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Drug Use for Secondary Prevention of Cardiovascular Diseases in Golestan, Iran: Results From the Golestan Cohort Study

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Abstract

Background: Little is known about secondary prevention of cardiovascular diseases, using cardio-protective drugs, in the community-level, especially in low- and middle-income countries. We aimed to assess main drug use and its predictors in Northeast of Iran.

Methods: This is a cross-sectional analysis on the Golestan Cohort Study data (2004–2008) with 50045 participants. We assessed drug use in those with a history of ischemic heart disease (IHD) or stroke, recorded by face-to-face interviews. We explored drug use predictors (i.e., age, gender, wealth, education, residency, smoking, body mass index, physical activity, hypertension, and diabetes) through multivariable logistic regression.

Results: A total of 3371 (6.7%) participants (56.7 ± 9.0 years, 58.1% female) reported a history of IHD, stroke or both. Median duration since diagnosis was 3.14 years (IQR: 1.25-6.30). Rates of using anti-platelets, statins, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and beta-blockers were 28.8% (95% CI: 27.3–30.3), 5.4 (4.7–6.2), 15.7 (14.5–17.0), and 40.6 (38.9–42.3), respectively. About 43% (41 – 45) of patients did not use any protective drugs. Use of ≥ three drugs was only 7.3% (6.6–8.2). Indicators of ≥1 drug use were: older age (OR for ≥60 vs. <50: 1.37), high wealth score (fifth vs first quintile: 1.60), literacy (1.56), city dwelling (1.32), body mass index (<18.5 and ≥30 vs. 25–29: 0.55 and 1.25, respectively), physical activity (third vs. first tertile: 0.64), hypertension (3.47), and diabetes (1.29); (all $P < 0.05$).

Conclusion: Drug use after IHD or stroke is low in Northeast of Iran. Comprehensive efforts to promote secondary prevention are urgently needed.

Keywords: Cardiovascular diseases, Drug, Iran, Secondary prevention

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Introduction

Cardiovascular diseases (CVDs), including ischemic heart disease (IHD) and stroke, are the leading causes of death globally.[1] In 2015, more than 85% of CVD mortality was due to IHD (8.9 million) and stroke (6.3 million)–the leading causes of premature mortality.[2]

Patients who have had a CVD are at high risk for recurrent events.[3,4] For example, in a large primary-care cohort study, those with prior CVD made up only 10.4% of the population but accounted for 42% of total cardiovascular events during an average follow-up of 2 years; so, these patients should be the highest priority for preventive management.[4]

Data from clinical trials has consistently proven the efficacy of anti-platelets (a-PLTs), 3-hydroxy-3-methyl-glutaryl–coenzyme A reductase inhibitors (statins), beta-blockers (BBs), and angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACE-I/ARBs) in reducing the risk of cardiovascular events in secondary prevention,[3] by about a quarter each.[5] Combined use of these medications can potentially reduce recurrent events in secondary prevention by about two-thirds to three-quarters.[5]

Despite the clear documented benefits of secondary prevention drugs, there is a wide gap between patients in need of treatment and those who actually receive

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it.[6-9] Most data about secondary prevention drugs are from hospital or clinic registries and little is known about individuals in the community, especially in low- and middle-income countries.[7] Iran is a middle-income country with high IHD/stroke mortality (37% of total death, about 10% more than the global average).[10] In this study, we assessed the utilization rates for evidence-based cardiovascular drugs for prevention of CVDs (i.e., IHD and/or stroke) in the large population-based Golestan Cohort Study (GCS). We also evaluated the individual-level determinants of use of main cardiovascular drugs.

Materials and Methods

This cross-sectional study analyzes the baseline data from the GCS. Details of the GCS have been described elsewhere.[11]

Study Population

In the GCS, 50045 participants (40 to 75 years old) were enrolled in Golestan province in Northeast of Iran from 2004 to 2008. About 80% of the participants were rural and 20% were urban residents.

