Intervention Research Center, Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, Iran

*** *Corresponding author:*** Behzad Fatemi, Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. Tel: +989127124359; Email: behzad.fatemi63@gmail.com

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Abstract

Background: All patients with stable coronary artery diseases (CADs) require medical therapy (MT) to prevent disease progression and recurrent cardiovascular events, alleviate symptoms, and reduce mortality. Nonetheless, little is known about the clinical outcomes of unrevascularized patients taking MT for stable CAD and the status of CAD risk factor control in Iran.

Objectives: This study aimed to evaluate the impact of MT in unrevascularized CAD patients on risk factor modification and re-hospitalization among patients referring to the Rajaie Cardiovascular Medical and Research Center, Tehran, Iran.

Methods: This unmatched cohort study was conducted to collect demographic, risk factors, comorbidity, and re-hospitalization data about stable CAD patients in 2014 and followed until 2021. A multivariate regression analysis was applied to explore the relationship between re-hospitalization as the dependent variable and independent variables.

Results: A total of 290 stable CAD patients were included in our cohort. More than 60% of the subjects were male. The mean age of the participants was obtained at 55.9±5.4 years. It was revealed that being male (adjusted odds ratio [AOR]=0.513, 95% confidence interval [CI], 0.24-0.85, P=0.048), having hypercholesterolemia (AOR=4.10, 95% CI, 1.07-15.62, P=0.040), having an ejection fraction of below 40% (AOR=4.05, 95% CI, 1.50-10.97, P=0.006), being a current smoker (AOR=2.18, 95% CI, 1.03-4.62, P=0.042), and involving three vessels (AOR=10.39, 95% CI, 2.37-45.77, P=0.002) were independently associated with re-hospitalization.

Conclusion: Gaps were identified concerning CAD risk factor control. Higher re-hospitalization was associated with female gender, smoking, hypercholesterolemia, and reduced ejection fraction. Therefore, it is essential to improve healthy lifestyle modification interventions tailored to individual patients with a particular focus on females.

Keywords: Beta-blockers, Calcium channel blockers, Heart disease risk factors, Odds ratio, Real-world evidence, Statin therapy

1. Background

Stable coronary artery disease (CAD) is defined as a reversible supply/demand disparity related to ischemia, the presence of atherosclerotic plaque-causing, or a history of myocardial infarction (MI) (1). Patients with suspected or established stable CAD include those with suspected CAD and 'stable' anginal symptoms and/or dyspnoea, patients with new-onset of heart failure (HF) or left ventricular (LV) dysfunction and suspected CAD, asymptomatic and symptomatic patients with stabilized symptoms for less than a year after an acute coronary syndrome (ACS), patients with recent revascularization, asymptomatic and symptomatic patients with more than a year after initial diagnosis or revascularization, patients with angina and suspected vasospastic or microvascular disease, and asymptomatic patients in whom CAD is detected at screening (2).

All patients with stable CAD require medical therapy (MT) to prevent disease progression, hinder recurrent cardiovascular events, alleviate symptoms, and reduce mortality (3). The three recommended medical therapies are lipid-lowering agents, antihypertensive medications, and antiplatelet agents (aspirin or clopidogrel). Angina symptom control can be achieved by beta-blockers, nitrates, calcium channel blockers, or any combination of these medications (4, 5). The results of different studies have shown no significant difference between clinical and patient outcomes with optimal medical therapy (OMT) versus revascularization approaches (e.g., percutaneous coronary interventions) (6-11).

The goal of OMT in patients with stable CAD is to decrease premature cardiovascular (CV) death, prevent nonfatal acute MI and congestive heart failure complications, improve functional capacity and quality of life, eliminate ischemic symptoms, and minimize the costs of healthcare by eliminating avoidable adverse effects (12). In addition, controlling CAD risk factors is essential to reduce morbidity and mortality associated with stable CAD (2, 13). Nonetheless, little is known about the patient's clinical outcomes taking MT for stable CAD and the level of CAD risk factor control in the Rajaie Cardiovascular Medical and Research Center (RCMRC), Tehran, Iran.

2. Objectives

This unmatched retrospective cohort study was conducted to evaluate the impact of medical therapy in unrevascularized CAD patients on risk factor modification and re-hospitalization among patients referring to the RCMRC.

3. Methods

3.1. Study area, design, and period

This facility-based unmatched retrospective cohort study was conducted within January 2014-March 2021 at RCMRC. The study was performed after getting ethical approval (REC.1398.031) from the Tehran University of Medical Sciences, Tehran, Iran, and an official letter from the RCMRC.

