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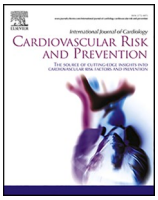

# Physical activity and risk of all-cause mortality in patients with stable angina pectoris: Effect modification by β-blocker treatment

Indu Dhar [a,*], Gard FT. Svingen [b], Eva KR. Pedersen [b], Arve Ulvik [c], Espen Ø. Bjørnestad [d], Simon N. Dankel [a,e], Gunnar Mellgren [a,e], Ottar K. Nygård [a,b]

[a] Mohn Nutrition Research Laboratory, Department of Clinical Science, University of Bergen, Bergen, Norway
[b] Department of Heart Disease, Haukeland University Hospital, Bergen, Norway
[c] Bevital AS, Bergen, Norway
[d] Department of Cardiology, Stavanger University Hospital, Stavanger, Norway
[e] Hormone Laboratory, Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway

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ABSTRACT

*Background:* Physical activity (PA) influences sympathetic stimulation, platelet activation as well as vascular function, and has been associated with improved health outcomes in patients with coronary heart disease. β-blocker therapy reduces sympathetic activity and improves platelet and endothelial function. We investigated if β-blocker treatment modifies the association of self-reported PA with the risk of all-cause mortality.

*Methods:* A total of 2284 patients undergoing elective coronary angiography for suspected stable angina pectoris (SAP) were studied. Using Cox modeling, we examined associations between PA (categorized as 'sedentary/inactive', 'low', 'moderate', and 'high') and all-cause mortality according to β-blocker therapy.

*Results:* During a median follow-up of 10.3 years, 390 patients (17.1%) died. Higher PA was generally associated with a more favorable cardiovascular risk profile. Compared to the patients who were sedentary or inactive, the age and sex adjusted HRs (95% CI) for all-cause mortality were 0.89 (0.66–1.20), 0.73 (0.57–0.95) and 0.72 (0.55–0.95) in the low, moderate and high PA group, respectively. However, and notably, these risk estimates were 0.85 (0.60–1.20), 0.65 (0.47–0.89) and 0.58 (0.41–0.81) in β-blocker treated subjects vs. 1.00 (0.57–1.78), 0.96 (0.61–1.52) and 1.20 (0.74–1.95) in non-treated groups ($P_{interaction} = 0.018$). The results were essentially similar in the multivariable adjusted models.

*Conclusions:* In patients with suspected SAP, increased PA was associated with reduced mortality risk primarily in patients treated with β-blockers.

## 1. Introduction

The potential benefits of a physically active lifestyle on cardiovascular health are well-known [1], yet physical inactivity remains a global problem, influencing mortality rates [2]. A recent meta-analysis including more than 1,000,000 individuals found that sedentary behavior was associated with increased mortality risk [3]. Similarly, an observational cohort study including 130,000 participants from 17 countries reported that physical activity (PA) reduced mortality risk [4], which is further corroborated by reports among patients with coronary heart disease (CHD) [5–7].

Treatment with β-blockers is common for symptom control and secondary prevention of cardiovascular events among patients with heart diseases [8] and is shown to improve survival in patients with heart failure with reduced ejection fraction (HFrEF) [9,10] and in patients with acute myocardial infarction [11,12]. The primary effect of β-blocking agents is attenuation of sympathetic activity via reduction in adrenal catecholamine hypersecretion [8,13], as well as blocking β-adrenergic receptors in the heart [13]. In addition, β-blockers have been shown to improve endothelial function [14,15] and inhibit platelet activation and aggregation [16,17], thus likely reducing the risk of atherothrombotic events. While PA has also been linked to improved endothelial [18,19] and platelet function [20–22], it is suggested to activate the sympathetic nervous system (SNS) [23,24]. This, in turn

* Corresponding author. Department of Clinical Science, University of Bergen, Laboratory Building, 9th floor, Haukeland University Hospital, Jonas Lies vei 87, Bergen N-5021, Norway.
*E-mail address:* Indu.Dhar@uib.no (I. Dhar).

