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Suboptimal Heart Rate Control Despite Beta-Blocker Use in Coronary Artery Disease: Evidence from the Fasa PERSIAN Cohort

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Running title: Heart rate control in the Fasa PERSIAN Cohort Study

Abstract

Background: Elevated resting heart rate (HR≥70bpm) is a strong prognostic factor in coronary artery disease (CAD). Although beta-blockers are guideline-recommended first-line therapy, their real-world effectiveness in controlling HR remains unclear, particularly in Middle Eastern populations. This study investigated HR distribution, its correlates, and the association between HR-lowering drugs and HR control in a large Iranian cohort.

Methods: We analyzed 10,138 adults aged 35-70 years from the Fasa PERSIAN Cohort with sinus rhythm ECGs. HR was obtained from resting 12-lead ECGs. Logistic regression examined associations between demographic, clinical, and pharmacological factors and HR<70bpm. Multivariable models were further stratified by CAD and hypertension (HTN) subgroups.

Results: A total of 7119 subjects (mean age 48.6±9.3 years; 43.4% men) entered this study, of which 803 (11.3%) had CAD. Overall, 48.6% had HR ≥70bpm. Beta-blockers were used by 9.4% of participants (40% of CAD patients). Despite therapy, 47.2% of beta-blocker users had HR ≥70 bpm. In univariable analysis, male sex (OR 4.07, 95% CI 3.68–4.50), current smoking (OR=2.59,95%CI:2.28–2.93), and higher physical activity were strong predictors of HR<70 bpm, while diabetes, hypertension, and higher BMI were inversely associated. In multivariable analysis, beta-blocker use was associated with HR<70 bpm in the total population (OR 1.64, 95% CI

1.36–1.98) and in HTN patients (OR=2.35,95%CI:1.72–3.22), but not in CAD or CAD+HTN subgroups.

Conclusion: Nearly half of CAD patients failed to achieve HR<70 bpm despite beta-blocker therapy, highlighting suboptimal control. Beta-blockers were effective only in patients with HTN but not in CAD or CAD+HTN groups. These findings emphasize the need for tailored therapeutic strategies and physician education to improve HR management in CAD.

Keywords: Beta-blockers; Heart rate; Coronary artery disease; Iran

Introduction

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide, with its burden rising rapidly in low- and middle-income countries undergoing epidemiological transition from infectious to non-communicable diseases due to unhealthy lifestyle shifts and healthcare improvements (1). According to the Global Burden of Disease 2021 study, ischemic heart disease remains the leading cause of death in Iran, with an increasing trend over the past two decades (2, 3). Between 1990 and 2021 the absolute number of cardiovascular disease cases in Iran more than doubled (from 2.9 to 8.3 million) (2), reflecting a dramatic rise in CAD burden in this population.

Among prognostic markers in CAD, elevated resting heart rate (HR) is well established as a predictor of myocardial ischemia, adverse vascular events, and mortality (4-8). In a large analysis of stable CAD patients, every 10-beat/min increase in resting HR was associated with about an 8% higher risk of major cardiovascular events, and patients with resting HR ≥70 bpm had ~40% higher all-cause mortality compared to those with lower HR (9). High resting HR independently predicts cardiovascular death even after adjusting for other risk factors (10). These data underscore that slowing the HR can reduce myocardial oxygen demand and ischemia, making HR reduction an important therapeutic goal (11).

Accordingly, early pharmacologic intervention to lower HR is central in CAD management. Beta-blockers are fundamental first-line agents in stable CAD because their negative chronotropic and inotropic effects slow

the HR and lower myocardial oxygen consumption (11, 12). By blocking cardiac β-adrenergic receptors, beta-blockers slow atrioventricular conduction and reduce cardiac contractility (11, 13). International guidelines endorse beta-blockers for both angina symptom relief and secondary prevention in CAD (for example, after myocardial infarction) (11). In theory, their long-term effect should be improved survival in CAD patients.

However, the long-term survival benefit of beta-blockers in modern CAD populations has been questioned. Recent meta-analyses have found no reduction in major adverse cardiovascular events among stable CAD patients without prior myocardial infarction treated with beta-blockers (12). In practice, many patients on beta-blockers do not achieve the recommended HR targets. For example, in a clinical registry of patients with angina and hypertension, only 15.5% achieved the target resting HR of 55–60 bpm despite beta-blocker use (14). This suboptimal rate control may explain in part why the expected mortality benefit of beta-blockade is often not observed in observational studies. In addition to observational studies and stable CAD patients, a recent randomized trial (15) demonstrated that among patients discharged after acute myocardial infarction with preserved left-ventricular ejection fraction, continuation of beta-blocker therapy did not significantly reduce long term outcomes such as all-cause mortality, recurrent infarction, or hospitalization for heart failure, indicating the absence of prognostic benefit with beta-blocker use.

Most evidence on beta-blocker effects comes from Western cohorts, but prescribing patterns and drug responses can vary by region. Notably,

cardiologists in different countries use these drugs very differently: for example, investigators observed that beta-blockers “have a long tradition in Sweden” but “no major tradition” in Denmark (16). Such geographic variation in beta-blocker use underscores the need to study heart rate control and HR-lowering therapies in diverse populations.

To address these gaps, we analyzed data from the population-based Fasa PERSIAN Cohort. Our specific objectives are to: 1) describe the distribution of resting HR in the general population and its clinical correlates. 2) assess the prevalence and dosing patterns of HR-lowering medications, especially beta-blockers. 3) evaluate the association between HR-lowering drug use and achieving target HR in the overall cohort and among individuals with CAD and/or hypertension.

Materials and Methods

Study population

This cross-sectional analysis was conducted within the Fasa PERSIAN Cohort, a component of the nationwide PERSIAN (Prospective Epidemiologic Research Studies in Iran) cohort. The Fasa site recruited approximately 11,000 adults aged 35–70 years, residing in Sheshdeh, Fars Province, Iran (17). For the present study, we included participants who had a valid 12-lead electrocardiogram (ECG) recorded at baseline (n = 7,157). We excluded individuals with non-sinus rhythm or missing data on HR or medication use (n = 38), resulting in a final analytic sample of 7,119 participants. Body composition data were available for a subset of 3,217 participants; analyses requiring these variables were conducted on this subset and are reported separately. All participants provided written informed consent, and the study protocol was approved by the Ethics Committee of Fasa University of Medical Sciences.

