American Journal of Cardiovascular Disease Research, 2024, Vol. 9, No. 2, 10-16
Available online at http://pubs.sciepub.com/ajcdr/9/2/1
Published by Science and Education Publishing
DOI:10.12691/ajcdr-9-2-1

Unlocking the Puzzle: Sex, Hypertension, and SGLT2 Inhibitors - Determinants of LDL-C Target Achievement in Coronary Heart Disease

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Received April 28, 2024; Revised May 30, 2024; Accepted June 06, 2024

Abstract **Background:** - Globally, cardiovascular diseases (CVD) are the primary cause of death. According to estimates, ischemic heart disease and cerebrovascular illnesses were responsible for 85% of 18 million CVD-related fatalities that occurred globally in 2017. One of the main causative risk factors for atherosclerotic cardiovascular disease is elevated low-density lipoprotein cholesterol (LDL-C). LDL particles can migrate from plasma into the subendothelial region of the artery, where they induce inflammation and lead to the development of atherosclerotic plaques. Thus, LDL-C lowering should be tailored to reach the target objective suggested by guidelines to reduce cardiovascular disease risk. **Objective:** -Assessment of low-density lipoprotein cholesterol target attainment and associated factors among patients with established coronary heart disease at the cardiology clinic, Tikur Anbessa Specialized Hospital. **Methods:** - Institutional-based retrospective cross-sectional study design was conducted from August 2023 to October 2023. In this study, among 240 planned participants, 221 participants were extracted, making a chart retrieval rate of 91.7%. Data analysis was done by using SPSS version 26. Multiple regression was applied to identify associated factors. **Result:** - In this study, about two-thirds of the participants were male, and more than one-third were between the ages of sixty-one and seventy. The level of LDL-C target attainment was 41%. The factors significantly associated with the LDL-C target attainment were male sex (AOR=1.8, 95%CI=1.44, 3.42), hypertension (AOR=0.57, 95%CI=0.31, 0.91), and taking SGLT2 inhibitors (AOR=1.5, 95%CI=1.37, 4.85). **Conclusion:** The level of LDL-C target attainment was low. Male sex and taking sodium-glucose transporter 2 (SGL2) inhibitors were favorable factors, but hypertension was associated with a low level of LDL target attainment.

Keywords: *low-density lipoprotein, cholesterol target, coronary heart disease*

Cite This Article: Desalegn Aychiluhm Abate, Senbeta Guteta Abdissa, Zekarias Seifu Ayalew, Gebeyehu Tessema Azibte, and Zelalem Belay Ayele, "Unlocking the Puzzle: Sex, Hypertension, and SGLT2 Inhibitors - Determinants of LDL-C Target Achievement in Coronary Heart Disease." *American Journal of Cardiovascular Disease Research*, vol. 9, no. 2 (2024): 10-16. doi: 10.12691/ajcdr-9-2-1.

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death globally. According to estimates, ischemic heart disease and cerebrovascular illnesses accounted for 85% of the estimated 18 million CVD-related deaths worldwide in 2017 [1]. About one-third of mortality has decreased as a result of the adoption of healthy lifestyles and pharmaceutical therapies [2,3]. CVD remains the most common cardiac condition seen by cardiologists, affecting roughly half of all heart disease patients [4].

Elevated LDL-C is a significant risk factor for atherosclerotic cardiovascular disease (ASCVD) because LDL particles can form atherosclerotic plaques, which can rupture and lead to ischemia [5,6]. In China, patients with established ASCVD are regarded as extremely high risk, with an LDL-C treatment target of below 70 mg/dL [7]. Lowering LDL-C is crucial for reducing ASCVD risk in adults. However, the recent European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines advocate for even more aggressive goals: less than 70 mg/dL for high-risk ASCVD patients, less than 55 mg/dL for very high-risk or those with established ASCVD; and less than 40 mg/dL for very high-risk patients who have had a second vascular event within two years [8].

Despite progress in lowering LDL-C and advancing preventive measures, a significant gap remains between treatment goals and achieving LDL-C targets. [9,10,11]. In Europe, ASCVD accounts for nearly half of all deaths [12]. While managing ASCVD benefits from a long-term, team-based approach, many patients still struggle to reach

their LDL-C goals [13]. This highlights the need for improvement in LDL-C management.

Global studies showed a substantial gap between LDL-cholesterol treatment goals and target achievement. The Dyslipidemia International Study (DYSIS) found that only 21.7% of 44,015 very high-risk patients in 30 countries met their LDL-C target of less than 70 mg/d [14]. Similarly, an African study reported that 71% of patients did not reach their target LDL-C levels [15].