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should intuitively provide adrenergic stimuli to the heart, also supported by the findings that PA induces up-regulation and functioning of β-adrenoceptors [25] and increases catecholamine biosynthesis [26]. PA may thus be detrimental in higher-risk patients by increasing sympathetic activity, which is a key feature of many cardiovascular diseases (CVDs) ([27]).

Taken together, PA and β-blocker therapy may interfere with each other through multiple shared biological pathways; however, it is unknown whether β-blocker therapy influences the prognosis associated with PA among patients with stable angina pectoris (SAP). We therefore investigated the association between self-reported PA and risk of all-cause mortality in a large cohort of patients with suspected SAP, with a particular focus on potential effect modifications by β-blocker treatment.

## 2. Patients and methods

### 2.1. Study subjects

The study population has been described in previous reports [28]. Briefly, 4166 patients underwent coronary angiography for suspected SAP at Haukeland or Stavanger University Hospitals in Western Norway, in the period 2000–2004. Of these, 61.8% participated in the Western Norway B-Vitamin Intervention Trial (WENBIT) (clinicaltrials.gov: NCT00354081). Because β-blockers have been shown to improve survival in patients with HFrEF [9,10] and in patients with AMI [11,12], we excluded patients with left ventricular ejection fraction (LVEF) < 40% and patients with prior AMI, as well as those with missing baseline PA data, yielding 2284 subjects eligible for the present study. Written informed consent was obtained from all patients. The study was in accordance with the Declaration of Helsinki principles, and approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Medicines Agency, and the Norwegian Data Inspectorate.

### 2.2. Baseline data and biochemical analyses

Information about CVD history and prescription of medications at baseline was obtained from self-reported questionnaires and verified by hospital records, when available. Diabetes mellitus was classified by self-reports and/or having fasting or non-fasting serum glucose ≥7.0 or ≥11.1 mmol/L, respectively, and/or having baseline glycated hemoglobin ≥6.5%. Hypertension was defined by pre-existing diagnosis, and smoking status according to self-reported smoking habits and/or serum cotinine concentrations ≥85 nmol/L [28]. Left ventricular ejection fraction (LVEF) was determined by echocardiography prior to or ventriculography performed during cardiac catheterization. PA was based on a self-administered questionnaire assessing the frequency of the most common lifestyle activities such as brisk walking, jogging, swimming, bicycling, etc as recalled by patients using '4' predefined responses ranging from "rarely to never" to "4 or more times per week. In accordance with other reports [7], PA frequency data was divided into following categories: i) Inactive/sedentary, mostly sedentary without much PA; ii) Low, participation in PA at least once per week; iii) Moderate, practicing some form of PA two to three days per week; iv) High, four or more days of PA per week.

Details concerning the collection and storage of blood samples and the biochemical analyses for clinical indices have been described previously [28]. Briefly, venous blood samples at baseline were collected usually 1–3 days before or immediately after the coronary angiography and stored at −80 °C until analysis.

### 2.3. Follow-up and clinical end points

The participants were followed up from baseline to the date of death or throughout 2012 (the end of follow-up). Information on fatal events was collected from the Cause of Death Registry at Statistics Norway. The primary event was all-cause mortality, which included deaths attributable to both cardiovascular and non-cardiovascular diseases.

### 2.4. Statistical analysis

Categorical variables are given as percentages (%) and continuous as medians (25th–75th percentiles). Baseline characteristics are presented according to PA groups and trends were assessed with unadjusted linear or logistic regression.