Data collection and baseline characteristics

Trained interviewers collected demographic information (age, sex, ethnicity), lifestyle variables (smoking status, physical activity), and medical history (diabetes, hypertension, coronary artery disease [CAD], myocardial infarction, stroke, chronic lung disease, thyroid disease, and psychiatric disorders) using a standardized electronic questionnaire. Self-reported medication use during the two weeks prior to enrolment was recorded and verified by direct inspection of medication packages brought by participants.

Clinical and laboratory measurements

Anthropometry and body composition: Height and weight were measured using a stadiometer and digital scale (precision 0.1 cm and 0.1 kg). BMI was calculated as kg/m^2. Hip circumference was measured at the level of the greatest gluteal protuberance using a non-elastic tape.

Blood pressure: After ≥15 minutes of seated rest, two blood pressure readings were obtained at 5-minute intervals, and the average systolic and diastolic pressures were recorded.

Biochemical assays: Venous blood samples were collected after 10–14 hours of overnight fasting. Fasting blood glucose (FBG) was determined using glucose oxidase assay. Serum total cholesterol, triglycerides, and HDL cholesterol were measured with a Mindray BS380 autoanalyzer (Mindray Medical International, China). LDL cholesterol was calculated using the Friedewald formula.

Physical activity: Physical activity was assessed using a validated questionnaire. The duration (hours/day) of different activities was multiplied by their respective metabolic equivalent (MET) value, and summed to derive total physical activity (MET/24h).

Electrocardiography and heart rate: Resting 12-lead ECGs were recorded after 15 minutes of supine rest using the Cardiax® system. Participants were instructed to breathe normally and remain still and awake. Resting HR was automatically calculated from the 10-second ECG recording.

Definition of CAD and hypertension

CAD was defined as a self-reported history of myocardial infarction, angina, coronary revascularization (PCI or CABG), or physician-diagnosed CAD. Hypertension (HTN) was defined as a self-reported history of hypertension, antihypertensive medication use, or systolic/diastolic BP ≥140/90 mmHg at baseline.

Main independent variables assessment: cardiovascular medications

Medication classes of interest included beta-blockers (BB), calcium channel blockers (CCB; dihydropyridine [DHP] and non-DHP), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II receptor blockers (ARB). For beta-blockers, specific agents (atenolol, carvedilol, metoprolol tartrate, metoprolol succinate, propranolol) and mean daily doses were recorded (**Table 2**). However, detailed information on dose titration strategy, treatment duration, and adherence was not available in the cohort. Medication data reflected self-reported regular use within the preceding two weeks, verified through inspection of medication packages. Therefore, analyses reflect cross-sectional exposure rather than longitudinal dose-adjusted therapy. To assess potential HR-lowering combinations, drug classes were analyzed individually and in common combinations (e.g., BB only, BB + CCB, BB + ARB).

Dependent variable definition

The primary outcome was resting HR <70 bpm versus ≥70 bpm, based on prior prognostic studies and guideline recommendations for CAD risk

stratification. Secondary analyses examined HR as a continuous outcome (bpm).

Statistical analysis

Baseline characteristics were summarized as means ± SD for continuous variables and counts (percentages) for categorical variables. Group differences between medication users and non-users were compared using chi-square tests (categorical variables) or t-tests (continuous variables).

Logistic regression models estimated odds ratios (OR) with 95% confidence intervals (CI) for the association of demographic, clinical, biochemical, and lifestyle factors with HR <70 bpm. Multivariable logistic regression models were fitted to evaluate associations between medication classes (alone or in combination) and HR <70 bpm in the total population and in subgroups with CAD, HTN, or both. Additional stratification by other comorbidities (e.g., diabetes, thyroid disorders, psychiatric disease) was considered; however, these conditions are not clinical indications for beta-blocker initiation, nor are they expected to exert a direct pharmacologic interaction on heart-rate reduction. Furthermore, the number of participants with such comorbidity combinations while also receiving beta-blockers was inadequate for stable multivariable modelling. Because beta-blockers are prescribed primarily for CAD, hypertension, arrhythmias, or heart-failure–related indications, subgroup analyses were therefore limited to CAD, HTN, and CAD+HTN populations, where subgroup definitions are clinically meaningful and sample sizes allow reliable estimation.

Models were adjusted a priori for age, sex, ethnicity, smoking status, systolic and diastolic BP, BMI, lipid profile (HDL, LDL, triglycerides, total cholesterol), fasting blood glucose, physical activity, medical history (diabetes, hypertension, CAD, stroke, chronic lung disease, thyroid disease, psychiatric disorders), and family history of CVD, diabetes, and hypertension.

In secondary analyses, linear regression was used to estimate the association of each drug class with HR as a continuous outcome. Model assumptions were checked using residual plots and variance inflation factors. Statistical significance was defined as two-sided $P < 0.05$. Analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Figures were prepared in GraphPad Prism version 8.0.

Results

Study population

A total of 7,119 participants with interpretable ECGs were included in the analysis. The mean age was 48.6 ± 9.3 years, and 43.4% were male. Overall, 671 participants (9.4%) reported regular beta-blocker use (**Table 1**). Of beta-blocker users, 491 (73.2%) were female, suggesting a possible sex-related prescribing pattern that requires adjustment for comorbid conditions to avoid confounding.

Distribution of heart rate

The mean resting HR in the total population was 71.2 ± 12.2 bpm. Approximately half of participants (48.6%) had HR ≥70 bpm, while 51.4% had HR <70 bpm. Among beta-blocker users, 52.8% achieved HR <70 bpm, 39.2% had HR 71–89 bpm, and 8.0% had HR ≥90 bpm (**Figure 1**, **Table 1**).

