Evaluation of Aspirin Use for Primary and Secondary Prevention of Cardiovascular Diseases among Lebanese Population

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Abstract: More than 80% of cardiovascular deaths are reported in low- and middle-income countries. Data on aspirin use for primary and secondary prevention of CVD (cardiovascular diseases) in Lebanon are unknown. This study was conducted to understand aspirin use for these indications among Lebanese population and subgroup of diabetic patients. This is a cross-sectional observational study conducted on a random sample of patients presenting to randomized community pharmacies in Beirut and Mount Lebanon. Results showed that, overall, 315 patients participated in the study. About 49% of total sample and 40% of diabetic subgroup were taking aspirin for primary compared to secondary prevention of CVD. More patients in the primary prevention group were young ($P < 0.001$), of female gender ($P < 0.001$), current active smokers ($P = 0.004$), and had shorter duration of diabetes ($P < 0.021$). About 24% of patients were taking non-physician prescribed aspirin. Diabetic patients had higher body mass index ($P < 0.001$) and longer duration of aspirin use ($P = 0.022$) compared to non-diabetics. Despite newer evidence showing lack of aspirin benefit in primary prevention of CVD, its use appears to be very common among Lebanese population. While awaiting more evidence, alternatives to aspirin use for primary prevention should be counseled to these patients.

Key words: Aspirin, cardiovascular disease, primary prevention, secondary prevention, diabetes mellitus, community pharmacy, Lebanon.

1. Introduction

CVD (cardiovascular diseases) are complex and interrelated group of diseases that include CAD (coronary artery diseases), cerebrovascular diseases, and PAD (peripheral artery diseases) [1, 2]. According to the WHO (World Health Organization), CVD is the leading cause of death worldwide, with more than 80% of CVD deaths reported in low- and middle-income countries [3, 4]. In 2010, Lebanon-upper-middle-income country as classified by the WHO showed 45% CVD mortality from total

reported deaths [5]. This could be attributed to higher exposure rate to CV (cardiovascular) risk factors, lack of preventive campaigns, and unequal accessibility to health care resources [3].

CVD imposes physical, psychological, as well as economical [6-8] consequences on patients and communities. In the Eastern Mediterranean region, CVD-related total cost was reported to be about 18 billion USD (United States dollars) in 2010 [7]. Several predisposing risk factors have been identified, including older age, family history of CVD and genetics, dyslipidemia, hypertension, DM (diabetes mellitus), tobacco smoking, and sedentary life style—physical inactivity, and overweight and obesity

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[1, 9-10]. When looking at DM, the ADA (American Diabetes Association) considers the disease as an independent risk factor for CVD [11]. Furthermore, ADA recommends a minimum of yearly screening and assessment of CV risk factors in diabetic patients [11].

Most forms of CVD are prevented by tight control of risk factors [3]. Based on the ACCP (American College of Chest Physicians), primary prevention of CVD is applicable to individuals with asymptomatic CVD, while secondary prevention is used for patients with established CAD—defined as post-ACS (acute coronary syndrome), with prior revascularization, coronary stenosis > 50%, and/or diagnostic testing showing evidence of heart ischemia [12]. According to the AHA/ACCF (American Heart Association/American College of Cardiology Foundation), primary prevention intends to prevent the first CVD event in patients with no clinical CVD (or asymptomatic)—including DM patients [13]. In Nonvalvular AF (atrial fibrillation), primary and secondary prevention describe mainly the first and subsequent occurrence of stroke, respectively, with an overall limited efficacy and role for aspirin in both settings [14].

Many trials investigated the use of aspirin for primary and secondary prevention of CV events resulting in different guidelines and recommendations, with the main objective of reducing vascular mortality, MI (myocardial infarction), and stroke [2, 15-16]. Data on the use of aspirin for secondary prevention of heart diseases and stroke seem to bring more solid evidence to recommend its use [13]; however, benefit of aspirin for primary prevention of CVD is still controversial as it was shown by several meta-analysis studies [2, 17-20]. Despite the uncertainty, many guidelines still recommend aspirin use for primary prevention of CVD [Appendix A] [9, 11-14, 21-26]. Currently, there are no unified recommendations from these guidelines for the exact aspirin dose for primary CVD prevention; it can range from 81 to 325 mg daily

depending on the guideline and type of CV disease [Appendix A] [9, 11-14, 21-26] knowing that 75 to 81 mg daily dose can fully inhibit platelets [13].

Based on the Institute of Medicine, insufficient knowledge on CVD epidemiology is a barrier to appropriate disease prevention and control. Thus, research, including surveillance studies that generate better population data, constitutes an essential component of CVD prevention and management plan [27]. Knowing the health, economical, and social burden of CVD and stroke on populations and individual patients, the lack of epidemiological studies among Lebanese population, and the need of such data for better control of cardiac and stroke events as well as death, this study was conducted to understand the use of aspirin for primary and secondary prevention of CVD among the Lebanese population. Being an independent risk factor of CVD, and with the presence of numerous international guidelines recommending the use of aspirin for diabetes, it was essential to assess its appropriate use among diabetic patients [3, 9, 11, 22, 25].

2. Methods

2.1 Study Design

This is a cross-sectional observational study conducted on a random sample of patients presenting to randomized community pharmacies in Beirut and Mount Lebanon. Stratified randomization was used to select the participating pharmacies.

2.1.1 Sample Size

The study was conducted in 2 Lebanese districts – Beirut and Mount Lebanon where about 50% of the Lebanese population is residing [30-35] and 53% of pharmacies are located [28]. Using a CI (confidence interval) of 95% and an alpha (α) of 5%, 384 patients were needed. From the OPL (order of pharmacists of Lebanon) [28], lists of all pharmacies in Beirut and Mount Lebanon were separately retrieved, transferred to excel sheets, and randomized using SPSS (statistical package for social science) version 18 for

Windows. Randomized pharmacists mobile numbers were provided afterward by the OPL and added to the randomized excel sheets for contact. To account for pharmacists and/or patients decline in study participation and for unfilled questionnaires, sample size was increased by about 2.7 times. The sample of patients needed from Mount Lebanon was about 4 times larger than that from Beirut to respect the percentage of population distribution between the 2 districts [29-34]. Consequently, it was set to aim for 105 randomized community pharmacies (20 in Beirut and 85 in Mount Lebanon) and 1050 patients (200 in Beirut and 850 in Mount Lebanon) in order to obtain the 384 patients needed for this study.