3.2. Population

The study population consisted of adult patients being in the age range of 45-65 years old, having stable CAD, referring for MT, and lacking a history of ACS, percutaneous coronary intervention, and coronary artery bypass grafting at RCMRC in 2014.

3.3. Eligibility Criteria

Patients with stable CAD who were not a candidate for revascularization were included in the present study.

3.4. Study Variables

The dependent variable was the incidence of re-hospitalization related to CV disease (CVD). Moreover, the status of CAD risk factors was assessed.

Our Independent variables were demographic characteristics (gender, age, height, weight, body mass index, smoking status, a family history of CVD), comorbidities and risk factors (hypertension, diabetes, chronic kidney disease, HF, chronic obstructive pulmonary disease, hyperthyroidism, hypothyroidism, ischemic stroke, hemorrhagic stroke, dyslipidemia, low-density lipoproteins (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, total cholesterol, triglyceride, and serum creatinine), medications (angiotensin-converting-enzyme inhibitors [ACEIs], angiotensin-receptor blockers [ARBs], beta-blockers, calcium channel blockers, vasodilators, diuretics, lipid-lowering agents, antidiabetics, antiplatelets, levothyroxine, allopurinol, amiodarone, and digoxin), and disease-related factors (diagnosis [the number of vessels that have narrowing/stenosis], ejection fraction, and the presence of a lesion in the vessel).

3.5. Data processing and analysis

The abstracted data were daily checked for completeness and consistency by the principal investigator. Afterward, data entry, processing, and analysis were accomplished using SPSS (version 20.0). A descriptive statistic was computed for demographic factors, CV risk factors, comorbidities, medication-related factors, and disease-related factors. A bivariate analysis was performed to determine the presence of an association between independent variables and re-hospitalization. To avoid numerous variables and unstable estimates in the subsequent model, only the variables that reached a p-value of less than 0.05 at bivariate analysis were kept in the subsequent model analysis. Multivariate logistic regression analysis was employed to identify the functional independent predictors of re-hospitalization of patients with stable CAD referring for MT at RCMRC. Point estimates of the crude odds ratios (COR) and adjusted odds ratio (AOR) with 95% confidence interval (CI) were determined to assess the strength of association between independent and dependent variables. For all statistically significant tests, a p-value of < 0.05 was used as a cut-off point.

4. Results

4.1. Baseline characteristics of included patients

Among 5,749 patients' electronic angiography records in 2014, a total of 290 patients were included in our study based on defined eligibility criteria and followed until March 2021 (Figure 1).

More than half of the patients, 179 (61.7%), were males, and the mean age of the participants was obtained at 55.9±5.4 years, based on our study design ranging from 45 to 65 years. The most common comorbidities were hypertension, diabetes, and dyslipidaemia, respectively. Table 1 summarizes the baseline characteristics of included stable CAD patients.

Based on the grading scale provided by the Society of Cardiovascular Computed Tomography (SCCT) for stenosis severity, patients are divided into five classes, including no visible stenosis, minimal stenosis (1-24%), mild stenosis (24-49%), moderate stenosis (50-69%), severe stenosis (70-99%), and occluded (100%) (14).

Concerning the type of diagnosis based on the level of coronary artery obstruction, most patients had minimal CAD (Figure 2). Regarding the number of vessels involved, in the majority of patients, 247 (85.2%), one vessel was involved, followed by two- and three-vessel involvement with 33 (11.4%) and 10 (3.4%) subjects, respectively. It was found that 22 (7.6%) patients had a history of re-hospitalization with frequencies of 13 (59.1%), 4 (18.2%), 4 (18.2%), and 1 (4.5%) for once, twice, three times, and four times hospitalization, respectively. Concerning the number of hospital deaths, 3 (1.67%) male patients passed away in the hospital during the follow-up period. The mean duration of follow-up was calculated at 6.2±0.4 years.