Beta-blocker use and dosage

Among the total population, atenolol was the most frequently used beta-blocker (3.4%), followed by metoprolol tartrate (2.9%) and propranolol (2.5%). Carvedilol was used by 1.0% and metoprolol succinate by 0.04% of participants. The mean daily dosages were within guideline-recommended ranges only for atenolol (18, 19) (**Table 2**).

Medical history

Compared with the total population, beta-blocker users had a higher prevalence of diabetes (25.0% vs. 12.6%), hypertension (27.3% vs. 20.4%),

cardiovascular disease (62.3% vs. 14.4%), thyroid disease (15.5% vs. 9.1%), and psychiatric disorders (16.5% vs. 9.5%) (all p <0.001). Chronic lung disease was also slightly more common among beta-blocker users (3.0% vs. 1.9%; p = 0.04) (**Table 3**).

Baseline characteristics

On average, beta-blocker users were older (54.5 vs. 48.6 years), had higher systolic (122 vs. 111 mmHg) and diastolic blood pressures (78.8 vs. 74.2 mmHg), higher fasting blood glucose (101.7 vs. 93.4 mg/dL), higher BMI (27.4 vs. 25.7 kg/m²), greater fat mass (23.3 vs. 19.3 kg), and larger hip circumference (101.6 vs. 99.3 cm). They also reported lower physical activity levels (38.0 vs. 41.2 METs). Mean HR was similar between beta-blocker users and non-users (71.2 bpm in both groups) (**Table 4**).

Factors associated with HR <70 bpm (univariable analyses)

In univariable analyses, male sex (OR 4.07, 95% CI 3.68–4.50), current smoking (OR 2.59, 95% CI 2.28–2.93), and higher physical activity (per 5 MET increase, OR 1.42, 95% CI 1.35–1.49) were positively associated with HR <70 bpm. In contrast, higher BMI, fasting blood glucose, lipid parameters (LDL, TG, TC), fat percentage, fat mass, hip circumference, hypertension, diabetes, thyroid disease, and psychiatric disorders were inversely associated with HR <70 bpm (all p <0.05). Beta-blocker use itself was not significantly associated with HR <70 bpm (OR 1.06, 95% CI 0.90–1.24; p = 0.468) (**Table 5**).

Multivariable analyses

In multivariable logistic regression (**Table 6**), beta-blocker use was associated with higher odds of achieving HR <70 bpm in the total population (OR 1.64, 95% CI 1.36–1.98; p <0.001). Similarly, combined use of beta-blockers and CCBs was associated with HR <70 bpm (OR 1.65, 95% CI 1.08–2.51; p = 0.020).

In subgroup analyses, no significant associations were found among CAD patients. In participants with hypertension, beta-blocker use (OR 2.35, 95% CI 1.72–3.22; p <0.001), beta-blocker plus ARB (OR 1.95, 95% CI 1.03–3.68; p = 0.038), and beta-blocker plus CCB (OR 2.18, 95% CI 1.02–4.74; p = 0.049) were significantly associated with HR <70 bpm. No significant associations were observed in participants with both CAD and hypertension.

Multivariable Associations of Drug Combinations with Heart Rate Control

In multivariable logistic regression analyses, we examined the associations between various drug classes and HR <70 bpm, adjusting for key demographic, clinical, and lifestyle factors. The results were stratified by the total population, CAD, and hypertension (HTN) subgroups.

For the total population, beta-blocker (BB) use was associated with a modest increase in the likelihood of achieving HR <70 bpm (OR: 1.64, 95% CI: 1.36–1.98, P < 0.001). The combination of BB and calcium channel blockers (CCB) was also significantly associated with lower HR (OR: 1.65, 95% CI: 1.08–2.51, P = 0.020). However, combinations of BB with

angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) did not show significant effects (**Table S1**).

In the CAD subgroup, no significant associations were found between any drug class or combination and HR <70 bpm. Despite nearly two-thirds of CAD patients using beta-blockers, HR control remained inadequate in this group, with over 47% still having HR ≥70 bpm.

In the HTN subgroup, beta-blocker use (OR: 2.35, 95% CI: 1.72–3.22, P < 0.001) and combinations of BB with ARB (OR: 1.95, 95% CI: 1.03–3.68, P = 0.038) or BB with CCB (OR: 2.18, 95% CI: 1.02–4.74, P = 0.049) were significantly associated with HR <70 bpm.

Furthermore, multivariable linear regression (**Table S2**) showed that beta-blockers were associated with a reduction in HR in the total population (unstandardized beta: -3.00, P < 0.001), but this effect was less pronounced in CAD (unstandardized beta: -4.10, P < 0.001) and HTN groups.

These findings highlight that while beta-blockers may reduce HR to some extent, their effectiveness is limited in CAD patients, especially in combination with other antihypertensive therapies. This underscores the need for tailored management strategies that take into account patient-specific characteristics such as comorbidities and medication adherence.

Discussion

Our study's main findings were i) Almost half of the subjects had an HR of more than 70 bpm in the total population and CAD subjects. ii) Near 9.4% of subjects were receiving beta-blockers among the total population, and this percentage for CAD subjects was 40%. iii) CCB consumption among the total population and CAD subjects respectively were 4.1 and 16.1%. iv) By multivariable analysis and subsiding the effects of variables associated with the HR, only subjects who were receiving these three kinds of drug combinations (BB only, BB+ARB, and CCB+BB) had a significant OR for having HR <70 bpm just in subjects with HTN. v) Subjects with CAD didn't show any significant OR in any drug combination category for having HR <70 bpm. Our findings have clinical importance as higher HR is associated with poor clinical outcomes (5-7, 20-22). Thus, we observed insufficient HR control by beta-blockers in our population, which may cause a heavy burden on health economics by both expenditures for these medications and more cardiovascular outcomes. As mentioned, HR is an essential clinical prognostic determinant, but its correlates may not be well known. The present study enabled us to evaluate the correlates of elevated HR through univariate and multivariable analysis. Logistic regression with backward selection was used to find independent predictors of HR <70 bpm. Such variables were age, gender, BMI, MET, Medical and family histories of DM, HTN and CVD, blood pressure, ethnicity, TG, Chol, LDL, and FBS.