2.1.2 Data Collection and Eligibility Criteria

Patients were eligible to participate in this study if they met all the inclusion (Lebanese, age ≥ 18 years, buying aspirin for heart and stroke prevention for him or herself) and exclusion criteria (pregnant, taking aspirin for any other possible indication other than prevention of heart diseases and strokes, such as fever, pain or inflammation, etc.). Owners or chief pharmacists of each randomized pharmacy were responsible to fill 10 patient questionnaires for 10 consecutive and different eligible patients coming into their pharmacy and who accepted to participate in this study.

2.1.3 Ethics

Approval for this study was waived by the School of Pharmacy research committee at the Lebanese University since it is an observational study with no traceability of patients. The study was conducted following the Declaration of Helsinki. Patient informed consent was available on the front page of each patient questionnaire and pharmacists were asked to take oral approval from patients to participate in the study.

2.2 Patients Selection

2.2.1 Patient Questionnaire

The patient questionnaire included the following

major sections: patient's eligibility criteria and informed consent, patient demographic information, aspirin information, and patient risk factors information. It was constructed in English based on CVD guidelines and previous similar studies [9, 26, 36-39]. The Arabic translation of the text was included in the same English version to facilitate the pharmacists' communication with patients. A back translation was done to ensure comparability of questions in both languages.

2.2.2 Determination of Patients for Primary and Secondary Prevention

To determine whether a patient is taking aspirin for primary or secondary prevention of CVD, the following question was asked in the patient questionnaire: "Do you have any cardiovascular disease?" with a No/Yes answer corresponding to primary/secondary groups, respectively [12-13].

2.3 Calculation of Patients Parameters

2.3.1 Calculation of the Number of Risk Factors

It was not possible to calculate the 10-year CV risk of these patients, since exact laboratory parameters were not possible to obtain in this study. Instead, the number of common risk factors the study patients had was calculated from the following risk factors [9-10]: female ≥ 55 years or male ≥ 45 years, current active smoking (cigarettes and/or water pipe), passive smoking, diabetes, hypertension, hypercholesterolemia, low HDL, absence of diet, absence of exercise, overweight or obesity, presence of CVD, and family history of CVD. The number of risk factors was calculated only for patients who had data on all 12 risk factors and can range from 0 to 12 for each patient.

2.3.2 Calculation of BMI (Body Mass Index)

To assess obesity, the BMI of each patient was calculated using the following formula:

$BMI (Kg/m^2) = Weight (Kg)/Height^2 (m^2)$, and was classified into the following categories (BMI range $[Kg/m^2]$) following the NLBI (National Heart, Lung,

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and Blood Institute) scale: underweight (< 18.5), normal (18.5-24.9), overweight (25.0-29.9), obesity class I (30.0-34.9), obesity class II (35.0-39.9), and extremely obese (≥ 40) [35].

2.4 Study Endpoints

The primary endpoint of this study was the distribution of aspirin use between primary and secondary prevention of CVD. Main secondary endpoints evaluated and presented in this paper included: profile (including risk factors and source of aspirin prescription) of participating patients and aspirin data for total study population and for the

diabetic subgroup, comparison of patients profile and risk factors between primary and secondary prevention groups, and between diabetic and non-diabetic groups.

2.5 Statistical Analysis

Data analysis was performed using SPSS version 18 for Windows. All qualitative (n [%]) and quantitative (mean [standard deviation—SD] and range) variables were reported. Calculation of percentages was based on reported responses. Chi2 or Fisher's exact test were used to determine association between multinomial or dichotomous variables, respectively. Student (independent)

Fig. 1 Study flow chart and randomization procedure.

^aIncluded one maternity leave reason. ^bIncluded 2 pharmacists who passed away, 3 pharmacists whose mobile numbers were not provided by OPL, one pharmacy not found at listed address, one pharmacy moved to unknown location, and 2 non-operating pharmacies. ^cIncluded 6 pharmacists who refused to return study questionnaires to the pre-paid mailing service agency responsible for distribution and collection of study questionnaires.

T-test and Mann-Whitney test were used to determine association between qualitative and quantitative variables, when normal or abnormal distribution was assumed, respectively. A p -value < 0.05 was used to detect statistical significance. Valid percentages and 2-sided p -values were reported.

3. Results

3.1 Patients' Demographics

Data collection was conducted from June 20 to September 5, 2014. Overall, 50 randomized pharmacies participated in this study with a total of 315 patients, including 124 diabetic patients (Fig. 1). Overall, the majority of patients were males, married, received only school education, had an insurance, and did not drink alcohol (Table 1).

3.2 Aspirin Intake

About 49% of the total sample and 40% of the diabetic subgroup were taking aspirin for primary prevention of CVD compared to secondary prevention (Table 2). Most patients were taking aspirin 100 mg once per day. Even though majority of patients were prescribed aspirin by their physician—mostly cardiologists but also non-cardiologists, however, 23.8% of the total population patients still took it on their own or were advised by a pharmacist or a neighbor/friend/family relative. Furthermore, and although majority of patients in total population believed that benefits of aspirin outweighed its risks, about 23-24% were not sure of its benefit/risk ratio. About 22-24% of patients were taking other blood thinning medications, with clopidogrel being the most frequent.

3.3 Patients Risk Factors

As shown in Table 3, majority of patients were overweight or obese. More than 50% of the participating patients were either previous or current active smokers. The majority of diabetic patients had

type 2 diabetes for which about 78% were taking oral medications only. In addition, majority of the patients had hypertension, hypercholesterolemia, and family history of CVD. Of the surveyed patients, 76 (38.6%) and 38 (41.8%) patients in total sample and diabetic subgroup, respectively, did not know if they had a low or normal HDL. Noticeably, results showed that 21.3% and 22.5% of patients, respectively in total sample and diabetic subgroup, reported having RA (rheumatoid arthritis), and 24.7% and 22.1% were taking daily tablets of fish oil/omega 3 in in total sample and diabetic subgroup, respectively.