Data Collection

All participants were asked to provide written informed consent. Trained physicians and non-physician interviewers completed different parts of a questionnaire for each participant through face-to-face interviews and collected information on age, gender, ethnicity, place of residence, marital status, education, smoking, opium or alcohol consumption, ownership of several appliances, and history of IHD, stroke, hypertension, and diabetes mellitus. Individuals were asked to bring their medications to the health center. Height and weight were measured. A questionnaire about intensity and duration of physical activity was completed in 2 domains (usual daily activities and leisure-time activities). Based on the metabolic equivalent (MET), we calculated a person's overall energy expenditure during activity (MET-minutes per week) and categorized participants into three groups, accordingly. Wealth score was calculated for each participant based on appliances and other variables such as house ownership, structure, and size, using multiple correspondence analysis, as reported earlier.[12]

Definitions

Participants were considered to have experienced an IHD or stroke if they reported a physician diagnosis of IHD or stroke (with or without revascularization procedures). Medication usage was defined as regular intake of each medication for at least 20 days per month. The main medications counted for IHD were: a-PLTs (mainly aspirin and clopidogrel), statins, BBs, and ACE-I/ARBs; and for stroke were: a-PLTs, statins, ACE-I/ARBs, and other blood-pressure-lowering medications (e.g., BBs and Calcium-channel Blockers). History of hypertension and diabetes mellitus was based on self-report. Literacy was defined as more than one year of school attendance. Body mass index (BMI) was categorized as underweight (<18.5 kg/m^2), normal (18.5–24.9), overweight (25–29.9), and obese (≥ 30). We divided the duration of CVDs (time since the first diagnosis) into quartiles, physical activity into tertiles, and wealth score into quintiles.

Statistical Analysis

The categorical variables were summarized as n (%). We compared proportions between groups with a chi-square test. Multivariable logistic regression models were used to determine the association of medication use and independent covariates, to control for confounding, and to examine interactions. Also, we divided participants into different subgroups (based on age, gender, place of residence, and education) and examined the effects of drug use determinants. All statistical analyses were done with Stata statistical software (version 12, Stata Inc., College Station, TX). Values of $P < 0.05$ were considered significant.

Role of the Funding Sources

The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants

Of the 50045 participants in the GCS (52.1 ± 8.9 years at study baseline, 57.6% female), 3371 (6.7%) had a history of IHD, stroke or both (56.7 ± 9.0 years, 58.1% female). A total of 3044 participants reported a history of IHD and 418 reported a previous stroke, of whom 91 reported a history of both (Table 1). The median time since diagnosis was 3.14 (IQR: 1.25–6.30) years (IHD: 3.0, 1.2–6.1; Stroke: 4.2, 1.9–7.8). Demographic characteristics and risk factor details are shown in Table S1.

Medication Use

Table 1 and Figure S1 show rates of drug utilization in participants with CVDs. Low use of all main drugs was observed in both IHD and stroke individuals. Use of three or more key medications was only 7.3%. A total of 43.0% of these participants did not use any drug. Demographic and clinical correlates associated with the number of main medication use are shown in Figure 1

Table 1. Use of Secondary Prevention Drugs for CVDs in the Golestan Cohort Study

	IHD (N = 3044)	Stroke (N = 418)	IHD or Stroke (N = 3371)
a–PLTs	888 (29.17, 27.6–30.8)	111 (26.56, 22.4–31.1)	970 (28.77, 27.3–30.3)
Statins	176 (5.78, 5.0–6.7)	17 (4.07, 2.4–6.4)	183 (5.43, 4.7–6.2)
BBs	1256 (41.26, 39.5–43.0)	159 (38.04, 33.4–42.9)	1368 (40.58, 38.9–42.3)
ACE–I/ARBs	488 (16.03, 14.7–17.4)	57 (13.64, 10.5–17.3)	529 (15.69, 14.5–17.0)
CCBs	356 (11.70, 10.6–12.9)	52 (12.44, 9.4–16.0)	394 (11.69, 10.6–12.8)
Diuretics	253 (8.31, 7.4–9.3)	34 (8.13, 5.7–11.2)	278 (8.25, 7.3–9.2)
Other anti–HTN	83 (2.73, 2.2–3.4)	17 (4.07, 2.4–6.4)	97 (2.88, 2.3–3.5)
Anti–HTN drug user	1703 (55.95, 54.2–57.7)	225 (53.83, 48.9–58.7)	1868 (55.41, 53.7–57.1)
Main drug count*			
0 drug	1301 (42.74, 41.0–44.5)	179 (42.82, 38.03–47.7)	1451 (43.04, 41.4–44.7)
1drug	940 (30.88, 29.2–32.6)	134 (32.06, 27.6–36.8)	1043 (30.94, 29.4–32.5)
2 drugs	578 (18.99, 17.6–20.4)	72 (17.22, 13.7–21.2)	631 (18.72, 17.4–20.1)
≥3 drugs	225 (7.39, 6.5–8.4)	33 (7.89, 5.5–10.9)	246 (7.30, 6.4–8.2)

CVDs: cardiovascular diseases; IHD: ischemic heart disease; a–PLTs: anti–platelets; BBs: beta–blockers; ACE–I/ARBs: angiotensin converting enzyme inhibitors or angiotensin receptor blockers; CCBs: calcium channel blockers; HTN: hypertension.
*Main drugs for IHD: anti–platelets, beta–blockers, ACEIs or ARBs, and satins; main drugs for stroke: anti–platelets, ACE–I/ARBs, statins and other blood presser lowering drugs (e.g., beta–blockers, diuretics, or CCBs). Data are shown as n (prevalence, 95% CI).

and Table S2.