There is a lack of data on how Ethiopian patients with established coronary heart disease achieve LDL-C goals according to recent guidelines, particularly for high-risk patients. Therefore, this study aimed to evaluate LDL-C target achievement and related factors in patients with established coronary heart disease at the cardiology clinic of Tikur Anbessa Specialized Hospital.

2. Methods and Materials

Study design

An institutional-based cross-sectional study was conducted at the cardiology clinic of Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia, from August 01, 2023–to October 31, 2023, to assess LDL-C target attainment and associated factors among patients with established coronary heart disease. All patients with established coronary heart disease who had cardiac clinic follow-up at TASH during the study period fulfilled the inclusion criteria included in the study. Patients on Lipid-lowering drugs for less than three months and incomplete data were excluded from the study.

Sampling Determination and Sampling Procedures

All patients who fulfilled the eligibility criteria were included in the study, and there was no need for sample size calculation sampling procedures.

Operational definitions

- **CHD:** ACS and CCS
- **ACS:** STEMI, NSTEMI), or unstable angina
- **CCS:** Clinical diagnosis by treating cardiologist (cardiology fellow or cardiologist)
- **LDL Target Attainment:** We will consider patients to have achieved their LDL target if their LDL level is below 70 mg/dL after three months of statin treatment.
- **Statin Therapy Intensity:** Statin medications are categorized based on their expected LDL-C reduction:
  - **Low-intensity:** This includes daily treatment with Simvastatin 10mg, which is expected to reduce LDL-C by less than 30%.
  - **Moderate-intensity:** This includes daily treatment with Simvastatin 20-40mg, Atorvastatin 10-20mg, or Rosuvastatin 5-10mg, and is expected to reduce LDL-C by 30 to 50%.
  - **High-intensity:** This includes daily treatment with Atorvastatin 40-80mg or Rosuvastatin 20-40mg and is expected to reduce LDL-C by 50% or more.
- **Smoker:** history of cigarette smoking (ever smoking)

Study Procedures

The questionnaire was developed by compiling several questions from similar study materials and reviewing relevant literature and articles that could address the study's objective. A questionnaire pre-test was carried out, and modification was done based on feedback from the pre-test. The questionnaire generally included information about sociodemographic characteristics, comorbidity, concomitant drugs, and laboratory results. Data was collected from electronic medical records.

Statistical Analysis

Data was checked and cleaned for completeness and consistency, then coded, entered, and analyzed using SPSS version 26. Simple descriptive analysis was used to show the frequencies and percentages of variables. Bivariate logistic regression examined the association between independent and dependent variables. Those with a p-value less than 0.25 were transferred to multivariate logistic regression. Variables with a p-value <0.05 were declared as having statistical significance.

3. Results

Socio-demographic characteristics of the study participants

In this study, among 240 planned participants, 221 participants were extracted, making a chart retrieval rate of 91.7%. Most study participants were 61-70 years old, with a mean and SD of 59.64±10.86 years. The majority (63.3%) of the study participants were male, and only 1.3% had a smoking history, as shown in Table 1.

Table 1. Socio-demographic characteristics of the study participants with established coronary heart disease at a cardiology clinic, TASH, 2023

Variable	frequency	Percent
Age in years		
30-40	11	5.0
41-50	38	17.2
51-60	57	25.8
61-70	82	37.1
>70	33	14.9
Sex of the study participants		
Male	140	63.3
Female	81	36.7
History of cigarette smoking		
Yes	3	1.3
No	218	98.7

characteristics of coronary heart disease

In this study, 78.3% of the study participants had chronic coronary syndrome at diagnosis, 73.3% of the participants had 1-5 years duration of coronary heart disease, and 11.3% of the CHD patients had primary coronary intervention procedures, as shown in Table 2.

characteristics of comorbid disease

Most (88.7%) of the study participants had comorbid disease. Of those who had the comorbid disease, 63.8% of them had hypertension, 49% of them had diabetes mellitus, 15.8% of them had CKD, and 12.8% had heart failure, as shown in Table 3.