3.4 Comparison between Primary and Secondary Prevention Groups

3.4.1 Variables Showing Statistically Significant Difference between the Two Groups

When compared to the secondary prevention group, significantly more patients in the primary prevention group were young, of female gender, received university education, and had shorter duration of diabetes (Table 4). Moreover, results showed that significantly more patients who received a health care education were taking aspirin for primary prevention (61.5%) compared to secondary prevention (38.5%) ($P = 0.017$). This was not different for patients with non-health care education, with more patients in non-health care filed were taking aspirin for primary prevention (58.3%) compared to secondary prevention (41.7%) ($P = 0.017$). In addition, more patients in the primary prevention group were taking aspirin in frequencies other than one tablet every day, had a shorter duration of aspirin use, decided to take aspirin on their own or following the advice of a pharmacist or neighbor/friend/family relative, and were prescribed aspirin by a non-cardiologist. Furthermore, majority of physicians prescribing for primary prevention were family and internal medicine physicians, endocrinologists, or with other specialty; whereas only about 28% of primary prevention prescriptions originated from cardiologists.

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Table 1 Demographic information of both total sample and diabetic subgroup participating patients.

Patient characteristic	No (%) of patients or Mean $\pm$ SD when specified	
	Total (N = 315)	Diabetics (N = 124)
Age (years) Mean$\pm$SD [Min-Max]	63.5 $\pm$ 11.6 [36-89]	64.8 $\pm$ 11.2 [39-87]
Gender		
	Male 181 (58.6%)	76 (62.8%)
	Female 128 (41.4%)	45 (37.2%)
Married	233 (87.6%)	98 (90.7%)
Weight (Kg) (Mean$\pm$SD [Min-Max])	78.1 $\pm$ 15.6 [33-185]	82.4 $\pm$ 17.0 [54-185]
Height (cm) (Mean$\pm$SD [Min-Max])	167.9 $\pm$ 9.2 [145-195]	168 $\pm$ 8.4 [150-185]
Currently working		
	No 154 (52.9%)	61 (49.2%)
	Yes 135 (46.4%)	55 (44.4%)
	Disabled 2 (0.7%)	2 (1.6%)
Living district		
	Mount Lebanon 228 (72.8%)	94 (77.0%)
	Beirut 70 (22.4%)	20 (16.4%)
	Bekaa 7 (2.2%)	3 (2.5%)
	South Lebanon 4 (1.3%)	3 (2.5%)
	North Lebanon 4 (1.3%)	2 (1.6%)
Highest educational level		
	School 206 (66.8%)	95 (77.8%)
	Not specified 14 (4.5%)	6 (4.9%)
	Less than high school 109 (35.4%)	57 (46.7%)
	High School 83 (26.9%)	32 (26.2%)
	University 102 (33.1%)	27 (22.2%)
	Not specified 14 (4.5%)	0 (0.0%)
	Health care field 13 (4.2%)	4 (3.3%)
	Non-health care field 75 (24.4%)	23 (18.9%)
Family monthly income (in LBP)		
	No current monthly income 33 (11.8%)	12 (10.5%)
	<1 million 54 (19.3%)	25 (21.9%)
	1-1.9 million 88 (31.4%)	32 (28.1%)
	2-3 million 62 (22.1%)	32 (28.1%)
	>3 million 43 (15.4%)	13 (11.4%)
Insurance^a	221 (77.8%)	89 (78.1%)
Alcohol intake		
	No 199 (65.9%)	81 (66.9%)
	Yes 103 (34.1%)	40 (33.1%)
	On Occasions 86 (78.2%)	31 (73.8%)
	1-3 times/week 17 (15.5%)	9 (21.4%)
	Daily 7 (6.4%)	2 (4.8%)

LBP: Lebanese pound; SD: Standard deviation. ^aDefined as public, private, army, or any other insurance.

Table 2 General information on the use of aspirin and other blood thinning medications among study participants.

Aspirin related information	No (%) of patients or Mean $\pm$ SD when specified	
	Total (N = 315)	Diabetics (N = 124)
Indication		
Primary prevention	150 (49.2%)	48 (39.7%)
Secondary prevention	155 (50.8%)	73 (60.3%)
Frequency		
One tablet everyday	269 (90.9%)	105 (92.9%)
One tablet every other day	12 (4.1%)	2 (1.8%)
One tablet once per week	8 (2.7%)	3 (2.7%)
Other 7 ^a	(2.4%)	3 ^b (2.7%)
Duration of aspirin use (years)		
Mean $\pm$ SD [Min-Max]	7.6 $\pm$ 6.1 [0.04-40]	8.6 $\pm$ 6.9 [0.5-40]
Source of aspirin prescription		
Self-prescription	28 (9.5%)	6 (5.2%)
Neighbor/friend/family relative	15 (5.1%)	6 (5.2%)
Pharmacist	27 (9.2%)	6 (5.2%)
Physician	224 (76.2%)	98 (84.5%)
Prescribing physician specialty		
Patient does not know	4 (1.6%)	3 (2.9%)
Family physician	46 (18.7%)	17 (16.3%)
Internal medicine	14 (5.7%)	2 (1.9%)
Cardiologist	162 (65.9%)	71 (68.3%)
Endocrinologist	12 (4.9%)	10 (9.6%)
Other	8 (3.3%)	1 (1.0%)
Personal knowledge of the reason for taking aspirin		
Patient does not know	25 (8.1%)	8 (6.6%)
Everyone takes it for heart protection	54 (17.4%)	17 (13.9%)
Avoid heart problem for first time	79 (25.5%)	23 (8.9%)
Treat heart or stroke condition	83 (26.8%)	31 (25.4%)
Diabetes	15 (4.8%)	14 (11.5%)
Other	23 (7.4%)	7 (5.7%)
>1 answer	31 (10.0%)	22 (18.0%)
Patient assessment of aspirin benefit/risk ratio		
Benefits exceed risks	224 (75.9%)	81 (70.7%)
Risks exceed Benefits	4 (1.4%)	4 (3.4%)
Unsure	67 (22.7%)	30 (25.9%)
Occurrence of any episode of MI, angina or stroke after starting aspirin: for secondary prevention group		
No	92 (59.4%)	38 (52.1%)
Yes	63 (40.6%)	35 (47.9%)
Intake of other blood thinning medications		
No	230 (75.4%)	84 (69.4%)
Yes	74 (24.3%)	36 (29.8%)
Patient does not know	1 (0.3%)	1 (0.8%)
Clopidogrel brand		
Plavix® 75mg	29 (45.3%)	18 (56.3%)
Plavix® 300 mg	1 (1.6%)	0 (0.0%)
Generic	34 (53.2%)	14 (43.9%)

MI: Myocardial Infarction; SD: Standard Deviation. ^aAll week days except Sunday (1); As patient wants (1); one tablet every day for one week followed by one week holiday then the cycle starts again (1); one tablet twice per week (1). ^bAll week days except Sunday (1); one tablet twice per week (1).