Rates of medication use in patients with and without history of hypertension were: a-PLTs: 31.0 versus 26.5% ($P=0.004$), statins: 6.6 versus 4.3% ($P=0.003$), ACE-I/ARBs: 24.5 versus 6.9% ($P<0.001$), BBs: 54.0 versus 27.2 ($P<0.001$), and all anti-hypertensive drugs: 76.1 versus 34.8% ($P<0.001$), respectively.

The unadjusted analysis shows that use of one or more main drugs was significantly greater in elders, females, urban residents, and literates (Table 2). History of hypertension, history of diabetes mellitus, overweight and obesity, older versus newer CVDs, and higher wealth status were associated with higher use of medications. Medication use was inversely associated with current smoking, low BMI, and high physical activity. Ethnicity, marital status, history of former smoking versus nonsmoking and alcohol or opium use were not associated with medication use. The full model adjusting attenuated

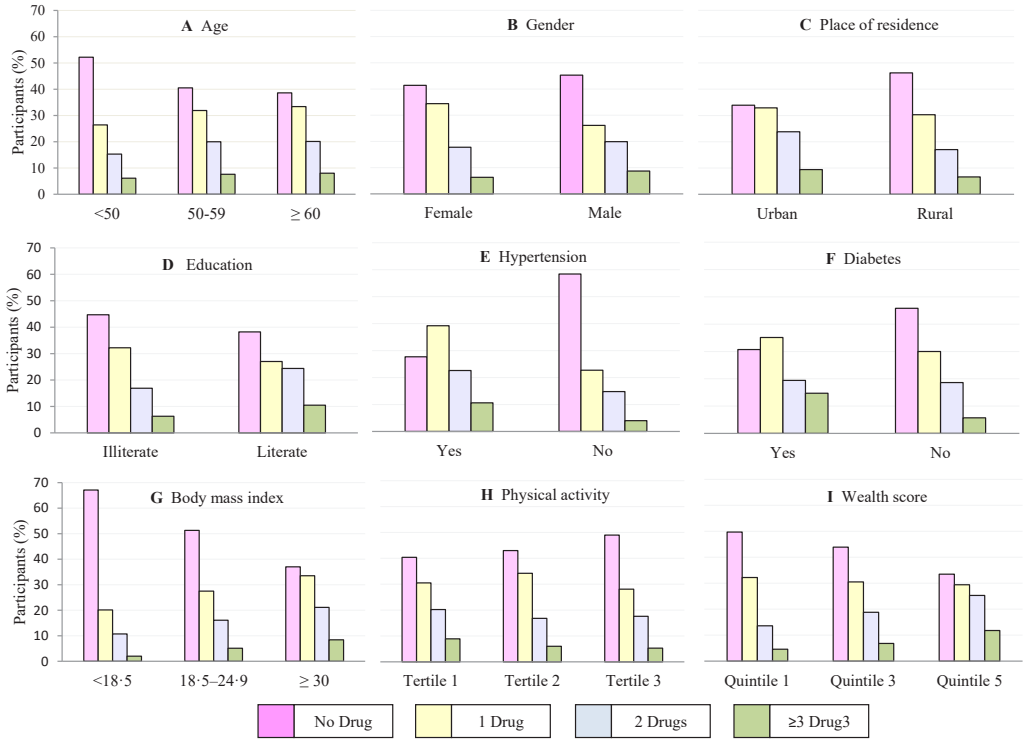

Figure 1. Number of Drugs Used by Participants Based on **A)** Age; **B)** Gender; **C)** Place of Residence; **D)** Education; **E)** History of Hypertension; **F)** History of Diabetes; **G)** Body Mass Index; **H)** Physical Activity; **I)** and Wealth Score. For drug counting, see Table 1. See appendix Table S2 for more details.