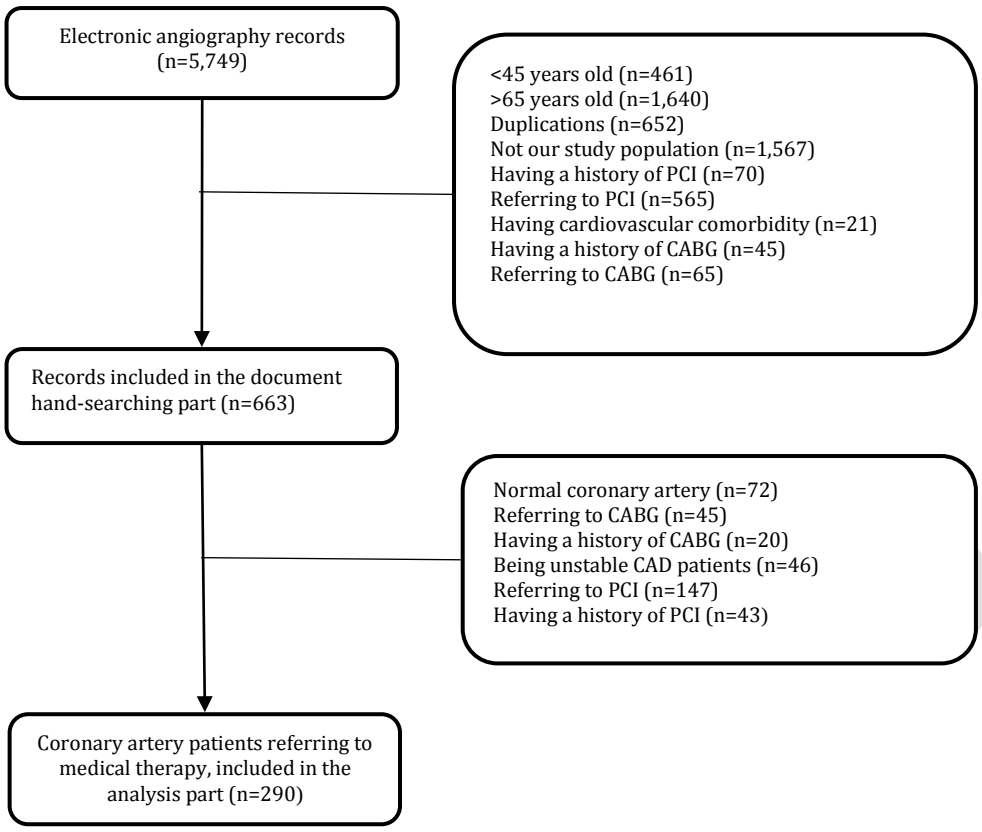

Figure 1. Patient recruitment follow-diagram

Table 1. Demographic and baseline characteristics of included patients

		Gender	
		Male (n=179)	**Female (n=111)**
Age	45-50 years	34 (19.0%)	16 (14.4%)
	51-55 years	62 (34.6%)	31 (27.9%)
	56-60 years	39 (21.8%)	30 (27.0%)
	> 61-65 years	44 (24.6%)	34 (30.6%)
BMI	Less than or equal to 18 kg/m^2	1 (0.5%)	1 (0.9%)
	18.1-24.9 kg/m^2	53 (29.6%)	12 (10.8%)
	25-29.9 kg/m^2	82 (45.8%)	42 (37.8%)
	30-39.9 kg/m^2	42 (23.5%)	50 (45.1%)
	Greater than or equal to 40 kg/m^2	1 (0.5%)	6 (5.4%)
Hypertension	No	104 (58.1%)	35 (31.5%)
	Yes	75 (43.5%)	76 (68.5)
Chronic kidney disease	No	176 (98.3%)	109 (98.2%)
	Yes	3 (1.7%)	2 (1.8%)
Hemorrhagic stroke	No	178 (99.4%)	110 (99.1%)
	Yes	1 (0.6%)	1 (0.9%)
Diabetes	No	135 (75.4%)	71 (64%)
	Yes	44 (24.6%)	40 (36%)
Hyperthyroidism	No	178 (99.4%)	109 (98.2%)
	Yes	1 (0.6%)	2 (0.8%)
Hypothyroidism	No	174 (97.2%)	103 (92.7%)
	Yes	5 (2.8%)	8 (7.3%)
COPD	No	177 (98.8%)	109 (98.2%)
	Yes	2 (1.2%)	2 (0.8%)
Dyslipidemia	No	126 (70.4%)	50 (45.1%)
	Yes	53 (29.6%)	61 (54.9%)
Current smoker	No	96 (53.6%)	103 (97.7%)
	Yes	83 (46.4%)	8 (7.3%)