Survival analyses were carried out with Cox proportional hazards regression to evaluate the relationship between PA as an ordinal variable and all-cause mortality, using the inactive/sedentary group as reference category. Model 1 was adjusted for age and sex. A multi-adjusted Model 2 additionally included established risk factors such as body mass index (BMI), angiographic extent of coronary artery disease, diabetes mellitus, hypertension, smoking, estimated glomerular filtration rate (eGFR), atrial fibrillation and total cholesterol. Model 3 was further adjusted for cardiovascular medications including angiotensin-converting enzyme inhibitor and/or angiotensin receptor blockers, and statins. Potential effect modification by β-blocker treatment on risk associations of PA was explored according to medication use and tested by adding interaction product terms to the Cox models. We considered $p$-values <0.05 significant and all analyses were carried out using SPSS 27 (SPSS Inc, IBM, NY, USA).

## 3. Results

### 3.1. Baseline characteristics

The median (25th–75th percentiles) age at baseline was 61 (55–69) years. Approximately 67% were male and 66% received treatment with β-blockers. As shown in Table 1, patients in the higher PA groups were slightly older and had higher plasma arginine compared to persons in the sedentary group. PA was negatively associated with BMI, glycated hemoglobin (HbA1c), serum C-reactive protein (CRP), fibrinogen, triglycerides (TG), as well as platelet count, eGFR and resting heart rate. Furthermore, patients with higher PA group less often were smokers, had diabetes or were prescribed statins. The proportion of patients prescribed β-blocker therapy did not differ according to PA groups.

### 3.2. Associations of self-reported PA with mortality risk

A total of 390 (17.1%) patients died during a median (25th–75th percentiles) follow-up time of 10.3 (9.3–11.6) years. As shown in Table 2, increasing PA was related to improved survival. More specifically, both moderate and higher PA were inversely associated with risk of all-cause mortality in model 1 (HR [95% CI]: 0.73 [0.57–0.95] and 0.72 [0.55–0.95], respectively), and the risk relationship remained essentially unaltered after multivariable adjustments.

The associations between PA and all-cause mortality according to baseline β-blocker treatment are presented in Table 3 and Supplemental Fig. 1. Among patients receiving β-blockers, PA showed a graded and strong inverse association with all-cause mortality (HR [95% CI]: 0.85 [0.60–1.20], 0.65 [0.47–0.89] and 0.58 [0.41–0.81] in low, moderate and high PA group, respectively in age and sex adjusted model). However, there was either no association or actually a trend towards an increased mortality risk with higher PA among those not treated with β-blocker therapy ($P_{interaction}$ = 0.018). The risk estimates did not appreciably change after multivariable adjustments (Table 3).

## 4. Discussion

### 4.1. Principal findings

In this study of patients with suspected stable angina pectoris, both moderate and higher PA was associated with decreased risk of all-cause