Table 2. Factors Associated with ≥1 Main Drug* Using in CVDs in the Golestan Cohort Study (n = 3371)

	0 drug N = 1451 (43.0)	≥1 Drug N = 1920 (57.0)	Crude OR	Adjusted OR–1	Adjusted OR–2	Adjusted OR–3
Age (y)				NA	NA	
<50	482 (52.22)	441 (47.78)	1			1
50–59	493 (40.54)	723 (59.46)	1.60 (1.35–1.90)			1.31 (1.07–1.59)
≥60	476 (38.64)	756 (61.36)	1.73 (1.46–2.06)			1.37 (1.11–1.69)
Gender				NA	NA	
Male	640 (45.26)	774 (54.74)	1			1
Female	811 (41.44)	1146 (58.56)	1.17 (1.02–1.34)			1.22 (0.99–1.50)
Place of residence						
Rural	1160 (46.2)	1353 (53.8)	1	1	NA	1
Urban	291 (33.9)	567 (66.1)	1.67 (1.42–1.96)	1.60 (1.36–1.89)		1.32 (1.09–1.61)
Education						
Illiterate	1134 (44.65)	1406 (55.35)	1	1	NA	1
Literate	317 (38.15)	514 (61.85)	1.31 (1.11–1.54)	1.83 (1.52–2.20)		1.56 (1.24–1.95)
Duration of disease						
Quartile 1	395 (48.95)	412 (51.05)	1	1	1	1
Quartile 2	345 (42.86)	460 (57.14)	1.28 (1.05–1.56)	1.28 (1.05–1.55)	1.23 (1.01–1.50)	1.16 (0.94–1.44)
Quartile 3	329 (40.82)	477 (59.18)	1.39 (1.14–1.69)	1.33 (1.09–1.63)	1.29 (1.06–1.58)	1.27 (1.03–1.58)
Quartile 4	316 (39.21)	490 (60.79)	1.49 (1.22–1.81)	1.39 (1.14–1.70)	1.31 (1.07–1.61)	1.20 (0.97–1.50)
Current smoking						
No	1286 (42.1)	1768 (57.9)	1	1	1	1
Yes	165 (52.1)	152 (47.9)	0.67 (0.53–0.84)	0.73 (0.57–0.93)	0.69 (0.54–0.88)	0.79 (0.60–1.04)
History of HTN						
No	985 (58.42)	701 (41.58)	1	1	1	1
Yes	466 (27.66)	1219 (72.34)	3.68 (3.18–4.25)	3.58 (3.09–4.16)	3.77 (3.24–4.39)	3.47 (2.95–4.07)
History of DM						
No	1263 (45.78)	1496 (54.22)	1	1	1	1
Yes	188 (30.72)	424 (69.28)	1.90 (1.58–2.30)	1.82 (1.50–2.19)	1.74 (1.43–2.10)	1.29 (1.05–1.59)
BMI (kg/m^2)						
<18.5	100 (67.11)	49 (32.89)	0.52 (0.36–0.74)	0.50 (0.35–0.72)	0.52 (0.36–0.76)	0.55 (0.36–0.83)
18.5–24.9	485 (51.32)	460 (48.68)	1	1	1	1
25–29.9	476 (38.95)	746 (61.05)	1.65 (1.39–1.96)	1.68 (1.41–2.00)	1.59 (1.33–1.90)	1.35 (1.11–1.63)
≥30	390 (37.00)	664 (63.00)	1.80 (1.50–2.15)	1.86 (1.54–2.24)	1.73 (1.43–2.09)	1.25 (1.01–1.54)
Physical activity						
Tertile 1	673 (40.37)	994 (59.63)	1	1	1	1
Tertile 2	352 (43.03)	466 (56.97)	0.89 (0.76–1.06)	0.80 (0.66–0.96)	0.75 (0.62–0.91)	0.78 (0.63–0.96)
Tertile 3	418 (49.00)	435 (51.00)	0.70 (0.60–0.83)	0.68 (0.57–0.82)	0.62 (0.51–0.75)	0.64 (0.52–0.79)
Wealth score						
Quintile 1	337 (49.71)	341 (50.29)	1	1	1	1
Quintile 2	288 (50.09)	287 (49.91)	0.98 (0.79–1.23)	1.03 (0.82–1.29)	1.01 (0.81–1.27)	0.95 (0.74–1.22)
Quintile 3	381 (43.89)	487 (56.11)	1.26 (1.03–1.55)	1.38 (1.12–1.69)	1.33 (1.08–1.64)	1.27 (1.01–1.60)
Quintile 4	217 (38.07)	353 (61.93)	1.61 (1.28–2.02)	1.71 (1.36–2.15)	1.52 (1.20–1.92)	1.48 (1.14–1.91)
Quintile 5	228 (33.53)	452 (66.47)	1.96 (1.57–2.44)	2.16 (1.72–2.70)	1.74 (1.37–2.22)	1.60 (1.23–2.09)

CVDs: cardiovascular diseases; HTN: hypertension; DM: diabetes mellitus; BMI: body mass index. OR–1: adjusted for age and gender; OR–2: adjusted for age, gender, place of residence, and education; OR–3: adjusted for all variables in the table. *For drug counting, see Table 1.

the effects of gender, duration of disease, and current smoking (Table 2). In another analysis, we assessed correlates of using 2 or more medications. The results of fully adjusted model were almost unchanged, but current smoking became significant (OR: 0.6, 95% CIs 0.4–0.8) and overweight and obesity were non-significant (Table S3). Also, fully adjusted ORs for specific drugs are shown in Table S4.