Table 1. Continued			
Family history of CAD	No	144 (80.4%)	82 (73.9%)
	Yes	35 (19.6%)	29 (26.1%)
Hypercholesterolemia	No	166 (92.7%)	106 (95.5%)
	Yes	13 (7.3%)	5 (4.5%)
Heart failure	No	179 (100%)	110 (99.1%)
	Yes	0	1 (0.9%)
History of MI	Yes	8 (4.46%)	3 (2.7%)
	No	171 (95.54%)	108 (97.3%)

BMI: Body mass index; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; MI: Myocardial infarction

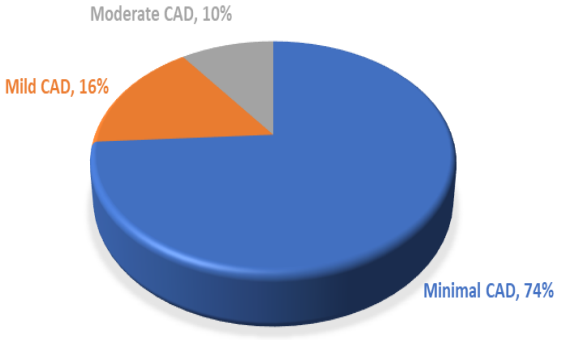

Figure 2. Classification of patients based on the type of coronary artery disease

The mean ejection fraction was 49.05%±8.22, ranging from 15% to 60%. In addition, 69 (24.7%) patients had ejection fractions below 50%.

4.2. Medication therapy

The more commonly prescribed classes of medications were beta-blockers, ACEIs, long-acting nitrates, and antiplatelet in descending order. Table 2 presents the prescription status of each medicine in the study population.

4.3. Status of coronary artery disease risk factors

4.3.1. Hypertension

When the systolic blood pressure of 14 was considered a threshold, about one-fourth of the included patients (22.4%) had uncontrolled hypertension. Considering stringent blood pressure control based on the Systolic Blood Pressure Intervention Trial criteria (i.e., <130/80 mmHg), which is also the goal of CAD risk factor, 127 (43.7%) patients had uncontrolled hypertension (Supplemental Data File 1).

4.3.2. Hypercholesterolemia

Out of 163 documented blood LDL-cholesterol results, only 43 (26.4%) cases had the LDL target value of < 70 mg/dL. Similarly, 97 (59.5%) patients had HDL-cholesterol level of < 40 mg/dL (a very high risk for atherosclerotic CVD). The total cholesterol was measured and documented for 129 patients; accordingly, 18 (9.3%) patients had a total cholesterol value of > 200 mg/dL. Out of 165 documented blood triglycerides, 67 (40.6%) cases were above 150 mg/dL (Supplemental Data File 2).

4.3.3. Chronic kidney disease

The presence of chronic kidney disease (CKD) was documented in 5 (1.7%) of total cases during the initial diagnosis. Throughout the therapy, serum creatinine was registered for 265 (91.4%) patients. The overall mean serum creatinine level was 0.833±0.22 mg/dL ranging at 0.3-1.6 and 0.5-2.2mg/dL for females and males, respectively.

The prevalence of chronic kidney disease varied by gender; in this regard, 18.3% and 64.4% of males and females developed CKD, respectively, and 3 (3%) females and none of the males developed kidney failure (Supplemental Data File 3).

Table 2. Baseline characteristics of prescribed medicines for included patients

Class of medication	Medication	Frequency (n)	Percent (%)
Beta-blockers (n=200)	Metoprolol	169	84.50
	Atenolol	4	2
	Propranolol	3	1.50
	Carvedilol	24	12
ACEIs (n=126)	Captopril	107	84.90
	Enalapril	7	5.60
	Lisinopril	12	9.50
ARBs (n=73)	Losartan	60	82.20
	Valsartan	13	17.80
Diuretics (n=47)	Hydrochlorothiazide	18	38.30
	Spironolactone	9	19.10
	Furosemide	2	4.30
	Triamterene	8	17.00
	Spironolactone + Furosemide	10	21.30