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Table 3 List of participating patients' risk factors for both total sample and diabetic subgroup.

Risk factor	No (%) of patients or Mean $\pm$ SD when specified	
	Total (N = 315)	Diabetics (N = 124)
BMI		
Mean $\pm$ SD (Kg/m ²) [Min-Max]	27.7 $\pm$ 4.9 [14.7-63.3]	29.2 $\pm$ 5.6 [20.1-63.3]
Classification ^a		
Underweight/normal	80 (27.0%)	22 (19.0%)
Overweight/obese	216 (73.0%)	43 (82.7%)
Active Smoking		
No	129 (41.5%)	54 (43.5%)
Previous	99 (31.8%)	39 (31.5%)
Current	83 (26.7%)	31 (25.0%)
Passive Smoking (Live with smoker)		
	86 (35.0%)	36 (35.0%)
CVD		
Presence	155 (50.8%)	73 (60.3%)
Years of CVD (Mean $\pm$ SD [Min-Max])	10.2 $\pm$ 8.8 [0.5-48]	10.6 $\pm$ 8.1 [0.5-36]
DM		
Presence	124 (40.7%)	124 (100.0%)
Years of DM (Mean $\pm$ SD [Min-Max])	10.4 $\pm$ 6.9 [0.33-30]	10.5 $\pm$ 6.9 [0.33-30.0]
Type		
DM1	8 (6.5%)	8 (6.6%)
DM2	115 (93.5%)	114 (93.4%)
Currently taking DM medications	111 (99.1%)	49 (94.2%)
Oral medications only	93 (78.2%)	92 (78.6%)
Insulin only	9 (7.6%)	8 (6.8%)
Both	17 (14.3%)	17 (14.5%)
Hypertension		
Presence	198 (65.3%)	85 (71.4%)
Years of hypertension (Mean $\pm$ SD [Min-Max])	10.1 $\pm$ 6.7 [0.17-36]	7.9 $\pm$ 5.7 [0.4-20]
Currently taking hypertension medications	183 (98.4%)	82 (96.5%)
Dyslipidemia		
Hypercholesterolemia	165 (60.4%)	73 (65.8%)
Low HDL	52 (26.4%)	24 (26.4%)
Currently taking dyslipidemia medications	167 (85.2%)	25 (75.8%)
FHx of CVD		
	177 (59.8%)	81 (68.1%)
FHx of premature^{b,c} CVD		
	47 (14.9%)	21 (16.9%)
Rheumatoid arthritis		
	64 (21.3%)	27 (22.5%)
Daily intake of fish oil/omega-3		
	69 (24.7%)	25 (22.2%)
Special diet^d		
	160 (52.8%)	76 (63.9%)
Current regular exercise		
	108 (37.0%)	37 (32.2%)

BMI: Body mass index; CVD: Cardiovascular disease; DM: Diabetes Mellitus; DM1: Diabetes Mellitus type 1; DM2: Diabetes Mellitus type 2; FHx: Family history; HDL: High density lipoprotein; SD: Standard deviation. ^aThe 6 BMI categories were grouped to form 2 classes: (1) underweight/normal and (2) Overweight/obese (including: overweight, obesity class I, obesity class II, and extremely obese). ^bDefined as death of first degree male or female relative before the age of 55 or 65 years, respectively [9]. ^cCalculated as the sum of all patients who chose at least one of the defined conditions. ^dSpecified as no/low fat, salt, or sugar, or high fiber.

Table 4 Comparison of the characteristics of patients taking aspirin for primary or secondary prevention of CVD in total population.

Characteristic	No (%) of patients or Mean±SD when specified		
	Total (N = 305) ^a		p-value
	Primary 150 (49.2%)	Secondary 155 (50.8%)	
Age (years) (Mean ± SD)	60.9 ± 12.3	66.1 ± 10.3	< 0.001 ^b
Gender			
Male	69 (39.7%)	105 (60.3%)	< 0.001 ^c
Female	78 (62.4%)	47 (37.6%)	
Weight (Kg) (Mean ± SD)	75.8 ± 16.6	79.9 ± 14.4	0.025 ^b
Education			
School	87 (43.3%)	114 (56.7%)	0.001 ^c
University	62 (63.3%)	36 (36.7%)	
University education			
Health care field	8 (61.5%)	5 (38.5%)	0.017 ^c
Non-health care field	42 (58.3%)	30 (41.7%)	
Aspirin regimen			
One tablet everyday	120 (46.0%)	141 (54.0%)	< 0.001 ^d
One tablet every other day	12 (100.0%)	0 (0.0%)	
One tablet once per week	8 (100.0%)	0 (0.0%)	
Other	4 (66.7%)	2 (33.3%)	
Years of aspirin use (Mean ± SD)	5.5 ± (5.8)	9.7 ± (6.7)	< 0.001 ^b
Source of aspirin prescription			
Self-prescription	24 (85.7%)	4 (14.3%)	< 0.001 ^c
Neighbor/friend/family relative	13 (86.7%)	2 (13.3%)	
Pharmacist	17 (63.0%)	10 (37.0%)	
Physician	86 (39.8%)	130 (60.2%)	
Prescribing physician specialty			
Patient does not know	3 (75.0%)	1 (25.0%)	< 0.001 ^d
Family physician	32 (71.1%)	13 (28.9%)	
Internal medicine	7 (53.8%)	6 (46.2%)	
Cardiologist	44 (28.0%)	116 (72.0%)	
Endocrinologist	8 (66.7%)	4 (33.3%)	
Other	5 (83.3%)	1 (16.7%)	
Personal knowledge of the reason for taking aspirin			
Patient does not know	11 (45.8%)	13 (54.2%)	< 0.001 ^c
Everyone takes it for heart protection	39 (73.6%)	14 (26.4%)	
Avoid heart problem for first time	59 (76.6%)	18 (23.4%)	
Treat heart or stroke condition	7 (8.6%)	74 (91.4%)	
Diabetes	7 (46.7%)	6 (53.3%)	
Other	14 (63.6%)	8 (36.4%)	
> 1 answer	12 (40.0%)	18 (60.0%)	
Intake of other blood thinning medications			
No	144 (64.3%)	80 (35.7%)	< 0.001 ^d
Yes	1 (1.4%)	71 (98.6%)	
Patient does not know	0 (0.0%)	1 (100.0%)	
Active smoking			
No	68 (53.5%)	59 (46.5%)	0.004 ^c
Previous	34 (35.4%)	62 (64.6%)	
Current	47 (58.8%)	33 (41.3%)	
Years of DM (Mean ± SD)	8.4 ± 6.3	11.7 ± 6.9	0.021 ^b
Currently taking dyslipidemia medications	63 (38.9%)	99 (61.1%)	0.012 ^c