The factors associated with ≥ 1 main drug use, based on age, gender, place of residence, and education are shown in Table 3. Significant interactions were observed for age with gender (P = 0.002 in age ≥ 60 vs. <50, and P = 0.04 in 50–59 vs. < 50 years), age with place of residence (P = 0.001 in both age ≥60 and 50–59 vs. <50 years), and gender with place of residence (P = 0.007). The direct effect of age on drug use was significant only in women and in urban participants. Women used medications more frequently than men only in urban areas. The effects of BMI, physical activity, and current smoking on drug use were observed only in illiterate participants (Table 3).

Discussion

This study shows alarmingly low rates of using effective proven medications for secondary prevention of IHD

Table 3. Factors Associated with ≥ 1 Main Drug Use in CVDs in the Golestan Cohort Study Based on Age, Gender, Place of Residence, and Education*

	Age			Gender		Place of Residence		Education	
	< 50 years	**50–59 years**	**≥60 years**	**Male**	**Female**	**Rural**	**Urban**	**Illiterate**	**Literate**
Age (y)									
< 50	-	-	-	1	1	1	1	1	1
50–59	-	-	-	1.06 (0.77–1.46)	1.48 (1.15–1.91)	1.08 (0.86–1.35)	2.58 (1.67–3.99)	1.23 (0.97–1.56)	1.46 (1.01–2.10)
≥ 60	-	-	-	1.02 (0.73–1.42)	1.71 (1.29–2.27)	1.11 (0.87–1.41)	2.84 (1.80–4.48)	1.23 (0.96–1.57)	1.97 (1.27–3.07)
Gender									
Male	1	1	1	-	-	1	1	1	1
Female	0.69 (0.44–1.06)	1.29 (0.91–1.83)	1.71 (1.23–2.38)	-	-	1.06 (0.85–1.34)	1.92 (1.17–3.17)	1.26 (1.00–1.58)	1.12 (.68–1.85)
Place of residence									
Rural	1	1	1	1	1	-	-	1	1
Urban	0.77 (0.51–1.18)	1.73 (1.24–2.40)	1.42 (1.03–1.95)	0.95 (0.70–1.30)	1.62 (1.25–2.11)	-	-	1.52 (1.20–1.94)	0.99 (0.69–1.43)
Education									
Illiterate	1	1	1	1	1	1	1	-	-
Literate	1.13 (0.76–1.69)	1.49 (1.02–2.16)	2.30 (1.49–3.55)	1.74 (1.31–2.30)	1.16 (0.78–1.73)	1.62 (1.23–2.13)	1.73 (1.14–2.63)	-	-
Duration of disease									
Quartile 1	1	1	1	1	1	1	1	1	1
Quartile 2	1.02 (0.69–1.50)	1.68 (1.17–2.41)	0.84 (0.57–1.24)	0.94 (0.67–1.32)	1.26 (0.95–1.67)	1.12 (0.88–1.43)	1.29 (0.80–2.08)	1.30 (1.02–1.66)	0.80 (0.51–1.24)
Quartile 3	1.29 (0.85–1.96)	1.79 (1.26–2.55)	0.86 (0.59–1.26)	0.99 (0.71–1.40)	1.48 (1.11–1.96)	1.27 (1.00–1.63)	1.29 (0.80–2.07)	1.37 (1.07–1.75)	0.96 (0.60–1.52)
Quartile 4	1.27 (0.81–1.97)	1.34 (0.94–1.91)	1.01 (0.69–1.48)	0.87 (0.62–1.23)	1.47 (1.10–1.96)	1.30 (1.01–1.68)	0.99 (0.63–1.56)	1.36 (1.06–1.75)	0.80 (0.50–1.27)
Current smoking									
No	1	1	1	1	1	1	1	1	1
Yes	0.85 (0.51–1.41)	0.77 (0.47–1.24)	0.71 (0.44–1.14)	0.76 (0.56–1.04)	0.90 (0.44–1.84)	0.72 (0.52–1.01)	1.12 (0.66–1.90)	0.63 (0.43–0.92)	1.06 (0.69–1.63)
History of HTN									
No	1	1	1	1	1	1	1	1	1