High resting heart rate often accompanies hypertension (23), so we stratified our cohort into groups with CAD only, HTN only, and both. The prevalence of cardiovascular diseases and HTN in our population has been reported previously (24). Among CAD patients (with or without HTN) we observed no significant association between any β-blocker regimen and achieving HR < 70 bpm, a prognostic cut point in CAD patients (5, 6, 25-27). In fact, although roughly two-thirds of CAD patients received β-blockers, nearly half still had HR > 70 bpm, illustrating that heart rate was inadequately controlled despite therapy. This mirrors the international CLARIFY registry, which found that ~75% of stable CAD outpatients were on β-blockers but “heart rate is insufficiently controlled in many patients” (28). Likewise, the Euro Heart Survey reported that 67% of stable angina patients were treated with β-blockers (29), yet most patients remained above the guideline-recommended target (55–60 bpm). In our study, β-blocker users tended to be older and more often female. The frequency of beta-blockers' use was consistent with the Euro Heart Survey data that reported about two-thirds (67%) of patients with stable angina in Europe were on a beta-blocker (30). Beta-blocker users were older, and the female gender was more frequent (73.2%). These findings were entirely in contrast to the CLARIFY(31) and the REACH(32) projects, which reported beta-blockers users were younger, and there were no differences in gender among users. The gender difference in our population may be due to better medication compliance and drug adherence in female subjects, which Lin et al. suggested in the Iranian population(33) and a review(34) previously.

Current guidelines advocate a resting HR of 55–60 bpm in symptomatic CAD as a target for antianginal therapy, reflecting the anti-ischemic benefits of β-blockade (35, 36). Yet only about 19% of our CAD patients had HR≤60 bpm, far from guideline goals, and in practice many physicians may not aggressively titrate β-blockers to such targets. This may be due to the lack of knowledge of the optimal resting HR among physicians. Steg et al (37) reported that only 22% of patients with anginal symptoms had a HR≤60 bpm. Our observation was also in line with the EuroHeart Survey on angina (38), in which 19% of patients had HR≤62 bpm. Indeed, β-blockers have known beneficial effects (they reduce HR and blood pressure and thereby lower myocardial oxygen demand), and they are indicated for primary and secondary prevention in ischemic heart disease, heart failure, and hypertension (36). Management guidelines for stable angina suggest beta-blockers as the first-line anti-anginal therapy in patients (30, 39), which may be due to their anti-ischemic and anti-anginal effects (40) and improved clinical outcomes (41). However, emerging evidence has questioned their long-term survival benefit in stable CAD. For example, A recent open-label randomized trial published in the New England Journal of Medicine (15) found that among post-MI patients with preserved ejection fraction (LVEF >40%), long-term beta-blocker therapy did not significantly reduce all-cause mortality, recurrent infarction, or heart-failure hospitalization. Although that trial specifically evaluated a post-MI preserved-EF subgroup, its neutral prognostic results parallel our finding that beta-blocker therapy alone does not ensure adequate heart-rate control in real-world CAD populations. These observations are

further supported by a contemporary individual-patient meta-analysis integrating five randomized trials (REBOOT, REDUCE-AMI, BETAMI, DANBLOCK, CAPITAL-RCT) (42), which collectively enrolled nearly 17,800 MI survivors with preserved EF and demonstrated no significant reduction in composite outcomes of death, reinfarction, or heart failure. Together, these high-quality randomized data and our population-level physiologic findings underscore an emerging paradigm: while beta-blockers remain effective for symptom relief in selected patients, their ability to achieve guideline-targeted heart-rate thresholds or confer prognostic benefit appears limited in many modern, well-treated CAD populations.

In addition to recent data, a large meta-analysis in the contemporary era showed no mortality reduction from β-blockers post-myocardial infarction (43), and analyses in stable CAD have similarly found no clear advantage of β-blockers over other therapies in reducing death. In addition to insufficient HR control of beta-blockers in other studies(32, 37), Bangalore et al (44) with a 44-month follow-up indicated that lower CVD events rate was not associated with beta-blocker use. Also, previously in a meta-analysis, the rates of cardiac death and myocardial infarction were not different when comparing beta-blockers and calcium antagonists (44). It seems the long-term use of beta-blockers for reducing CVD events and HR can be questioned. Taken together, these data suggest that while β-blockers remain first-line for symptom relief in CAD (35), their impact on major cardiovascular events may be limited when patients are otherwise optimally treated.

Multiple factors may contribute to the inadequate heart rate control we observed. Physicians often prescribe lower-than-recommended β-blocker doses due to fear of side effects or patient comorbidities, which can blunt HR-lowering. An additional limitation is the absence of detailed dose stratification or titration patterns. Although we captured the mean daily dose of each beta-blocker, we were unable to determine whether patients had undergone appropriate uptitration toward guideline-recommended targets, or whether treatment had recently been initiated. This distinction is clinically important because the effectiveness of beta-blockade is strongly dose-dependent, and insufficient uptitration may partly explain why nearly half of treated CAD patients remained above the recommended HR threshold. Likewise, lack of data on long-term treatment duration or adherence prevents us from differentiating between true pharmacologic inefficacy and suboptimal exposure. Pharmacogenetic variability may also play a role: specific β1-adrenergic receptor gene variants (e.g. ADRB1 Arg389) are known to influence how much β-blockers reduce heart rate (36). Poor patient adherence and gaps in physician awareness of HR targets are further barriers. Notably, education interventions can improve treatment effectiveness: in one randomized trial, a structured nurse-led education program significantly improved patients' medication adherence and self-management and reduced 12-month heart failure readmissions from 27.1% to 10.4% (45). Similar efforts (e.g. teaching patients the importance of strict HR control and encouraging dose uptitration) might help overcome the adherence gap in CAD.