**Table 1**
Baseline characteristics according to self-reported physical activity levels.

| | Inactive/sedentary (n = 609) | Low[a] (n = 447) | Moderate[b] (n = 736) | High[c] (n = 492) | P-value |
|---|---|---|---|---|---|
| Age, y | 62 (55–70) | 59 (53–66) | 62 (54–69) | 64 (56–71) | 0.006 |
| Male sex, (%) | 66.3 | 67.6 | 65.1 | 68.5 | 0.73 |
| BMI, kg/m$^2$ | 26 (24–29) | 27 (24–30) | 25 (24–28) | 25 (23–28) | <0.001 |
| Hypertension, % | 47.8 | 48.1 | 45.9 | 44.1 | 0.18 |
| Diabetes mellitus, % | 46.3 | 35.3 | 32.1 | 31.5 | <0.001 |
| Current smoking, % | 31.4 | 33.6 | 27.2 | 25.2 | 0.005 |
| Atrial fibrillation, % | 7.6 | 7.8 | 8.4 | 10.0 | 0.16 |
| HbA1c, % | 6.34 (5.7–7.1) | 5.96 (5.3–6.8) | 5.93 (5.2–6.7) | 6.03 (5.4–6.7) | <0.001 |
| eGFR, mL/min per 1.73m2 | 92 (82–100) | 94 (82–102) | 91 (79–99) | 88 (78–96) | <0.001 |
| Serum CRP, mg/L | 1.86 (0.93–4.0) | 1.92 (0.92–3.7) | 1.53 (0.73–3.1) | 1.45 (0.72–3.1) | 0.003 |
| LVEF, % | 70 (60–70) | 70 (60–70) | 70 (63–71) | 70 (65–73) | 0.001 |
| Arginine, μmol/L | 75 (62–88) | 79 (64–93) | 79 (63–93) | 81 (66–94) | <0.001 |
| Platelet Count, K/μL | 249 (216–292) | 246 (210–285) | 240 (205–278) | 236 (202–275) | <0.001 |
| Fibrinogen, g/L | 3.70 (3.2–4.1) | 3.50 (3.1–4.1) | 3.50 (3.1–4.0) | 3.50 (3.1–4.0) | 0.01 |
| Diastolic pressure, mmHg | 80 (75–89) | 80 (75–90) | 81 (75–90) | 80 (75–87) | 0.56 |
| Systolic pressure, mmHg | 141 (128–160) | 140 (129–155) | 140 (128–155) | 140 (127–156) | 0.24 |
| Heart rate, bpm | 65 (57–73) | 63 (56–71) | 61 (55–69) | 61 (55–68) | <0.001 |
| Serum lipids, mmol/L | | | | | |
| Total cholesterol | 5.0 (4.3–5.8) | 5.2 (4.4–6.0) | 5.1 (4.5–5.9) | 5.0 (4.4–5.8) | 0.93 |
| Triglycerides | 1.5 (1.1–2.2) | 1.7 (1.2–2.3) | 1.4 (1.0–2.0) | 1.4 (1.0–2.1) | 0.001 |
| LDL-C | 2.9 (2.4–3.6) | 3.2 (2.5–4.0) | 3.1 (2.6–3.9) | 3.0 (2.4–3.8) | 0.08 |
| HDL-C | 1.3 (1.0–1.6) | 1.2 (1.0–1.40) | 1.3 (1.1–1.6) | 1.3 (1.1–1.6) | 0.44 |
| Extent of CAD, n (%) | | | | | 0.61 |
| No significant stenosis | 30.0 | 37.1 | 36.4 | 31.7 | |
| 1-vessel disease | 23.2 | 22.6 | 21.9 | 22.8 | |
| 2-vessel disease | 20.5 | 18.6 | 20.5 | 19.5 | |
| 3-vessel disease | 26.5 | 21.7 | 21.2 | 26.0 | |
| Aspirin | 78.2 | 76.1 | 77.7 | 79.3 | 0.61 |
| ACE and/or ARB | 27.1 | 25.1 | 23.1 | 23.6 | 0.10 |
| Statins | 76.8 | 74.7 | 72.7 | 72.0 | 0.04 |
| β-blockers | 65.8 | 66.7 | 63.3 | 70.5 | 0.35 |

Continuous variables are presented as medians (25th–75th percentiles) and categorical variables are reported as numbers (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI body mass index; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction.

[a] Physical activity 1 day per week.

[b] Physical activity = 2–3 days/week.

[c] Physical activity ≥4 days/week.

**Table 2**
Risk of all-cause mortality over 10.3-year median follow-up in relation to self-reported physical activity.

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P*-Value | HR (95% CI) | *P*-Value | HR (95% CI) | *P*-Value |
| Groups[a] | | | | | | |
| Inactive/ sedentary | Reference | | Reference | | Reference | |
| Low | 0.89 (0.66-1.20) | 0.44 | 0.85 (0.63-1.15) | 0.28 | 0.86 (0.64-1.17) | 0.34 |
| Moderate | 0.73 (0.57-0.95) | 0.02 | 0.71 (0.55-0.92) | 0.01 | 0.71 (0.55-0.92) | 0.01 |
| High | 0.72 (0.55-0.95) | 0.02 | 0.72 (0.54-0.95) | 0.02 | 0.71 (0.54-0.94) | 0.02 |
| Trend | 0.89 (0.81-0.97) | 0.01 | 0.89 (0.81-0.97) | 0.01 | 0.88 (0.81-0.96) | 0.01 |