Table 2. Continued

Oral nitrates (n=128)	Nitroglycerin SR 2.6	97	75.80
	Nitroglycerin SR 6.4	18	14.10
	Nitroglycerin SR 0.4 SL pearl	3	2.30
	Isosorbide dinitrate	5	3.90
	Isosorbide dinitrate + Nicorandil	1	0.80
	Nitroglycerin SR 2.6 + Nitroglycerin SR 0.4 SL pearl	1	0.80
	Nitroglycerin SR 6.4 + Nitroglycerin SR 0.4 SL pearl	3	75.80
Calcium channel blockers (n=47)	Diltiazem hydrochloride	18	38.30
	Amlodipine	28	59.60
	Verapamil hydrochloride	1	2.10
Dyslipidemia management (n=271)	Atorvastatin 10 mg	20	7.40
	Atorvastatin 20 mg	110	40.60
	Atorvastatin 40 mg	135	49.80
	Atorvastatin 20 mg + Fenofibrate	2	0.70
	Atorvastatin 10 mg + Gemfibrozil	1	0.40
	Atorvastatin 20 mg + Gemfibrozil	2	0.70
	Atorvastatin 20 mg + Ezetimibe	1	0.40
Anti-platelets (n=284)	ASA 80 mg tab	228	80.30
	Clopidogrel 75 mg	3	1.10
	ASA 80 mg + Clopidogrel 75 mg	48	16.90
	ASA + Warfarin sodium	3	1.10
	ASA + Clopidogrel + Warfarin sodium	2	0.70
Antidiabetic medication (n=84)	Glibenclamide 5 mg	10	11.90
	Insulin isophane human + Insulin regular human	4	4.80
	Metformin	34	40.50
	Insulin glargine pre-filled pen	1	1.20
	Glibenclamide + Metformin	25	29.80
	Glibenclamide + Metformin + Pioglitazone	3	3.60
	Metformin + Repaglinide	1	1.20
	Insulin Aspart	1	1.20
	Metformin + Insulin isophane human + Insulin regular insulin	5	6.00
Levothyroxine (n=290)	No	277	95.50
	Yes	13	4.50
Digoxin (n=290)	Yes	1	0.30
	No	289	99.70
Allopurinol (n=290)	No	288	99.30
	Yes	2	0.70
Amiodarone (n=290)	No	289	99.70
	Yes	1	0.30

ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; ASA: Acetylsalicylic Acid; SL: Sublingual; SR: Sustained-release

Table 3. Cross-tabulation ejection fraction and drug therapy for included stable coronary artery disease patients

		Ejection fraction		
		< 40% (n=27)	**41-49% (n=42)**	**50-70% (n=210)**
Taking BBs	Yes	23 (85.2%)	30 (71.4%)	140 (66.7%)
	No	4 (14.8%)	12 (26.8%)	70 (33.3%)
Taking vasodilators	Yes	17 (62.9%)	20 (47.6%)	88 (41.9%)
	No	10 (37.1%)	22 (52.3%)	122 (58.1%)
Taking ACEIs	Yes	18 (66.7%)	18 (42.8%)	86 (40.9%)
	No	9 (33.3%)	24 (57.2%)	124 (59.1%)
Taking diuretics	Yes	17 (62.9%)	7 (16.7%)	21 (10%)
	No	10 (37.1%)	35 (83.3%)	189 (90%)
Taking CCBs	Yes	1 (3.7%)	8 (19.1%)	35 (16.7%)
	No	26 (96.3%)	34 (80.9%)	175 (83.3%)

ACEIs: Angiotensin-converting enzyme inhibitors; BBs: Beta-blockers, CCBs: Calcium channel blockers

4.3.4. Management of left ventricular dysfunction (reduced ejection fraction)

In our study, 279 (96.2%) patients were recorded for ejection fraction. Among these subjects, 62 (22.2%) and 42 (15.1%) individuals had LV dysfunction (below 50%) and ejection fraction (below 40%), respectively. It was also reported that 193 (69.2%) patients were taking beta-blockers, and of patients with LV dysfunction, 53 (76.8%) cases were taking beta-blockers (Table 3).

4.3.5. Diabetes and hypertension comorbidity and stable CAD medication therapy

Hypertension was the most common comorbidity in patients with stable coronary heart disease affecting 151 (52.1%) subjects, followed by diabetes in 84 (29%) cases. The majority of patients with diabetes, 69 (82.1%), were taking metformin alone or combined with other antidiabetic medications (Supplemental Data File 4). Hypertension co-existed with diabetes in 61 (72.6%) stable CAD patients, and