Table 2. The characteristics of coronary heart disease

Variable	Frequency	Percent
Types of coronary heart disease at diagnosis		
Acute coronary syndrome	48	21.7
Chronic coronary syndrome	173	78.3
Duration of coronary heart disease in years		
<1	31	14.0
1-5	162	73.3
>6	28	12.7
The primary coronary intervention was done		
Yes	25	11.3
No	196	88.7

Table 3. The comorbid disease characteristics of the study participants

Variable	frequency	Percent
Presence comorbid disease		
Yes	196	88.7
No	25	11.3
Specific types of comorbid disease (n=196)		
DM	96	49
Hypertension	125	63.8
Chronic kidney disease	31	15.8
Heart failure	25	12.8
Chronic lung disease	8	4.1
Stroke	14	7.1
PAD	6	3.1
AF	15	7.7
HIV	5	2.6
Dyslipidemia	20	10.2
Pre-diabetes	7	3.6
LV Apical thrombus	11	5.6
BPH	7	3.6
DVHD	4	2.1
Gouty Arthritis, Osteoarthritis	7,3	3.5,1.5
supraspinatus tendon tear, cervical radiculopathy	2	1.1
Metabolic Syndrome	2	1.1
NAFLD	3	1.5
Obesity	8	4.1
Polycythemia Vera	3	1.5
PTE	2	1.1
Thyrotoxicosis	2	1.1
Vascular Dementia	3	1.5
Others	21	10.7

4. Medications

In this study, 93.2% of the study participants took antiplatelets, and of those taking antiplatelets, 87.8% were receiving aspirin. Almost ninety-three percent of the participants received beta-blockers. Of those taking beta blockers, 76.6% used metoprolol, 93.7% of the study participants took ACEI, and 47.5% took spironolactone. Almost thirty-nine percent of the study participants took SGL2 inhibitors, 18.6% received Calcium channel blockers, and 33.5% took oral glucose-lowering agents.

Characteristics of lipid-lowering drugs

All the study participants took lipid-lowering drugs, all lipid-lowering drugs were statin, and 97.3% took atorvastatin. Ninety-two percent of the participants take a high-intensity statin, and 73.8% of the participants were taking a statin for 1-5 years (Table 4).

Table 4. Characteristics of lipid-lowering drugs

Variable	Frequency	Percent
Types of statins		
Atorvastatin	215	97.3
Rosuvastatin	4	1.8
Simvastatin	2	.9
Dose of statin		
Moderate intensity	17	7.7
High intensity	204	92.4
Duration of statin treatment in years		
<1	32	14.5
1-5	163	73.8
>5	26	11.8

Level of LDL C target attainment after statin treatment

In this study, a lipid profile was done after 24 months of treatment for 60.2% of participants; 6.2% had ≥200 total cholesterol, and 21.3% had ≥150 triglycerides, as shown in Table 5 and Figure Overall, only 41% of patients achieved LDL-C target.

Table 5. Characteristics of the lipid profile done After Diagnosis of Coronary heart disease

Variable	frequency	Percent
Time of lipoprotein profile done in months		
At three months	20	9.0
At six months	11	5.0
At nine months	9	4.1
At 12 months	21	9.5
At 18 months	9	4.1
At 24 months	18	8.1
After 24 months	133	60.2
Total cholesterol		
<200	207	93.7
≥200	14	6.3
Triglyceride		
<150	174	78.7
≥150	47	21.3
HDL		
≤40	133	60.2
>40	88	39.8
LDL		
<70	91	41.2
≥70	130	58.8
Creatinine		
<1.2	4158	78.2
≥1.2	44	21.8
Urea		
<20	48	27
≥20	130	73

Factors associated with low-density lipoprotein target attainment.

As shown in Table 6 below, the study participant's sex, hypertension, and taking SGL2 inhibitors were associated with LDL-C target attainment on bivariate logistic regression. The multivariate logistic regression revealed that being male was associated with a1.6 1.6-fold increase in LDL-C target attainment compared to females (AOR=1.6, 95%CI=1.24, 3.42). Hypertension was

associated with a 43% less likelihood of LDL-C target attainment (AOR=0.57, 95%CI=0.31, 0.91). Study participants who took SGLT2iinhibitor had a 1.5-fold increase in LDL-C target attainment compared to those not taking (AOR=1.5, 95% CI=1.37, 4.85).