DM: Diabetes Mellitus; SD: Standard deviation. ^aData missing for 10 patients. ^bStudent (Independent) T-Test. ^cChi² Test. ^dFisher's Exact Test.

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Fig. 2 Percentage of each risk factor in total sample, presented from the most to the least frequent risk factor among the primary prevention group.

Fig. 3 Mean number of risk factors for primary and secondary prevention groups in total sample and diabetic subgroup.

Data on at least one risk factor were missing for 29 patients in total group and 12 patients in diabetic subgroup. The Ranges of the numbers of risk factors were as follows: Total Primary: 1-10, Total Secondary: 2-10, Diabetic Primary: 2-10, Diabetic Secondary: 2-9.

3.4.2 Risk Factors Comparison between the Two Groups

Frequency of Each Risk Factor

As shown in Fig. 2, the most prevalent risk factors (50% or more) among the primary prevention group were overweight/obesity and absence of exercise. As for the secondary prevention group, the most prevalent risk factors were history of CVD, hypertension,

overweight/obesity, male gender ≥ 45 years of age, absence of exercise, family history of CVD, and hypercholesterolemia. As for the difference among the percentages of each risk factor, the 2 groups were only similar in the percentage of patients who were overweight/obese, active smokers, not following a specific diet, and had low HDL. The primary prevention group had significantly more females ≥ 55

Table 5 Comparison between diabetic and non-diabetic patients: Variables with statistically significant difference.

Variable	No (%) of patients or Mean $\pm$ SD when specified		
	Total (N = 305) ^a		p-value
	Diabetics 124 (40.7%)	Non-Diabetics 181 (59.3%)	
Age (years) (Mean$\pm$SD)	64.8 $\pm$ 11.2	62.6 $\pm$ 11.8	0.107 ^b
Gender			
	Male 76 (43.9%)	97 (56.1%)	0.153 ^c
	Female 45 (35.7%)	81 (64.3%)	
Education: University	26 (26.3%)	73 (73.7%)	< 0.001 ^c
BMI (Kg/m²) (Mean $\pm$ SD)	29.2 $\pm$ 5.6	26.7 $\pm$ 4.2	< 0.001 ^b
Duration of aspirin use (years) (Mean $\pm$ SD)	8.6 $\pm$ 6.9	6.8 $\pm$ 6.3	0.022 ^b
Prescribing physician specialty			
	Patient does not know 3 (75.0%)	1 (25.0%)	0.003 ^d
	Family physician 17 (38.6%)	27 (61.4%)	
	Internal medicine 2 (15.4%)	11 (84.6%)	
	Cardiologist 71 (45.2%)	86 (54.8%)	
	Endocrinologist 10 (83.3%)	2 (16.7%)	
	Other 1 (12.5%)	7 (87.5%)	
FHx of CVD	81 (46.8%)	92 (53.2%)	0.015 ^c
FHx of DM	83 (62.4%)	50 (37.6%)	< 0.001 ^c
FHx of obesity	44 (49.4%)	45 (50.6%)	0.048 ^c

CVD: Cardiovascular disease; DM: Diabetes Mellitus; FHx: Family history; SD: Standard deviation. ^aData missing for 10 patients.

^bStudent (Independent) T-Test. ^cChi² Test. ^dFisher's Exact Test.

years of age and current active smokers. The rest of the risk factors were significantly more present in the secondary prevention group. Similar results were observed among the primary and secondary prevention groups of the diabetic subgroup.

Number of Risk Factors

In addition, the primary prevention groups in both total sample and diabetic subgroup had significantly lower means of number of risk factors compared to secondary prevention groups (Fig. 3). Furthermore, analysis of the total population showed that significantly ($P < 0.001$) more patients in primary prevention group (105 [72.4%]) had 1-5 risk factors compared to secondary prevention group (28 [19.8%]); on the other hand, significantly ($P < 0.001$) more patients in secondary prevention group (113 [80.1%]) had 6-10 risk factors compared to primary prevention group (40 [27.6%]). Similar findings (± 1 risk factor) were observed in the diabetic primary and secondary prevention subgroups.

3.5 Comparison between Diabetic and Non-diabetic Groups

As presented in Table 5, diabetic patients had significantly less university education, higher BMI, and more family history of diabetes compared to non-diabetic patients. No age or gender difference was observed between the 2 populations. Interestingly, diabetic patients had been using aspirin for a significantly longer duration compared to non-diabetics (8.6 and 6.8 years, respectively) ($P = 0.022$). In addition, majority of endocrinologists' (83.3%) and cardiologists' (54.8%) prescriptions were reported, respectively, by diabetic and non-diabetic patients.