Table 4. Factors associated with re-hospitalization

Factors associated with re-hospitalization			COR	95% CI for COR	P-value	AOR	95% CI for AOR
Gender	Female (ref)		1			1	
	Male	0.023	0.86	0.35-0.96	0.048*	0.513	0.24-0.85
Hypercholesterolemia	No (ref)		1			1	
	Yes	0.028	3.89	1.16-13.04	0.040*	4.10	1.07-15.62
Ejection fraction	50-70% (ref)		1			1	
	41-49%	0.52	1.34	0.56-3.27	0.513	1.54	0.42-5.61
	< 40%	0.012	3.26	1.29-8.23	0.006**	4.05	1.50-10.97
Involvement of vessels	Single vessel (ref)		1				
	Two vessels	0.008	4.19	1.45-12.06	0.297	1.90	0.57-6.39
	Three vessels	0.000	12.56	3.12-50.51	0.002**	10.39	2.37-45.77
Current smoker	No (ref)		1				
	Yes	0.024	1.86	1.09-3.19	0.042*	2.18	1.03-4.62

AOR: Adjusted odds ratio; COR: Crude odds ratio; CI: Confidence interval; Ref: Reference category, for which OR is 1.
*Significant at P < 0.05; **Significant at P < 0.01

62 (73.8%) stable CAD patients with diabetes took ACEIs/ARBs (Supplemental Data File 5).

4.4. Factors associated with re-hospitalization

The results of binary logistic regression analysis showed that re-hospitalization was associated with being male (COR=0.86, 95% CI, 0.35-0.96; P=0.023), having hypercholesterolemia (COR=3.89, 95% CI, 1.16-13.04; P=0.028), having an ejection fraction of < 40% (COR=3.26, 95% CI, 1.208-11.637; P=0.012), involving three vessels (COR=12.56, 95% CI, 13.12-50.51; P=0.000), being a current smoker (COR=1.86, 95% CI, 1.09-3.19; P=0.024), taking beta-blockers (COR=4.889, 95% CI, 1.118-21.385; P=0.035), and taking ACEIs (COR=3.031, 95% CI, 1.196-7.678; P=0.019). The mentioned variables were analyzed using multivariable logistic regression. After adjusting for confounding factors, only being male, being a current smoker, having hypercholesterolemia, having an ejection fraction of below 40%, and involving three vessels were independently associated with re-hospitalization (Table 4).

5. Discussion

This unmatched retrospective cohort study evaluated the impact of OMT on the level of re-hospitalization and the risk factor modification in the unrevascularized stable CAD patients. They were referred to a large tertiary cardiovascular center. The researchers of the current study identified gaps concerning the CAD risk factor control status of included patients. Based on the results, 42 (23.5%) and 50 (45.1%) males and females were obese, respectively, and 6 (5.4%) females were morbidly obese. Diabetes was the second comorbidity in both genders, affecting 44 (24.6%) and 40 (36%) males and females.

It was revealed that 83 (46.4%) males and 8 (7.3%) females were smokers. A total of 27 (9.6%) subjects had an ejection fraction of below 40%. More than one-third of patients, 127 (43.7%), had uncontrolled hypertension. Only 43 (26.4%) subjects achieved the LDL-cholesterol target value of < 70 mg/dL. Similarly, 97 (59.5%) patients had HDL-cholesterol level below 40 mg/dL. A total of 67 (40.6%) patients had a triglyceride level of above 150 mg/dL. More than one-third of patients, 95 (35.8%), had an estimated glomerular filtration rate (GFR) value of less than 60 mL/min/1.73 m2. Blood glucose level and physical activity status were not documented.

These findings are in line with those of a study conducted among CAD patients across 27 European countries to evaluate lifestyle and its impact on cardiovascular risk factor control. The results of the mentioned study showed that 19% of the subjects were cigarette smokers (of whom 55% cases were current smokers), 38% were obese (body mass index of ≥ 30 kg/m2), 42% had a blood pressure of ≥ 140/90 mmHg, 71% had LDL-cholesterol of ≥ 70 mg/dL, 29% reported having diabetes, 93% were taking antiplatelets, 81% were taking beta-blockers, 75% were taking ACEIs/ARBs, and 80% were taking statins (15).

The recommended CAD risk factor control goals include aspirin use, systolic blood pressure of < 130 mmHg, diastolic blood pressure of < 80 mmHg, LDL-cholesterol of < 70 mg/dL, HDL-cholesterol of > 40 mg/dL, triglycerides of < 150 mg/dL, fasting glucose of < 126 mg/dL, non-smoking status, body mass index of < 25 kg/m2, and exercise for ≥ 4 days per week (2, 13). The identified gaps in risk factor control need more efforts from health behavior intervention aspects, including dietary modification, physical activity, and stress reduction. Recommended lifestyle interventions include smoking cessation, healthy diet, physical activity, or weight reduction through controlling energy intake and increased physical activity (16-19).