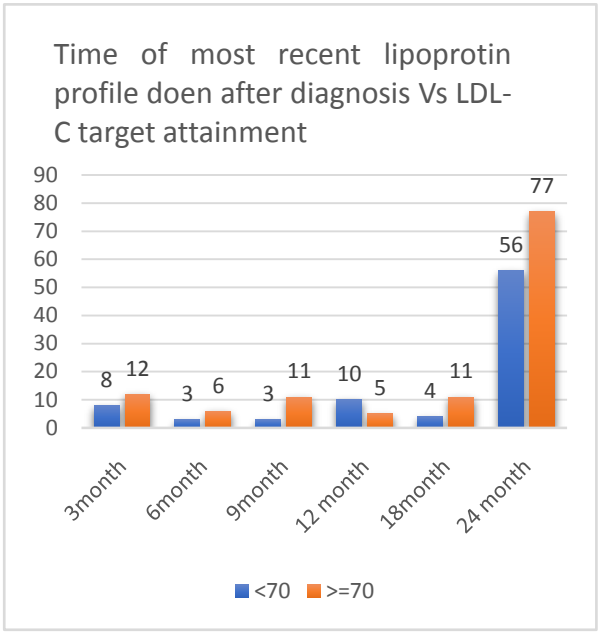

Figure 1. Time of most recent LDL determination and LDL-C target attainment

Table 6. The bivariate and multivariate logistic regression of association between the independent variable and LDL-C target attainment among established coronary heart disease patients at TASH cardiac clinic, 2023

Variable	LDL-C target attainment		COR with 95%CI	p-value	AOR with 95%CI
	<70	≥70			
Sex of the participants					
Male	65	75	1.8(1.03, 3.25)	0.045*	**1.6(1.24, 3.42)**
Female	26	55		1	
Primary coronary innervation					
Yes	14	11		1	
No	77	119	0.51(0.22, 1.18)	0.404	0.65(0.23, 1.80)
Hypertension					
Yes	82	114	0.57(0.31, 0.92)	0.048*	**0.57(0.31, 0.906)**
No	9	16			
Dyslipidemia					
Yes	5	15	0.43(0.15, 1.23)	0.243	0.52(0.17, 1.57)
No	77	99		1	
Beta-blocker					
Yes	86	119	1.6(0.53, 4.74)	0.658	1.2(0.37, 3.92)
No	5	11		1	
SGL2 inhibitor					
Yes	43	43	2.7(1.32, 10.96)	0.038*	**1.5(1.37, 4.85)**
No	48	87		1	
Statin dose					
Moderate intensity	6	11	0.76(0.27, 2.15)	0.512	0.65(0.17, 2.39)
High intensity	85	119		1	

*Statistically significant association

5. Discussion

This study found that the level of LDL-C target attainment was 41%. The factors significantly associated with the LDL-C target attainment were male sex (AOR=1.8, 95%CI=1.44, 3.42), hypertension (AOR=0.57, 95%CI=0.31, 0.91), and taking SGLT2 inhibitors (AOR=1.5, 95%CI=1.37, 4.85).

Hypertension, diabetes mellitus, and CKD were the most common co-morbidities in our study, similar to studies done in Kenya where hypertension, dyslipidemia, and diabetes mellitus were the most prevalent diseases among patients with coronary heart disease [16]. The difference in dyslipidemia may be because our study participants had a missing baseline lipid profile.

The finding of this study revealed that 41% of the study participants had good LDL-C target attainment. This finding was higher than the study done in the European Society of Cardiology (36.9%) [17], Thailand (27%) [18], South Africa 19 % [19], Kenya 17.1 % [16], but this is lower than the studies done in Sweden and Canada 52 % [20], Spain 56.7 % [21] and Korea [22] ,and a study done by Groenhaf et al. [23]. These differences in LDL-C target attainment rate could be due to different factors related to the study population, such as age, sex, ethnicity, and overall cardiac condition. These factors can all influence how well someone responds to treatment.

Male study participants had a 1.8-fold increase in LDL-C target attainment compared to females (AOR=1.8, 95%CI=1.44, 3.42). This finding was similar to a study done by Groenhaf et al. and a study done in China [23,24]. This may be due to the observation that LDL-C target attainment may differ between males and females in some cases and could be influenced by various factors, especially hormonal influence [25]. In other studies, statins are less effective in females than in males and are associated with more side effects and poor adherence due to the pronounced side effects. The other explanation for this unfavorable target attainment for females is that female patients have additional comorbidities than males [26].

In our study, participants with hypertension had 43% LDL-C off target compared to those patients without hypertension (AOR=0.57, 95%CI=0.31, 0.91). This finding is comparable with previous studies [19, 27]. This may be due to patients with hypertension who may have metabolic syndrome with dyslipidemia. In many previous studies, hypertension and other metabolic disorders are associated with increased failure to achieve target LDL [22]. Patients with metabolic syndrome and hypertension had more difficulty achieving the target LDL levels [19]. It is more difficult to achieve target cholesterol levels, especially in patients with obesity and hypertension [28].