4. Discussion

Despite the current uncertainty prevailing the use of aspirin for primary prevention of CVD, it appears that about half of patients from Beirut and Mount Lebanon are using it for such indication. In fact, numerous RCT

(randomized controlled trials) and meta-analyses have showed that aspirin was not effective for primary prevention of CVD, even for patients with a CVD risk equivalent such as PAD or DM [17, 20, 40-42]. For instance, the AAAT (aspirin for asymptomatic atherosclerosis trialists) conducted a randomized placebo-controlled trial to investigate the effectiveness of once daily 100 mg aspirin in primary prevention of vascular events in asymptomatic patients with high risk of CV and cerebrovascular events, identified by low (≤ 0.95) ABI (ankle brachial index) [42]. Results of that study showed no significant reduction in vascular events – even for participants ≥ 62 years of age, nor in all-cause mortality, with occurrence of major bleeding events requiring hospitalization. Furthermore, The US FDA (Food and Drug Administration) has rejected approval of daily aspirin (75 to 325 mg) for primary prevention of CV events in 1998 and 2003 even for individuals with a 10-year coronary heart disease risk of $\geq 10\%$; this decision was based on the presence of insufficient evidence on overall risk-benefit ratio in certain relevant populations (including women), the lack of mortality benefit, and a seen trend toward excess strokes [43]. The high rate of use for primary prevention can be explained by the fact that many guidelines were and are still recommending its use for such indication [Appendix A] [9, 11-14, 21-26]. In fact, Hissett et al. investigated the use of aspirin in the US from 2007 to 2011 following guidelines changes in recommendation of aspirin for primary prevention of CVD [44]. Their research included a total of 131,050 individuals aging more than 17 years from 33 primary care practices from 6 different states. Their results showed an overall and disease-specific yearly increase in the use of aspirin despite new emerging evidence and recommendations against the use of aspirin in such setting.

Importantly, majority of patients who were taking aspirin for primary prevention were following their own or the neighbor/friend/family relative advice, or

the recommendation of a pharmacist compared to secondary prevention patients. This could be explained by the fact that aspirin is an inexpensive over-the-counter medication that is reimbursed by the Lebanese social security insurance which makes it an easy access to patients [45-46].

Our study findings were very similar to a Canadian study conducted in 2009-2010 in 2 family medicine clinics in Alberta, where among patients taking aspirin for CVD, 53.1% were using it for primary and 46.9% for secondary prevention (a difference of about 3-4% from our results) [47]. Furthermore, they had more males than females, older patients in the secondary prevention group, more patients in the primary prevention group initiating aspirin on their own, and majority of patients believing that benefits of aspirin outweigh its risks. Interestingly, and similar to our study results, more male patients were taking aspirin for secondary prevention (50.0% vs. 43.6%) and more females were taking it for primary prevention (56.3% vs. 50.0%) in the Canadian study. This could be due to availability of published guidelines recommending the use of aspirin particularly in women [36-37]. However, studies have shown that the effect of aspirin in women is limited to reduction of non-fatal ischemic stroke [48-49]. In addition, data have documented that gender difference exists for the benefit of aspirin in primary prevention with a possible decrease in MI events in men and ischemic stroke events in women, but without reduction in CV or all-cause mortality [17, 20, 36, 48].

In our study, physicians were the prescribing source to 40% of patients for primary and 60% for secondary CVD prevention. When looking at the literature, an American survey was conducted in 2011-2012 to assess the use of aspirin for primary and secondary CVD prevention in the US [50]; the authors found that age and health insurance were predictors of physician's recommendation for patients to take aspirin for both high and low risk patients, while education level and obesity were factors in low risk

patients. Interestingly, the risk level of individuals was not an influencing factor affecting physician's prescription of aspirin for CVD primary prevention. The authors interpreted this subjective prescription of aspirin to lead to under or overtreatment of some patients. This may be projected to our study, however, future research are needed to confirm this pattern.

About 21% of the total sample and 22% of diabetic subgroup patients in our study reported having RA. In fact, many studies have linked MI to RA [51-53]. Wolfe and Michaud conducted a nested case-control study involving 17,738 RA patients and the risk of MI in these patients was significantly higher (1.9 ; $P = 0.005$) than patients with non-inflammatory rheumatic disorders, especially in patients taking corticosteroids, since the latter is a predisposing factor for hypertension and diabetes [51]. In addition, the investigators of a Danish cohort study conducted on over 4 million individuals, with 10,477 RA and 130,215 DM patients, found that the overall incidence rate ratio of MI in patients with RA was 1.7, and interestingly, was similar ($P = 0.64$) to that in DM patients [52]. Furthermore, similar conclusion was derived from a meta-analysis conducted on 17 trials that included 124,894 patients and showed that RA was associated with high risk of MI and stroke, which both in turn were a cause for higher mortality in these patients [53].

As for omega 3, about 22-25% of our patients reported its intake. The AHA published a report in 2002 to illustrate the benefits of omega 3 in reducing incidence of CVD and to recommend consumption of foods and oils containing a source of omega 3 for primary prevention of CAD and adding omega 3 supplements for secondary prevention patients after physician consultations [54]. Later reviews also recommended omega 3 derivatives for both primary and secondary prevention of CAD [55-57]. However, in their review of 11 studies on 39,044 patients, Marik and Varon found that the major benefit of omega 3 in preventing fatal and non-fatal CV events was in high

risk (recent MI, heart failure, implanted cardioverter defibrillator) or moderate risk secondary but not primary prevention patients [58]. A more recent expanded meta-analysis of 20 studies including 68,680 primary and secondary patients published in JAMA (Journal of the American Medical Association) found no significant reduction in MI, stroke, or death (cardiac, sudden and all-cause mortality) following omega 3 intake [59]. This might lead to new inconclusive benefit and recommendations at the current moment.

When studying the diabetic subgroup, a lower percentage (about 40%) than the total sample was using aspirin for primary CVD prevention. When looking at the ADA guideline, it previously recommended 75-162 mg of daily aspirin for primary prevention of CVD for all diabetic patients above the age of 40 years or who have additional risk factors, such as hypertension or smoking [60]. However, as of 2010, ADA changed its recommendation to include consideration of such therapy for high risk patients—defined as 10-year CVD risk $> 10\%$ [61]. Later in 2012, they expended their recommendations by warning that aspirin should not be prescribed for such indication if 10-year CVD risk is $< 5\%$ because bleeding risk outweighs the benefit, and that clinical judgment is needed for patients with 10-year CVD risk of 5-10% [62]. In all cases, the level of recommendations was mostly C [60-62]. However, current evidence, including RCTs [40-41, 63] and meta-analyses [64-65] did not find a benefit from using aspirin for primary prevention of CVD in diabetic patients. In addition, these meta-analyses concluded a heterogeneity among RCT, which might necessitate more trials for further more solid evidence [64-65].