Model 1 was adjusted for age, and sex.
Model 2 was adjusted for age, sex, BMI, angiographic extent of coronary artery disease, diabetes mellitus, hypertension, smoking, estimated glomerular filtration rate, atrial fibrillation, and total cholesterol.
Model 3 was adjusted for variable in Model 2 plus treatments with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers and statins.

[a] Sedentary, Never or rarely active; Low, 1 day/week; Moderate, =2-3 days/week; High, ≥4 days/week.

mortality as compared to sedentary lifestyle. This beneficial association was, however, primarily confined to patients receiving β-blockers at discharge from the baseline visit.

### 4.2. PA, and baseline characteristics

PA is reported to have several physiological effects which are beneficial for cardiovascular health [1]. An increase in PA has been shown to improve the serum lipid profile, lower the systemic inflammation, and leads to a more favorable CVD risk profile [1,21]. A meta-analysis of 13 randomized controlled trails also showed that resistance training reduced both BMI and improved glycemic control [29]. Moreover, available evidence indicates that being physically active may facilitate smoking cessation [30]. Accordingly, we observed an inverse relationship between increasing PA and several CVD risk factors, including BMI, HbA1c, diabetes mellitus, serum CRP, and current smoking. We also found an inverse association of PA with plasma TG, although these associations may have not been influenced by statin treatment as patients who reported higher PA were less likely receiving statins.

### 4.3. PA, β-blockers and mortality

The mortality benefit from β-blocker treatment in patients with HFrEF and in patients with acute myocardial infarction has been reported in landmark trails [9–12]. Some cohort studies [31,32], including our recent report [33] have also demonstrated mortality reduction in stable CHD with β-blocker use, which was received by 24%, 79% and 72.5% of patients in these population, respectively. Patients with angina

**Table 3**
HR (95%CI) for all-cause mortality and self-reported physical activity[a] according to β-blocker prescription.

| Events/*n* | β-blocker use | | *P*interaction |
|---|---|---|---|
| | Non-treated | Treated | |
| | 126/772 | 264/1512 | |
| Model 1 | | | 0.018 |
| Sedentary | Reference | Reference | |
| Low | 1.00 (0.57-1.78) | 0.85 (0.60-1.20) | |
| Moderate | 0.96 (0.61-1.52) | 0.65 (0.47-0.89) | |
| High | 1.20 (0.74-1.95) | 0.58 (0.41-0.81) | |
| Trend | 1.05 (0.89-1.22) | 0.83 (0.74-0.92) | |
| Model 2 | | | |
| Sedentary | Reference | Reference | 0.022 |
| Low | 0.95 (0.53-1.70) | 0.81 (0.57-1.15) | |
| Moderate | 0.92 (0.57-1.46) | 0.62 (0.45-0.86) | |
| High | 1.27 (0.77-2.08) | 0.57 (0.40-0.80) | |
| Trend | 1.06 (0.90-1.25) | 0.82 (0.73-0.91) | |
| Model 3 | | | |
| Sedentary | Reference | Reference | 0.039 |
| Low | 0.95 (0.53-1.70) | 0.83 (0.58-1.19) | |
| Moderate | 0.92 (0.57-1.47) | 0.64 (0.46-0.89) | |
| High | 1.26 (0.76-2.09) | 0.57 (0.40-0.80) | |
| Trend | 1.06 (0.90-1.25) | 0.82 (0.74-0.92) | |

Model 1 was adjusted for age, and sex.
Model 2 was adjusted for age, sex, BMI, angiographic extent of coronary artery disease, diabetes mellitus, hypertension, smoking, estimated glomerular filtration rate, atrial fibrillation, and total cholesterol.
Model 3 was adjusted for variable in Model 2 plus treatments with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers and statins.
[a] Inactive/sedentary, Never or rarely active; Low; 1 day/week; Moderate, =2-3 days/week; High, ≥4 days/week.