Our study showed that patients who took SGLT 2 inhibitors had a lower probability of achieving target LDL with an AOR of 1.5 (95% CI: 1.37, 4.85). Dapagliflozin suppresses potent atherogenic LDL-C and increases HDL-C, a favorable cardiometabolic marker. Although LDL-C levels are increased after using dapagliflozin, this was because of increased concentrations of the less atherogenic lb LDL-C. So, these failures to achieve the target number of LDL could be due to elevated 1b LDL-C [29]. SGLT2 inhibitors are effective antihyperglycemic agents by inhibiting glucose reabsorption in the kidney's

proximal tubule. Besides improving glycemic control in patients with type 2 diabetes, they also have additional favorable effects, such as lowering body weight and fat [30]. Even though the exact mechanisms are unknown, recent studies suggest that SGLT-2 inhibitors could provide extra-glycemic benefits in lipid metabolism. It may pronounce lipolysis, normalizing the lipid metabolism and preventing or improving dyslipidemia [31].

Some studies showed that the achievement of target LDL could be affected by different factors such as statin dose and type, patient-related factors, provider-related factors [29]. Treating physicians and concomitant drug use while treating may affect the achievement of target LDL. In contrast, our study found that the intensity of statin was not associated with LDL target attainment.

Managing comorbidities and achieving target levels of LDL-C are crucial to managing cardiovascular health. In our study, most (88.7%) participants had comorbid disease. Of those having comorbid disease, 63.8% of them had hypertension, 49% of them had diabetes mallets, 15.8% of them had CKD, and 12.8% had heart failure; the target levels of LDL can vary based on an individual's risk factors and existing health conditions. Medical guidelines, such as those from organizations like the American College of Cardiology (ACC) and the American Heart Association (AHA), provide recommendations for LDL-C target levels based on risk categories. These guidelines are regularly updated to reflect the latest research findings. Accordingly, in these guidelines, LDL-C <70 was used for target attainment [32].

Strength and limitation

It is the first study to explore secondary LDL-C target attainment in Ethiopia. However, the retrospective nature of the study design presents a limitation. Additionally, lacking baseline LDL-C levels for most patients might inflate the target attainment rate. Finally, while the study considered LDL-C values updated within the past six months, it did not account for the specific duration of statin treatment each participant received. This lack of information could influence the interpretation of target achievement.

6. Conclusion

In this study, the level of LDL-C target attainment was 41%, which is better than the studies done in Kenya and South Africa but lower than those done in Sweden, Canada, and Spain. Factors significantly associated with LDL-C target attainment were being male (AOR=1.8, 95%CI=1.44, 3.42), and Hypertension (AOR=0.57, 95%CI=0.31, 0.91) and taking SGLT2 Inhibitors (AOR=1.5, 95%CI=1.37, 4.85).

Abbreviations

ACEI -angiotensin-converting enzyme inhibitor
ACS -acute coronary syndrome
AF -atrial fibrillation
AOR -adjusted odds ratio
ASCVD -atherosclerotic cardiovascular disease
BPH -benign prostatic hyperplasia
CCS-chronic coronary syndrome
CHD -coronary heart disease
CI -confidence interval
CKD -chronic kidney disease
COR -crude odds ratio
CVD -cardiovascular diseases
DM -diabetes mellitus
DVHD -degenerative valvular heart disease
DYSIS -Dyslipidemia International Study
EAS -European Atherosclerosis Society
ESC -European Society of Cardiology
HDL-C -high-density lipoprotein cholesterol
HIV -human immunodeficiency virus
LDL-C -low-density lipoprotein cholesterol
LV -left ventricle
NAFLD -nonalcoholic fatty liver disease
NSTEMI -non-ST-segment elevation myocardial infarction
PAD -peripheral arterial disease
PTE-pulmonary thromboembolism
SD- standard deviation
SGLT2 inhibitor -sodium-glucose cotransporter-2 inhibitor
STEMI -ST-segment elevation myocardial infarction
TASH -Tikur Anbessa Specialized Hospital

Declarations

Author Contributions: conceptualization, Methodology, Investigation, Analysis, and Writing of the manuscript- Desalegn Aychiluhm Abate, Senbeta Guteta Abdissa, Zekarias Seifu Ayalew.

Methodology, Data curation, Drafting, Interpretation, and Supervision and edition of the manuscript- Gebeyehu Tessema Azibte, Zelalem Belay Ayele.

All authors revised the manuscript and have approved the final version of the manuscript.

Funding: This research received no external funding.

Ethical Clearance

Institutional Review Board Statement: The study was conducted by the Declaration of Helsinki and approved by the Institutional Review Board of Addis Ababa University, College of Health Sciences.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article.

Acknowledgments: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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