Among several factors associated with HR <70 bpm, which remained at the last step of logistic regression with backward selection, the male sex was ranked first. In other words, being male had a higher chance of having HR <70 bpm in our population, which has been reported previously. Mitoff et al(46) showed that males had lower HRs than females in normal left ventricular function subjects. TC, MET, and age were also associated with the HR <70 bpm. Wells et al(47) evaluated the effects of gastric infusions of fat in healthy subjects and observed that HR was significantly greater during the 3.5 h after intragastric infusions of lipid. Although our study indicated that TC has associated with the HR <70 bpm, the long-term effects of lipids on HR should be investigated. In the physical activity, having higher physical activity was associated with the HR <70 bpm. Morseth et al(48), in 20,484 adults in the Tromsø Study, reported lower HR means by increasing the intensity of physical activity, which was in line with our results.

As the linear relationship between beta-blocker use and HR was inverse, its consumption may be linked to HR-lowering effects. Still, it is not sufficient to reduce the HR below 70 bpm. Besides the factors mentioned above, which play a significant role in controlling HR, there may be other reasons which made HR control insufficient. Reasons such as comorbidities may change the tolerance to beta-blockers. Their side effects, marketing, and advertising for newer and other medications may be other reasons. Bangall et al(44) suggested two important factors on this issue. The first one was inadequate knowledge of physicians' evidence or treatment goals, and the second one was patients stop taking their

medication without instruction from their doctor, which can lead to worse outcomes(49, 50). While beta-blockers are the most popular class of drugs prescribed for patients with stable CAD, they are used at low doses. Physicians' tendency to prescribe lower doses than those recommended was previously indicated (51-53). It may be due to concern over the risk of adverse effects or hesitation related to different comorbidities(31) or over-responsiveness in Iranian population(54). Another reason of this ineffectiveness may be due to pharmacogenetics which Arnett et al. in a review suggested that variants in the beta-adrenergic receptor gene may play a role in determining response to beta blockers(55). Moreover, pharmacodynamics and pharmacokinetics differences should be considered in further studies. However, Salehifar et al. in a study reported that the pharmacokinetic differences are not able to justify over-responsiveness of Iranian population to propranolol(54). The role of education of physicians in these cases may be a matter of interest as it has been reported previously that a structured education program with regular performance was associated with improvements in prescribing and an observed decrease in chronic heart failure related readmissions (56).

Our study’s strengths include its large, community-based cohort and its focus on heart rate and its pharmacologic correlates in an Iranian population – a perspective seldom reported in the literature. We systematically evaluated HR control across multiple drug regimens and used multivariable analysis to identify independent predictors. Because our cohort is part of an ongoing longitudinal study, we will be able to assess these relationships over time. However, several limitations warrant

mention. First, the cross-sectional design precludes causal inference. Second, we lacked data on heart failure status and current anginal symptoms, both of which can influence heart rate and treatment. Third, although we recorded prescribed doses of β-blockers, we did not measure serum drug levels to confirm adherence or exposure. Forth, our participants were non-hospitalized community dwellers, so the number of known CAD patients was relatively small; larger studies with more CAD cases are needed to validate these findings. Fifth, despite verifying medication use through package inspection, we did not have information on treatment duration, adherence behavior, or historical dose adjustments, all of which critically influence the effectiveness of beta-blockade. As a result, we could not distinguish between true pharmacologic inefficacy and insufficient exposure due to poor adherence or inadequate uptitration. This limitation may partly explain the observed disconnect between beta-blocker use and actual heart-rate control. Sixth, the cohort was drawn from a single geographic region, reflecting the demographic and clinical characteristics of a rural Middle Eastern population. While this is a strength in terms of internal validity and regional relevance, it may limit generalizability to more urban or ethnically diverse populations, or to countries with different prescribing practices and healthcare structures. Finally, because this analysis is cross-sectional, it does not evaluate clinical event rates or long-term outcomes. The cohort did not include patient-reported outcomes (PROs) such as anginal symptom burden, exercise tolerance, perceived exertion, or quality-of-life indices. These measures often complement physiologic markers such as

heart rate and may provide additional context, particularly when evaluating adequacy of beta-blocker therapy. Because PROs were not collected within the ECG/medication assessment module of the Fasa PERSIAN Cohort, we were unable to quantify functional capacity or symptom response to therapy. Future cohort waves incorporating validated symptom and quality-of-life instruments (e.g., SAQ, EQ-5D) would strengthen the interpretability of HR measurements in real-world populations.

Conclusion

Despite β-blocker use in 40% of CAD patients, nearly half of those treated still had inadequate heart rate control (HR >70 bpm). In fact, among all β-blocker users more than 47% remained above 70 bpm. This highlights that multiple patient and treatment factors contribute to elevated HR in CAD. Attention to all modifiable factors, including medication dosing, patient education, and lifestyle, will be needed to improve heart rate control. Overall, our results indicate that substantial efforts are still required to optimize heart rate in stable CAD patients in order to enhance their prognosis.

Declarations

Ethics approval and consent to participate

This research was conducted in accordance with the ethical standards outlined by regional and national regulatory bodies and in full compliance with the Declaration of Helsinki. All participants provided written informed consent, and the study protocol was approved by the

Ethics Committee of Fasa University of Medical Sciences (approval code: IR.FUMS.REC.1399.127), which operates as an institutional review board (IRB).

Consent for publication

Not applicable

Availability of data and materials

In our institutional policy, it is not stated that the data should be made public, and a data and material transfer agreement should not allow further transfer of data without the provider's prior written consent. However, the data can be made available upon request from the corresponding author, who is a member of this team. Additionally, the dataset generated for this study is available upon request to the Fasa Non-Communicable Diseases Research Center management team. They can be contacted via telephone at +987153314068 or via email at ncdrc.fums.ac.ir@gmail.com.

Competing interests

This manuscript is an original work. All factual claims presented are grounded in the authors thorough research and verification. The manuscript has not been previously published or submitted for publication elsewhere. Every author has significantly contributed to this work and is willing to publicly endorse its content. The authors declare no conflict of interest regarding the findings presented in this article.