Yes	4.55 (3.26–6.34)	2.59 (1.99–3.37)	4.13 (3.14–5.42)	2.94 (2.27–3.79)	3.94 (3.19–4.86)	3.47 (2.88–4.17)	3.86 (2.75–5.42)	3.60 (3.00–4.31)	3.22 (2.25–4.61)
History of DM									
No	1	1	1	1	1	1	1	1	1
Yes	1.47 (0.93–2.31)	1.33 (0.96–1.84)	1.27 (0.90–1.80)	1.55 (1.09–2.20)	1.20 (.92–1.56)	1.41 (1.10–1.81)	1.00 (0.68–1.47)	1.08 (0.85–1.37)	2.21 (1.42–3.47)
BMI (kg/m^2)									
<18.5	0.48 (0.18–1.27)	0.73 (0.34–1.54)	0.51 (0.28–0.93)	0.68 (0.37–1.24)	0.45 (0.25–0.81)	0.63 (0.41–0.99)	0.21 (0.06– 0.72)	0.61 (0.39–0.96)	0.31 (0.09–1.01)
18.5–24.9	1	1	1	1	1	1	1	1	1
25–29.9	1.50 (1.02–2.21)	1.04 (0.74–1.45)	1.56 (1.14–2.13)	1.54 (1.17–2.02)	1.17 (0.89–1.55)	1.43 (1.14–1.78)	1.17 (0.76–1.79)	1.32 (1.05–1.66)	1.38 (0.93–2.03)
≥ 30	1.33 (0.88–2.01)	1.01(0.71–1.44)	1.47 (1.02–2.12)	1.30 (.92–1.84)	1.16 (0.88–1.54)	1.44 (1.13–1.83)	0.82 (0.52–1.28)	1.31 (1.02–1.66)	1.09 (0.70–1.71)
Physical activity									
Tertile 1	1	1	1	1	1	1	1	1	1
Tertile 2	0.63 (0.41–0.97)	0.91 (0.64–1.29)	0.69 (0.49–0.98)	0.98 (0.64–1.50)	0.74 (0.57–0.95)	0.74 (0.58–0.94)	0.92 (0.57–1.48)	0.74 (0.58–0.93)	0.83 (0.51–1.36)
Tertile 3	0.57 (0.39–0.83)	0.60 (0.44–0.83)	0.86 (0.55–1.34)	0.52 (0.36–0.74)	0.67 (0.51–0.88)	0.55 (0.43–0.69)	0.81 (0.49–1.32)	0.62 (0.49–0.79)	0.68 (0.44–1.05)
Wealth score									
Quintile 1	1	1	1	1	1	1	1	1	1
Quintile 2	0.63 (0.37–1.07)	0.77 (0.51–1.17)	1.36 (0.91–2.03)	0.58 (0.39–0.88)	1.27 (0.93–1.75)	0.91 (0.69–1.19)	1.02 (0.52–2.00)	1.00 (0.77–1.30)	0.48 (0.21–1.08)
Quintile 3	0.94 (0.59–1.50)	0.96 (0.65–1.41)	2.07 (1.41–2.04)	1.11 (0.76–1.61)	1.34 1.00–1.80)	1.28 (1.00–1.64)	1.04 (0.56–1.94)	1.23 (0.96–1.58)	1.01 (0.50–2.03)
Quintile 4	1.47 (0.87–2.48)	1.24 (0.80–1.92)	1.56 (1.02–2.38)	0.95 (0.63–1.45)	1.98 (1.41–2.78)	1.29 (0.96–1.73)	1.80 (0.98–3.28)	1.57 (1.17–2.11)	0.91 (0.45–1.84)
Quintile 5	1.51 (0.88–2.60)	1.19 (0.76–1.87)	2.21 (1.43–3.44)	1.29 (0.85–1.98)	1.85 (1.30–2.63)	1.69 (1.22–2.33)	1.66 (0.93–2.96)	1.65 (1.20–2.27)	1.08 (0.55–2.13)

CVDs: cardiovascular diseases; HTN: hypertension; DM: diabetes mellitus; BMI: body mass index. *Adjusted for all variables in the table.

and stroke in the Golestan province of Iran. The use of key medications was 29% for a-PLTs, 5% for statins, 41% for BBs, and 16% for ACE-I/ARBs. Only 7.3% of patients were on at least three protective medication types and 43.0% did not receive any of the four medications. Use of medication therapy was higher in older individuals, urban inhabitants, literate, overweight, obese, or wealthier participants. History of hypertension or diabetes mellitus was also associated with higher medication use. Low BMI and high physical activity were associated with low medication use.