In the POPADAD (Prevention of Progression of Arterial Disease and Diabetes) study, a multicenter, double-blinded, factorial RCT involving 1,276 diabetic adults from 16 centers in Scotland, aspirin, like antioxidants, failed to significantly reduce the risk

of death from coronary heart disease or stroke when taken for primary prevention of CAD and followed-up for 4.5 to 8.6 years [40]. Similar findings from the JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes) trial showed that low dose aspirin failed to reduce the risk of fatal and non-fatal CV events, including ischemic heart disease, stroke, and PAD in DM2 patients taking aspirin for primary prevention when followed-up for a median of about 4.4 years [41].

When evaluating this study's questionnaire, the fact that it was long (7 pages) could have been a major reason why most pharmacists &/or patients did not participate in the study. However, most of the questions were objective requiring the pharmacist only to check the patient's corresponding answer. Furthermore, when comparing the results of the primary objective question (do you have CVD) that was repeated on pages 2 and 7 of the questionnaire, only about 4% difference in patients answers was detected; this can be attributed to the detailed definition of CVD on page 7 compared to page 1.

Our study had some limitations. This was an interviewed questionnaire which could have resulted in recall bias, however it was completed under the supervision of a pharmacist. In addition, selection bias cannot be ruled out for 2 main reasons: (1) many patients might have refused to participate in the survey and thus not all pharmacists would have selected the first 10 consecutive eligible patients presenting to their pharmacies, and (2) randomization included only about 50% of the pharmacies and Lebanese population. Furthermore, the sample size collected was lower than the one calculated, thus have lowered the study power and consequently might have hindered the detection of certain differences. In addition, the use of aspirin for congenital heart disease, chronic kidney disease, and protection from cancer were not taken into consideration in this study. Moreover, we were not able to calculate the exact patient CV risk because it was a cross-sectional community pharmacy-based

survey where blood tests data might not have been readily available. Finally, although we identified the source of aspirin prescription, we were not able to assess if current intake of aspirin, particularly for primary prevention, was with or against medical advice, because some patients might refuse to stop taking aspirin even if advised to do so by their physician who could be following newer updated evidence. Therefore, we cannot identify if the clinical practice of physicians concerning the prescription of aspirin for primary prevention of CVD has changed or not and to what extent.

On the other hand, our study had many strengths. First, it was the first study conducted on a random sample of pharmacies and patients to assess aspirin use for CVD prevention in Lebanon. In addition, the study examined all adults and was not limited to patients above a restricted adult age. Furthermore, the study assessed aspirin use among a subgroup of diabetic patients. Finally, we were able to collect different and multitudinous data, including patients' types of risk factors and aspirin-related information; this can open the door for future more targeted epidemiological studies or RCT.

5. Conclusion

Despite newer evidence showing lack of aspirin benefit in primary prevention of CVD, its use appears to be very common among Lebanese population. Awareness should be raised to limit non-physician source of prescription. While awaiting more evidence, patients education on appropriate alternatives to aspirin use for primary prevention of CVD should be campaigned including life-style modifications (diet, exercise, smoking cessation) and tight control of risk factors like hypertension, DM, dyslipidemia and others as recommended by AHA [66-67]. As this study was conducted on a randomized sample representative of 50% of the population, including the capital Beirut, further studies to include all Lebanese districts are recommended to confirm these findings.

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Evaluation of Aspirin Use for Primary and Secondary Prevention of Cardiovascular Diseases among Lebanese Population

Appendix A. Guidelines recommendations for the use of aspirin in primary and secondary prevention of CVD

Table A.1 Guidelines recommendations for the use of aspirin monotherapy in primary prevention of CVD.

Organization	Year	Clinical Recommendation		
		Population	Aspirin regimen	Strength
ACCP [68]	2012	All individuals ≥ 50 years	75-100 mg daily	Grade 2B
		Asymptomatic PAD	75-100 mg daily	Grade 2B
ACCP [69]	2012	Non-rheumatic AF, and low risk of stroke (CHADS ₂ score = 0), and if patient chooses	75-325 mg daily	Grade 2B
ADA [70]	2014	DM, high ^a CVD risk, and not at high risk for bleeding ^b	75-162 mg daily	C
ACCF/AHA [71]	2010	DM and intermediate ^c CVD risk	75-162 mg daily	IIa, B
ACCF/AHA [72]	2011	Asymptomatic PAD and ABI ≤ 0.90 ^d	75-325 mg daily	E
		High ^e risk women	75-325 mg daily	IIb, C
AHA (Women) [73]	2011	At-risk ^f or healthy ^g women	81 mg daily	IIa, B
		Women ≥ 65 years (if BP controlled and benefit for ischemic stroke and MI prevention outweighs risk of GI bleeding and hemorrhagic stroke)	or 100 mg every other day	IIb, B
		Women < 65 years: for ischemic stroke prevention	81-325 mg daily	N/A
AHA/ACCF [74]	2009	No clinical evidence of atherosclerotic disease and high CVD risk	75-325 mg daily	IIb, C
AHA/ACC/ HRS [75]	2014	Nonvalvular AF and CHA ₂ DS ₂ -VASc score = 1	75-162 mg daily	IIb, C
Canadian [76]	2011	Asymptomatic PAD, ABI < 0.9, high risk (due to associated atherosclerotic risk factors), and low bleeding risk	75-162 mg daily	IIb, C
		No evidence of apparent vascular disease, and high vascular risk, and low bleeding	75-162 mg daily	IIb, B
		DM, aged > 40 years, low bleeding risk, and with other CV risk factors	Low-dose	III, A
ESC [77]	2012	Hypertensive patients, no CVD history, with reduced renal function, or at high CV risk	Not recommended	N/A
JBS3 [78]	2014	DM	75-100 mg daily	Grade A
USPSTF [79]	2009	Men Age 45-79 years: encourage aspirin use when potential CVD benefit ^h (MIs prevented) outweighs potential harm of GI bleeding	or 100-325 mg every other day	
		Women 55-79 years: encourage aspirin use when potential CVD benefit ⁱ (strokes prevented) outweighs potential harm of GI bleeding		

ACC: American College of Cardiology; ACCF: American College of Cardiology Foundation; ACCP: American College of Chest Physicians; ABI: ankle-brachial index; ADA: American Diabetes Association; AHA: American Heart Association; BP: Blood pressure; CHADS₂: Congestive heart failure/hypertension/age ≥ 75 years/diabetes mellitus/prior stroke or transient ischemic attack; CHA₂DS₂-VASc: Congestive heart failure/hypertension/age 65-74 years/age ≥ 75 years/diabetes mellitus/prior stroke or transient ischemic attack-vascular disease/female gender; CHD: Coronary heart disease; CV: Cardiovascular; CVD: Cardiovascular disease; DASH: Dietary approaches to stop hypertension; DBP: Diastolic blood pressure; DM: Diabetes Mellitus; ESC: European Society of Cardiology; GI: Gastrointestinal; HDL-C: High-density lipoprotein cholesterol; HRS: Heart Rhythm Society; IMT: Intima-media thickness; JBS3: Joint British Society (Report 3); MI: Myocardial infarction; N/A: Not available; NSAIDs: Non-steroidal anti-inflammatory drugs; PAD: Peripheral artery disease; SBP: Systolic blood pressure; USPSTF: United States Preventive Services Task Force.