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Authors Contribution

Conceptualization: M.F., M.Y., S.B.; Methodology: M.Y., M.K., S.B.; Software: M.Y.; Validation: M.F., B.F., N.J.M.K.; Formal analysis: M.Y.;

Investigation: S.B., S.R.; Resources: M.F., E.B.; Data curation: M.F., E.B., M.Y.; Writing (original draft preparation): S.B., S.R., M.Y.; Writing (review and editing): S.B., M.F., M.Y.; Supervision: M.F., M.K., B.F., N.J., S.B.; Visualization: M.Y.; Project administration: M.F.; All authors have read and approved the final version. All authors confirm that they had full access to all the data in the study and accept responsibility to submit it for publication.

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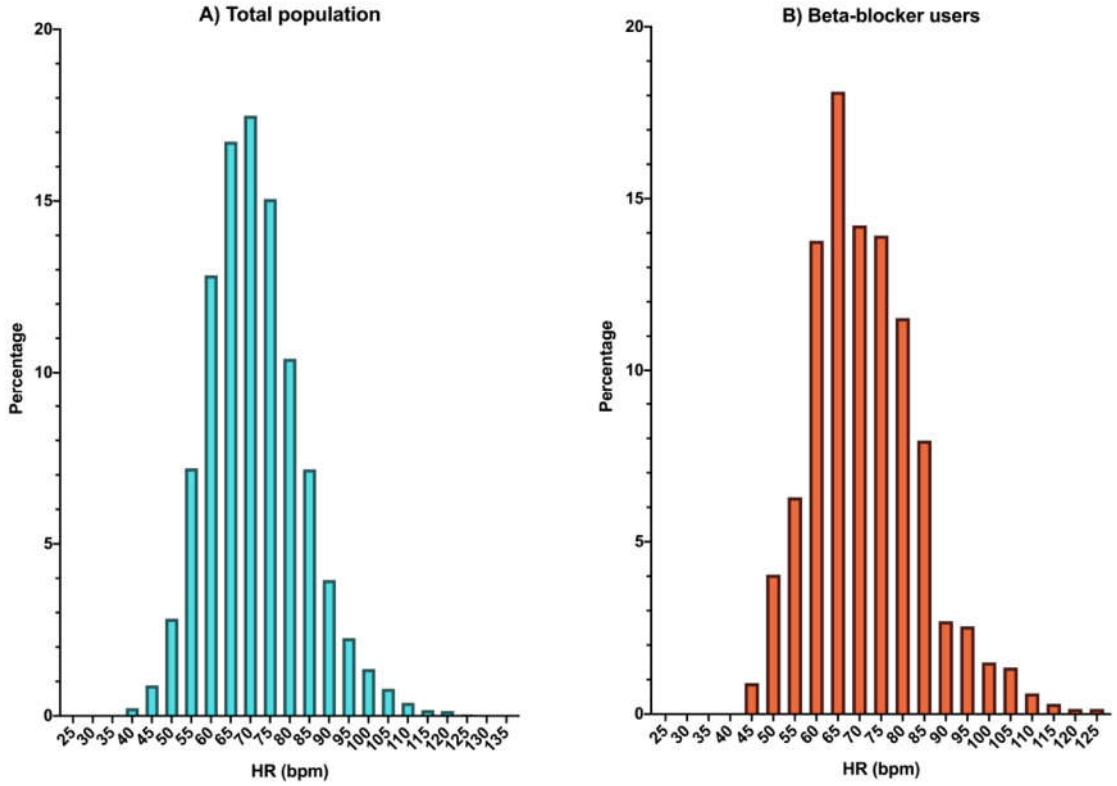


Figure 1. Frequency distribution of resting heart rate (HR) in the study population. (A) Distribution of HR in the total analytic population (n = 7,119). (B) Distribution of HR among participants using beta-blockers (n = 671). HR was derived from 12-lead ECG recordings at baseline.

Table 1. Distribution of beta-blocker use according to age, sex, and heart rate category.

	Total population	**Beta-blocker in use**
Age		
≤45 years	3061 (43.0)	115 (17.1)
46-59 years	2930 (41.2)	336 (50.1)
≥60 years	11 28 (15.8)	220 (32.8)
		***P-value < 0.001**
Gender		
Male	3092 (43.4)	180 (26.8)
Female	4027 (56.6)	491 (73.2)
		***P-value < 0.001**
Heart rate		
<70 bpm	3661 (51.4)	354 (52.8)
71-89 bpm	2920 (41.0)	263 (39.2)
≥90 bpm	538 (7.6)	54 (8.0)
		*P-value=0.580

Values are presented as number (percentage).
*P-value reported as the result of the Chi-square test in beta-blocker users' groups. Statistically significant P-values are bolded.

Table 2. Frequency and mean daily dosage of beta-blocker agents in the study population.

	N (%)	Dosage (mg/day) (Mean ± SD)
All of Beta-Blockers	671 (9.4)	
Atenolol	240 (3.4)	64.79 ± 22.86
Carvedilol	71 (1.0)	13.02 ± 2.53
Metoprolol Succinate	3 (0.04)	31.66 ± 13.71
Metoprolol tartrate	205 (2.9)	48.78 ± 14.59
Propranolol	179 (2.5)	17.98 ± 9.85

Values are presented as number (percentage) for frequency and as mean ± SD for daily dose. Dosages reflect self-reported regular use within two weeks before baseline, verified by medication inspection.

Table 3. Medical history of the total population and beta-blocker users.

	Total population	**Beta-blocker in use**
Diabetes		
Yes	899 (12.6)	168 (25.0)
No	6220 (87.4)	503 (75.0)
		P-value < 0.001
Hypertension		
Yes	1450 (20.4)	183 (27.3)
No	5667 (79.6)	488 (72.7)
		P-value < 0.001
CVD		
MI	130 (1.8)	65 (9.7)
CAD	803 (11.3)	321 (47.8)
Stroke	94 (1.3)	32 (4.8)
No CVD	6250 (85.6)	334 (37.7)
		P-value < 0.001
Chronic Lung Diseases		
Yes	138 (1.9)	20 (3.0)
No	6979 (98.0)	651 (97.0)
		P-value=0.040
Thyroid Diseases		
Yes	647 (1.9)	104 (15.5)
No	6470 (90.9)	567 (84.5)
		P-value < 0.001
Psychiatry Disorders		
Yes	671 (9.4)	111 (16.5)
No	6446 (90.5)	560 (83.5)
		P-value < 0.001

Values are presented as number (percentage).
*P-value reported as the result of the Chi-square test in beta-blocker users' groups. Statistically significant P-values are shown in bold.
CVD = cardiovascular disease; CAD = coronary artery disease; MI = myocardial infarction.