Similar to our study, other community-based studies have shown low drug utilization rates in individuals with CVDs.[7] In the community-based prospective urban rural epidemiological (PURE) study, rates of medication use in low- and high-income countries, after a median of 4–5 years from IHD/stroke diagnosis, were 8.8%–62.0% for a-PLTs, 3.3%–66.5% for statins, 9.7%–40% for BBs, and 5.2%–49.8% for ACE-I/ARBs, respectively.[7] These data in South Asia (India, Pakistan, and Bangladesh)[13] and South America (Argentina, Brazil, Chile, and Colombia)[14] were 9.3 and 28.2% for a-PLTs, 3.5 and 15.4% for statins,10.4 and 28.3% for BBs, and 5.3 and 36.0% for ACE-I/ARBs, respectively. Drug use rates will often be higher in studies conducted in hospitals or outpatient clinics.[6,15,16] These studies tend to overestimate drug utilization rates because they do not include all patients in the community.[7]

In this study, rates of use of all key medications were higher in patients with a history of hypertension. The differences were narrower for a-PLTs and statins than BBs and ACE-I/ARBs. Our data are consistent with the PURE study[7] about the considerable difference in utilization of BBs and ACE-I/ARBs between patients with and without hypertension, suggesting that the main focus of clinicians leans towards the reduction of blood pressure than the risk of future cardiovascular events.[7] BBs and ACE-I/ARBs not only reduce blood pressure but also reduce recurrent cardiovascular events, even in patients with normal blood pressure.[3,17] This notion indicates a need to evaluate clinicians' approach and to re-educate them in order to effective secondary prevention.

The potential explanations for the lack of effective secondary prevention can be categorized into the role of physicians (e.g., do not prescribe), the role of patients (e.g., non-adherence to prescribed medications), and the role of the health systems (e.g., availability and accessibility barriers).[14] A study showed that in the western provinces of Iran with 4 000 000 population in 74 000 km^2, during 2002–2012, there was only one cardiac rehabilitation center for systematic secondary prevention.[18] In the current study, we did not specifically assess causes of low medication use; instead, we assessed the utilization rate of proven drugs in the community as an indicator of the quality of secondary prevention care.

The effects of age and gender on drug use are inconsistent in previous studies.[6,7,13,14,16,19] We found a significant interaction between age and gender. In women, higher age was associated with more frequent use of medications. A study indicated some plausible explanatory factors: in women, due to approximately ten years later diagnosis, clustering risk factors and more advanced stage of CVDs can be observed; higher mortality rate for males in younger age leads to survival of those with a better risk profile in older age; and there could be a difference in optimal treatment, ability for lifestyle change, and psychological factors between genders.[20] Another study indicated that a misconception that women are at lower risk and women's caregiver responsibilities are barriers to looking after their health.[19] In a survey of 2300 women, caretaking responsibilities were the most common barrier to prevention of heart diseases because of increased stress, more exhaustion, less time for oneself, and so on.[21] According to our findings, it is likely that the family/social responsibilities of a younger woman, compared with an older one, may play a role in the underuse of essential medications. Interestingly, the direct effects of older age and female gender on medication use were significant only in urban residents (Table 3), suggesting likely higher responsibilities for women in the rural areas.

In the current study, older, hypertensive, diabetic, overweight or obese individuals were more likely to receive medication. Our data are consistent with the other studies.[7,14] Surprisingly, we showed more active participants and those with BMI <18.5 kg/m^2 were less likely to receive medications. Perception of the seriousness of illness and stronger beliefs of the necessity of medications contribute significantly to adequate adherence.[22] Patients with comorbidities, in our study, were more likely to be treated, which might be attributable to self-awareness of CVD risk and closer attention of the health system to these patients. On the other hand, a misconception of self-health-estimation (i.e., individuals who felt healthy e.g., young, thin, or active patients) is a determinant of underuse of effective drugs. Interestingly, the effects of physical activity and BMI were observed only in illiterate patients (Table 3).