^a10-year CVD events risk > 10%: most men > 50 years and women > 60 years with ≥ 1 of the following: smoking, hypertension, dyslipidemia, family history of premature CVD, and albuminuria. ^bBased on history of previous gastrointestinal bleeding or peptic ulcer disease or concurrent use of other medications that increase bleeding risk, such as NSAIDs or warfarin. ^cMen < 50 years and women < 60 years patients with ≥ 1 risk factors, or older patients with no risk factors, or patients with 10-year CVD risk of 5-10%.

^dTo reduce the risk of MI, stroke, or vascular death. ^eHigh risk (≥ 1 high-risk states): clinically manifest CHD, clinically manifest cerebrovascular disease, clinically manifest PAD, abdominal aortic aneurysm, end-stage or chronic kidney disease, DM, 10-year CVD risk $\geq 10\%$. ^fAt risk (≥ 1 major risk factor[s]): cigarette smoking, SBP ≥ 120 mm Hg, DBP ≥ 80 mm Hg, or treated hypertension, total cholesterol ≥ 200 mg/dL, HDL-C < 50 mg/dL, or treated for dyslipidemia, obesity – particularly central adiposity, poor diet, physical inactivity, family history of premature CVD occurring in first-degree relatives in men < 55 years of age or in women < 65 years of age, metabolic syndrome, evidence of advanced subclinical atherosclerosis (e.g., coronary calcification, carotid plaque, or

thickened IMT), poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise, systemic autoimmune collagen-vascular disease (e.g., lupus or rheumatoid arthritis), history of preeclampsia, gestational diabetes, or pregnancy-induced hypertension. [§]Ideal cardiovascular health (all of the following): total cholesterol < 200 mg/dL (untreated), BP < 120/ < 80 mm Hg (untreated), fasting blood glucose <100 mg/dL (untreated), body mass index < 25 kg/m², abstinence from smoking, physical activity at goal for adults > 20 years of age (≥ 150 minutes/week moderate intensity, ≥ 75 minutes/week vigorous intensity, or combination), healthy (DASH-like) diet. ^h10-year CVD risk ≥ 4%, 9%, and 12% in 45-59, 60-69, and 70-79 year old men respectively. ⁱ10-year CVD risk ≥ 3%, 8%, and 11% in 55-59, 60-69, and 70-79 year old women respectively.

Table A.2 Guidelines recommendations for the use of aspirin monotherapy in secondary prevention of CVD.

Organization	Year	Clinical Recommendation Population	Aspirin regimen	Strength
ACCP [68]	2012	Established CAD ^a	75-100 mg daily	Grade 1B
ACCP [69]	2012	Symptomatic PAD	75-100 mg daily	Grade 1A
		Ischemic stroke or TIA	75-100 mg daily	Grade 1A
ADA [70]	2014	DM and history of CVD	75-162 mg daily	N/A, A
ACCF/AHA [72]	2011	Symptomatic atherosclerotic lower extremity PAD ^{b,c}	75-325 mg daily	I, B
AHA (Women) [73]	2011	women with CHD	75-325 mg daily	I, A
		All patients with CAD	75-162 mg daily	I, A
AHA/ACCF [80]	2011	Patients after PCI	81 mg daily	IIa, B
		Extracranial carotid or vertebral atherosclerosis who had ischemic stroke or TIA	75-325 mg daily	I, B
		Symptomatic atherosclerotic PAD of lower extremity	75-325 mg daily	I, A
		DM and vascular disease	75-162 mg daily	I, A
		All patients with CAD, including PCI and CABG	75-162 mg daily	I, A
		Ischemic stroke or TIA	75-162 mg daily	I, A
		Symptomatic PAD, without overt CAD or CVD	75-162 mg daily	IIb, B
		Symptomatic PAD, with overt CAD or CVD	75-162 mg daily	I, A
Canadian [76]	2011	Chronic symptomatic PAD, with lower-extremity balloon angioplasty with or without stenting	75-162 mg daily	IIa, C
		All infrainguinal reconstructions in PAD patients	75-162 mg daily	IIa, B
		All patients with an AAA, particularly those with clinical or subclinical PAD	75-162 mg daily	IIb, C
			Alternative to either dipyridamole plus aspirin or clopidogrel	I, A
ESC [77]	2012	Non-cardioembolic TIA or ischemic stroke	75-100 mg daily	N/A
JBS3 [78]	2014	All patients post-MI	Not recommended ^d	N/A
		Stroke	Not recommended ^d	N/A
		PAD	Not recommended ^d	N/A

AAA: abdominal aortic aneurysm; ACCF: American College of Cardiology Foundation; ACCP: American College of Chest Physicians; ACS: Acute coronary syndrome; ADA: American Diabetes Association; AHA: American Heart Association; CABG: Coronary artery bypass graft; CAD: Coronary artery disease; CHD: Coronary heart disease; CV: Cardiovascular; CVD: Cardiovascular disease; DM: Diabetes Mellitus; ESC: European Society of Cardiology; JBS3: Joint British Society (Report 3); MI: Myocardial infarction; N/A: Not available; PCI: Percutaneous coronary intervention; PAD: Peripheral artery disease; TIA: Transient ischemic attack.

^aPost-acute coronary syndrome, with prior revascularization, coronary stenosis > 50%, and/or evidence for cardiac ischemia on diagnostic testing. ^bIncluding intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. ^cTo reduce the risk of MI, stroke, or vascular death.

^dClopidogrel 75 mg daily is recommended in this case.

Appendix A References

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