Table 4. Baseline characteristic of the total population and beta-blocker users

	Total population N = 7119	**Beta-blocker in use N = 671**
Age (years)	48.60 ± 9.34	54.50 ± 8.91
Current Smoker	1245 (17.5)	64 (9.5)
Systolic BP (mmHg)	110.70 ± 17.87	122.00 ± 21.01
Diastolic BP (mmHg)	74.19 ± 12.18	78.80 ± 12.69
Fasting Blood Glucose (mg/dL)	93.36 ± 30.80	101.67 ± 36.64
High-Density lipoprotein (mg/dL)	48.50 ± 12.87	48.61 ± 12.73
Low-Density lipoprotein (mg/dL)	109.66 ± 32.63	105.25 ± 36.572
Triglyceride (mg/dL)	132.97 ± 84.72	142.35 ± 77.75
Total Cholesterol (mg/dL)	184.79 ± 39.37	182.45 ± 42.64
Fat percentage (%)	27.68 ± 10.10	32.98 ± 8.90
Fat mass (Kg)	19.26 ± 9.20	23.29 ± 9.39
Body mass index (Kg/m^2)	25.66 ± 4.89	27.37 ± 4.96
Hip circumference (cm)	99.34 ± 8.79	101.61 ± 9.17
MET	41.16 ± 10.82	38.03 ± 8.16
Heart Rate (bpm)	71.19 ± 12.18	71.24 ± 13.13

Values are presented as mean ± SD for continuous variables and number (percentage) for categorical variables. BP = blood pressure; bpm = beats per minute; BMI = body mass index; HC = hip circumference; MET = metabolic equivalent of task.

Table 5. Univariable logistic regression of demographic, clinical, and pharmacological factors associated with heart rate <70 bpm.

Variable		OR (95% CI)	P-value
Age (per 10-year increase)		1.04 (0.99-1.09)	0.081
Sex (male)		4.07 (3.68-4.50)	**<0.001**
Current smoking		2.59 (2.28-2.93)	**<0.001**
Ethnicity	Fars	Ref	**-**
	Turk	0.88 (0.80-0.98)	**0.022**
	Arab	1.02 (0.82-1.28)	0.810
Blood Pressure	Systolic (per 10 mm Hg increase)	0.90 (0.88-0.93)	**<0.001**
	Diastolic (per 10 mm Hg increase)	0.84 (0.81-0.88)	**<0.001**
BMI (per 2 kg/m^2 increase)		0.85 (0.84-0.87)	**<0.001**
FBS (per 20 mg/dL increase)		0.76 (0.73-0.79)	**<0.001**
Lipid Profile	HDL (per 10 mg/dL increase)	0.94 (0.91-0.98)	**0.003**
	LDL (per 50 mg/dL increase)	0.76 (0.70-0.81)	**<0.001**
	TG (per 50 mg/dL increase)	0.90 (0.88-0.93)	**<0.001**
	TC (per 50 mg/dL increase)	0.73 (0.69-0.78)	**<0.001**

Body composition	Fat percentage (per 5% increase)	0.71 (0.69-0.74)	**<0.001**
	Fat mass (per 5 Kg increase)	0.74 (0.71-0.77)	**<0.001**
HC (per 10 cm increase)		0.72 (0.69-0.77)	**<0.001**
MET (per 5 MET increase)		1.42 (1.35-1.49)	**<0.001**
Medical history	Diabetes	0.48 (0.41-0.55)	**<0.001**
	Hypertension	0.69 (0.61-0.77)	**<0.001**
	CVD		
	MI	1.03 (0.73-1.46)	0.837
	CAD	0.96 (0.83-1.11)	0.608
	Stroke	0.98 (0.65-1.48)	0.946
	Chronic Lung Diseases	0.81 (0.58-1.14)	0.233
	Thyroid Diseases	0.59 (0.50-0.70)	**<0.001**
	Psychiatry Disorders	0.79 (0.67-0.93)	**0.005**
	Family history of		
	Diabetes	0.83 (0.76-0.91)	**<0.001**
	CVD	0.85 (0.78-0.94)	**0.001**
	Hypertension	0.75 (0.68-0.83)	**<0.001**
Drugs	Beta blocker	1.06 (0.90-1.24)	0.468
	ACE	0.50 (0.37-0.68)	**<0.001**
	ARB	0.73 (0.59-0.90)	**0.005**
	CCB		
	DHP	0.67 (0.52-0.87)	**0.003**
	Non-DHP	0.64 (0.36-1.15)	0.139

Values are presented as odds ratio (OR) with 95% confidence interval (CI). Statistically significant p-values are shown in bold. Abbreviations: bpm = beats per minute; BMI = body mass index; FBS = fasting blood sugar; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride; TC = total cholesterol; HC = hip circumference; CVD =