Therefore, such interventions as supporting patients to set their treatment goals, self-monitor, plan how to implement behavioral change, and get engaged in social support effectively improve lifestyle modifications. Multidisciplinary teams consisting of cardiologists, nurses, pharmacists, community health workers, and caregivers can help patients make healthy lifestyle changes and improve their cardiovascular health status (2, 20). Patients

with good cardiovascular health status were 33%, 14%, and 25% less likely to develop hypertension, chronic kidney disease, or cardiovascular disease, respectively, than individuals with poor cardiovascular health (21). In addition, the adoption of preventive cardiology programs to individual patients and at the national level accessible by all patients and providers is critical for controlling CAD risk factors (15, 22).

More than two-thirds of patients (i.e., 69%) were taking beta-blockers. The most commonly prescribed beta-blockers were metoprolol and carvedilol, accounting for 169 (84.5%) and 24 (12%) cases, respectively. A total of 126 (43.4%) patients were taking ACEIs, and the most prescribed ACEIs were captopril and Lisinopril with 107 (84.9%) and 12 (9.5%) cases, respectively. The number of patients taking long-acting nitrates accounted for 128 (44.1%) cases. The most commonly prescribed long-acting nitrate was nitroglycerin sustained-release (SR 2.6), 97 (75.7%), followed by nitroglycerin sustained-release (SR 6.4), 18 (14.1%). The guideline recommends starting treatment with beta-blockers and calcium channel blockers in patients with stable CAD. Angiotensin-converting enzyme inhibitors/ARBS are the first-line medications in the presence of diabetes, HF, or hypertension (2).

It is suggested that patients with hypertension, diabetes, and other CVDs take ACEIs/ARBs due to their reno-protective effects unless contraindicated. It was reported that hypertension co-existed with diabetes in 61 (72.6%) stable CAD patients, and 62 (73.8%) stable CAD patients with diabetes were taking ACEIs/ARBs. The majority of patients with diabetes, 69 (82.1%), were taking metformin alone or combined with other antidiabetic medications, which is supported by evidence from other studies. Metformin is the mainstay of the treatment of type 2 diabetes in patients with CAD when glucose levels are not adequately controlled despite lifestyle modifications. If glucose levels remain uncontrolled while on metformin, it is recommended to add insulin, sulfonylureas, or second-line agents, such as sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 agonist, to prevent secondary CVD events (23, 24).

Based on the results, 95 (35.8%) patients had an estimated GFR value of less than 60 ml/min/1.73 m2. The prevalence of CKD varied with gender; accordingly, 18.3% and 64.4% of males and females developed CKD, respectively, and 3 (2.7%) females and none of the males developed kidney failure. Thiazide diuretics may not be effective for blood pressure control in stages 4 and 5 CKD. Although statins can reduce lipid levels in patients with stage 5 CKD, this may not be associated with tangible clinical benefits (24-28). Moreover, ACEIs are indicated for hypertension, diabetes mellitus, CKD, abnormal LV function, systolic heart failure, or recent MI (1).

In our study, 42 (15.1%) patients had an ejection fraction of below 40%. More than one-half of patients, 193 (69.2%), were taking beta-blockers. For patients with LV dysfunction, evidence also suggests starting treatment as follows. Beta-blockers are the first-line therapy in patients with MI history, acute coronary syndrome, systolic HF, angina pectoris, atrial fibrillation, and atrial flutter. Calcium channel blockers can be considered for patients whose symptoms are not controlled with beta-blockers or who cannot tolerate beta-blockers. Ranolazine should be prescribed for patients with recent MI or stable CAD as adjunctive therapy, especially in patients whose symptoms are not controlled with BBs or CCBs or who do not tolerate BBs (1, 2).

Out of 163 documented blood LDL-cholesterol results concerning dyslipidemia control status, only 43 (26.4%) cases were below the LDL target value of < 70 mg/dL. Similarly, 97 (59.5%) patients had HDL-cholesterol level below 40mg/dL. Total cholesterol was measured and documented for 129 patients, and 18 (9.3%) of patients had a total cholesterol value of above 200 mg/dL. More than one-third of patients, 67 (40.6%), had a triglyceride level of above 150 mg/dL. The results of studies have indicated that LDL-cholesterol levels of < 70 mg/dL and glycosylated hemoglobin A1c of < 7% are associated with lower major cardiovascular events in patients with stable coronary heart disease (30, 31). There is an unmet need for patients with stable CAD to take MT concerning dyslipidemia management. Therefore, it is imperative to consider comprehensive team-based approaches to address lifestyle and socioeconomic determinants of health.