We determined the association of wealth and education with the higher use of protective drugs, consistent with prior studies.[7,13,14] A study showed that poverty is the most important determinant of cardiovascular drug adherence.[13] A systematic review indicated that groups with low education and income are at higher risk of cardiovascular mortality and morbidity. Poor adherence and incorrect medication are potential mechanisms

linking them with CVDs.[23]

Similar to the PURE study,[7] current smokers in our study were less likely to receive medication. The PURE study researchers concluded current smoking after CVDs with low medication use, suggesting that this group of patients might not be willing to use any behavioral or medication program.[7] Our finding revealed that this effect was significant only in illiterate patients (Table 3). So, health education, especially comprehensive multidisciplinary cardiac rehabilitation/secondary prevention programs,[3] may be useful in this group of patients. Moreover, the American Heart Association insists that medical training to achieve competency in lifestyle counseling is an essential foundation for prevention and treatment of CVDs that will improve lifestyle counseling competency among future physicians.[24]

Data about the effect of time since diagnosis on medication use are inconsistent.[9,16] A systematic review found that medication adherence was better in countries implementing universal health care.[8] In our study, there was an increase in the use of medication with duration of diseases even after adjustment for age, gender, place of residence and education, but it was attenuated in the full multivariate model. Eighty percent of participants in our study were from rural areas. Iranian rural primary health-care system (the Behvarz system)[25] could be effective in maintaining medication utilization with time.

Limitations and Strengths

Although a proportion of participants with self-reported CVDs might not have had these conditions, previous studies showed the validity of this type of evaluation.[7] For example, in a report from the GCS study, the specificity of self-reported diabetes mellitus was 97.6%.[26] So, participants who reported IHD or stroke probably had the diseases. Patient self-report is a simple, inexpensive, and acceptable method of measuring medication use.[27] In our study, however, trained interviewers, including a physician, used face-to-face interview and checked participants' medical documents and drugs objectively if they were presented.

We did not have data about hemorrhagic or obstructive types of stroke in order to report drug utilization (especially a-PLTs) separately. When we limited our analysis only to those with IHD, the results did not change (Table 1).

A meta-analysis showed that use of medications in CVDs is not greatly dependent on the class of medication prescribed.[9] In our study, as utilization of all preventive medications was poor and not specifically related to the class of agent, we considered general, rather than class-specific, predictors of medication use. Moreover, predictors of specific medication use were almost similar (Table S4).

To our knowledge, this is the only large community-based independent report of secondary prevention drug use from Iran. This study provides a more realistic estimation of cardiovascular drug use than hospital or clinic-based studies.

To improve guideline adherence for secondary prevention of CVDs, development of innovative secondary prevention programs that could involve non-physician health workers, use of fixed-dose combination therapy (poly-pill),[28] better education of both physicians and patients,[6,24] and enhancement of accessibility to systematic cardiac rehabilitation/secondary prevention services[29,30] have been recommended. It seems that primary health care system with the use of poly-pill can play a more effective role in the secondary prevention, especially in this population with less than 8% appropriate drug use. Quality promotion of secondary prevention can be an essential part of "25 by 25" goal (i.e., 25% reduction of premature death from non-communicable diseases by 2025) of the World Health Organization.[31]

Conclusion

Our study showed the considerable gap in medication use for secondary prevention of CVDs in Northeast of Iran. Younger age especially women, poverty, illiteracy, living in rural areas, active smoking, lower BMI and higher physical activity are determinants of low medication use.

Authors' Contribution

MN, RM, FK, AP, and HP contributed to the conception and design. MN, SGS, MS, HB, and FK contributed to the acquisition, analysis, or interpretation of data. MN drafted the manuscript. SGS, RM, FK, MS, AP, HP, and HB critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

The ethical review boards of the Digestive Disease Research Institute of Tehran University of Medical Sciences, the US National Cancer Institute and the International Agency for Research on Cancer approved the study protocol.[11]

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Supplementary File

Table S1. Baseline characteristics of participants with and without

CVDs in the Golestan Cohort Study.

Table S2. Characteristics of individuals with CVDs based on the number of main drugs taken in the Golestan Cohort Study (n = 3371).

Table S3. Factors associated with ≥ 2 main drug use in CVDs in the Golestan Cohort Study (n = 3371).

Table S4. Factors associated with use of specific drugs in CVDs in the Golestan Cohort Study (n = 3371).

Figure S1. Drug use in participants with ischemic heart disease or stroke based on main drug types. Classifications by A) age; B) gender; C) place of residence; D) education; E) hypertension; F) Diabetes mellitus; G) Body mass index; H) physical activity and I) wealth score were adjusted for all variables in the figure, current smoking, and duration of disease. a–PLTs: anti–Platelets; BBs: beta–Blockers; ACE–I/ARBs: Angiotensin–Converting Enzyme Inhibitors or Angiotensin Receptor Blockers. For drug counting, see Table 1.

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