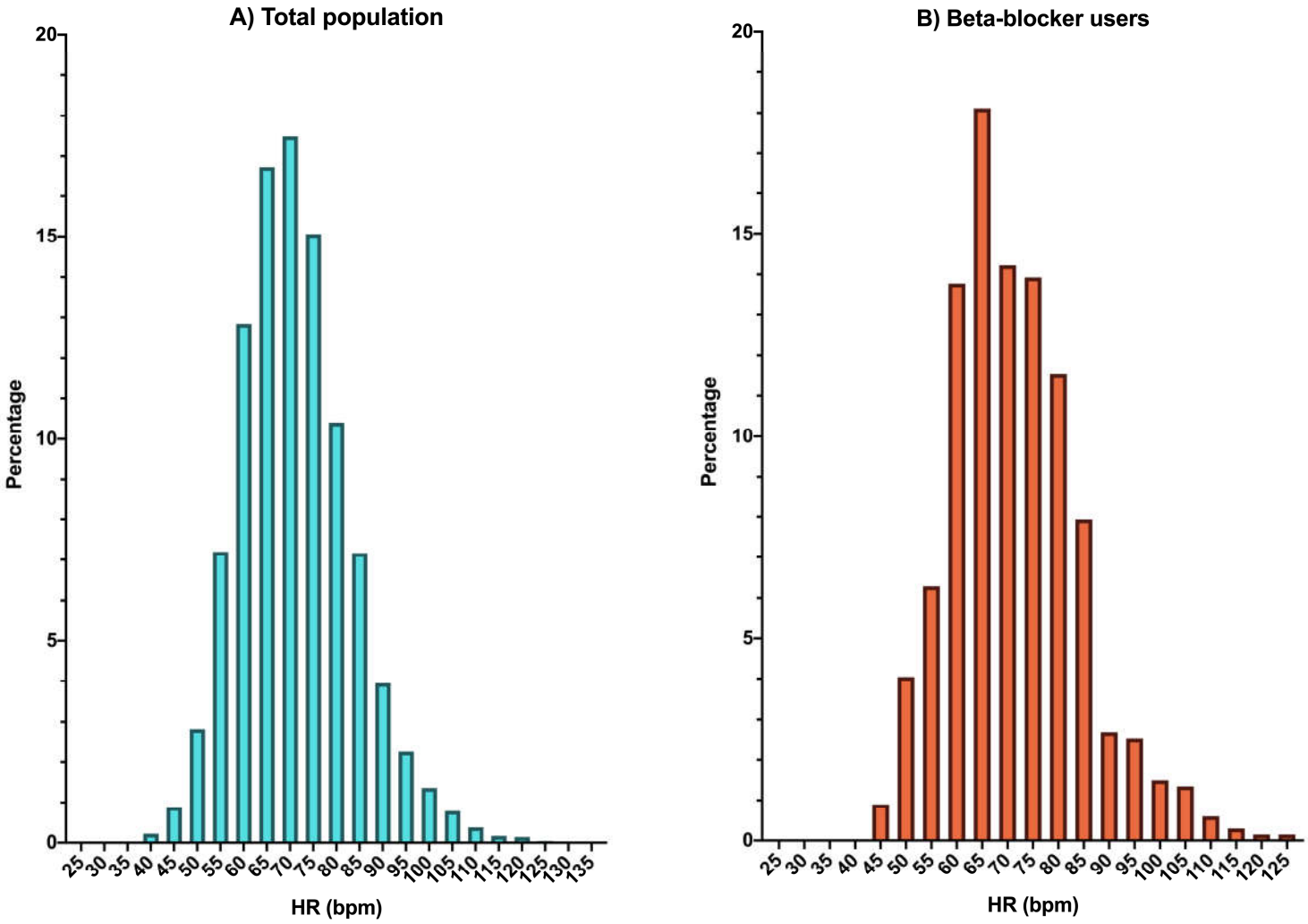
cardiovascular disease; MI = myocardial infarction; CAD = coronary artery disease; ACEI = angiotensin-converting-enzyme inhibitors; ARB = angiotensin II receptor blockers; CCB = calcium channel blockers; DHP = dihydropyridine.

Table 6. Multivariable logistic regression of beta-blocker and calcium channel blocker use, alone and in combination with other drugs, associated with heart rate <70 bpm in the total population and subgroups.

	Total population (n=7119)		**Sub-total population (n=1849)**					
			CAD (n=399)		**HTN (n=982)**		**CAD and HTN (n=468)**	
	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
BB only	418(5.8)	1.64 (1.36-1.98) ***P-value<0.001***	92 (23.0)	0.96 (0.57-1.59)	181 (18.4)	2.35 (1.72-3.22) ***P-value<0.001***	73 (15.6)	1.51 (0.99-2.30)
CCB only	125 (1.7)	1.05 (0.80-1.38)	11 (2.7)	0.87 (0.22-3.51)	49 (5.0)	0.75 (0.51-1.22)	61 (13.1)	1.24 (0.79-1.95)
>1 BB	12 (0.1)	1.47 (0.60-3.59)	0	N.A.	2 (0.2)	2.93 (0.63-13.53)	10 (2.1)	0.70 (0.23-2.14)
BB + ACEI	45 (0.6)	1.18 (0.69-2.02)	8 (2.0)	0.99 (0.18-5.24)	9 (0.9)	0.74 (1.08-2.00)	28 (6.0)	1.11 (0.54-2.29)
BB + ARB	82 (1.1)	1.40 (0.94-2.10)	8 (2.0)	0.81 (0.17-3.73)	19 (2.0)	1.95 (1.03-3.68) ***P-value=0.038***	55 (11.7)	0.72 (0.41-1.28)
CCB + ARB	45 (0.6)	0.99 (0.61-1.62)	2 (0.5)	0.74 (0.05-10.18)	10 (1.0)	1.05 (0.48-2.32)	33 (7.0)	0.85 (0.45-1.60)
CCB + ACEI	11 (0.1)	0.86 (0.39-1.87)	0	N.A.	8 (0.8)	0.44 (0.11-1.73)	3 (0.6)	1.13 (0.41-3.10)
CCB + BB	51 (0.7)	1.65 (1.08-2.51) ***P-value=0.020***	3 (0.7)	0.66 (0.03-13.58)	20 (2.0)	2.18 (1.02-4.74) ***P - value=0.049***	28 (6.0)	1.28 (0.74-2.20)

Values are presented as number (percentage) and odds ratio (OR) with 95% confidence interval (CI). Models adjusted for age, sex, smoking status, ethnicity, blood pressure, anthropometric measures, lipid profile, physical activity, and medical history variables. Statistically significant p-values are shown in bold. Abbreviations: CAD =

coronary artery disease; HTN = hypertension; BB = beta-blocker; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.


A) Total population
Percentage
HR (bpm)
B) Beta-blocker users
Percentage
HR (bpm)