Concerning statin therapy, the majority of patients, 135 (49.8%), were taking atorvastatin 40 mg, followed by atorvastatin 20 mg and Atorvastatin 10 mg in 110 (40.6%) and 20 (7.4%) subjects, respectively. Statins are recommended in all patients with stable CAD (2). According to the findings of studies, intense statin therapy was associated with lower cardiovascular risk than standard statin therapy. High-intensity atorvastatin (40 to 80 mg per day) or rosuvastatin (20 to 40 mg per day) is recommended for patients below 75 years of age (32). However, the proportion of patients taking a high-intensity statin was low. Based on the results of our study, patients in the age group of 45-65 were ideal candidates for high-intensity statins to achieve dyslipidemia control targets and reduce stable CAD-related morbidity and mortality.

Concerning re-hospitalization, 79 (41.36%) patients had a history of re-hospitalization during 7 years of follow-up, and only 18 (6.23%) deaths were reported. These results were higher than those reported in a study conducted in the Tabriz University Hospital, Tabriz, Iran, with the re-hospitalization and death rates of 21 (42%) and 11 (22%), respectively (33). This discrepancy could be explained by the type of patients

and the characteristics of the disease. The study performed in the Tabriz University Hospital only included patients of ≥ 80 years old having merely a three-vessel disease.

Regarding factors associated with re-hospitalization, being female increased the risk of re-hospitalization. This could be explained by the relatively higher level of risk factors, including obesity (50.5% vs. 24.0%), hypertension (68.5% vs. 43.5%), dyslipidemia (54.9% vs. 29.6%), presence of CKD (64.4% vs. 19.5%), in females than in males in our study. Evidence from a prospective multinational cohort study supported the increased risk of females for re-hospitalization, which showed that the prevalence of CAD risk factors was generally higher in women than in men. Women were more frequently diagnosed with diabetes (33% vs. 28%) and hypertension (79% vs. 69%), were less physically active, more likely to have angina (28% vs. 20%) (34), had worse health status at the time of angiography, and reported worse health-related quality of life 1 year after coronary angiography (35).

Hypercholesterolemia was found to be independently associated with re-hospitalization (AOR=4.10, 95% CI, 1.07-15.62, P=0.040); this is because atherosclerotic plaque rupture and erosion are the primary causes of cardiac ischemia and symptom development in patients with stable CAD. Moreover, an ejection fraction of below 40% (AOR=4.05, 95% CI, 1.50-10.97, P=0.006) was independently associated with re-hospitalization; t elaborate this, decreased left ventricular ejection fraction (LVEF) in patients with CCS may be associated with ischemic myocardial damage (2, 36, 37).

Finally, in the present study, care fragmentation was observed due to the separation of specializations. For example, blood glucose follow-up data were not recorded in patient charts because of the separation of the metabolic and endocrine research center from the heart center. Multimorbid illnesses, such as CAD and diabetes, need multidisciplinary and coordinated care because of shared risk factors (38-40).

Strengths and Limitations

The strength of this study was the inclusion of a large number of patients with a sufficient follow-up period. Because of being a retrospective single center-based unmatched cohort study and failure to include all possible determinants for re-hospitalization, such as adherence to medical therapy, extrapolating the findings beyond the study facility should be performed with caution. Furthermore, due to an insufficient number of events, it was impossible to determine factors associated with in-hospital mortality in the current study.

6. Conclusion

In conclusion, being female, having hyper-cholesterolemia, smoking, involving three vessels, and having an ejection fraction of below 40% were independent predictors of re-hospitalization. Therefore, designing and implementing strategies to address these CAD risk factors can reduce re-hospitalization. Moreover, increasing patients' awareness and reducing the current smoking level could reduce the mortality associated with stable CAD, especially in males.

Based on the findings of this study, it is essential to improve healthy lifestyle modification interventions tailored to individual patients with a particular focus on females. Secondly, strengthening the integration of the endocrine and metabolic disease research center with the heart center is critical to address shared risk factors, particularly diabetes and hypertension.

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Footnotes

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