pectoris from CHD however may be vulnerable to PA due to potentially detrimental sympathetic stimulation. Accordingly, the effects of PA on survival in CHD patients is less well established than in the general population, although most studies suggest a beneficial effect. In a British cohort of male patients, PA was associated with a lower risk of all-cause mortality [5]. In another CHD patient population, the lowest mortality risk was observed among those in the most active PA tertile [6]. Similarly, a Norwegian CHD cohort study reported risk reduction with increasing PA [7]. Our current study corroborates these findings, but also extends them by showing for the first time that such a survival benefit may primarily be present in stable SAP patients treated with β-blockers.

### 4.4. Possible mechanisms

The crosstalk between PA and β-blockers on mortality risk is not clear. An animal study showed that exercise training increases the protein content of eNOS [34], which catalyzes the production of endothelial nitric oxide (NO), which in turn causes vasodilation [18]. Accordingly, both clinical and preclinical studies have confirmed the ability of PA to increase NO availability, thus improving endothelial function [18,19]. It is therefore interesting that we observed a positive association between PA and arginine, an important determinant of endogenous NO formation in healthy and pathological conditions [35]. Notably, β-blocker therapy has also been suggested to modulate NO pathways [14]. Indeed, a meta-analysis of 16 studies including 1273 patients with CVD demonstrated an improvement by β-blockers therapy on endothelial function [15]. Thus, the joint survival benefit of PA together with β-blockers use could be related to a positive modulation of vascular function.

In addition, regular PA has been suggested to have a positive impact on platelet function [20]. Blood platelets contribute to hemostasis, and platelet activation and dysfunction plays a key role in cardiovascular disorders [36]. Results from randomized trials show that exercise blunts platelet aggregation in sedentary older adults [20] and heart failure patients [22]. Another report among patients with stable angina and in apparently sedentary heathy subjects indicated that regular or moderate PA was related to decreased platelet adhesiveness [37]. Accordingly, we observed an inverse association of PA with platelet count, described as risk factor for mortality [38] and fibrinogen, an important determinant of platelet aggregation/adhesiveness [36], further corroborated by results from the British Regional Heart Study among 3810 male subjects with and without CVD [21]. Of note, β-blockers have also been suggested to directly influence platelet activation [16]. A systemic review and meta-analysis of 31 studies demonstrated that β-blockers decrease platelet aggregation [17]. Thus, the combined benefits of PA and β-blocker use on survival may be linked to a protective regulation of platelet function.

Despite the reported favorable effects of PA, it has also been shown to increase the catecholamine production [26], supporting the hypothesis that PA stimulates SNS [23,24], which in turn is commonly associated with CVDs [27]. Notably, the predominant β-receptor antagonistic effect is observed during high SNS stimulation [13], which is supported by our observation of the lowest mortality risk with higher PA among β-blocker users, and no apparent survival benefit in those not taking β-blockers. Thus, our data suggest that any potential adverse effects from PA among CHD patients, who may be more vulnerable in terms of SNS overactivity [27], may be offset by concomitant β-blocker therapy. Importantly, we found an inverse association between PA and heart rate, suggesting low SNS activity at rest. Thus, further studies are needed to investigate if protective effect of β-blocker treatment together with high PA may be primarily present at high SNS activity during exercise.

### 4.5. Limitations

First, information about PA relied on self-report questionnaire data, which is crude, and at least prone to potential recall bias. However, our baseline characteristics results are consistent with previous literature showing an overall favorable cardiovascular risk profile with greater physical activity [1,21,29,30], which suggests that self-reported PA in our study is less likely to be imprecise. Second, due to lack of data, we could not account for medication compliance, possible individual changes in the medication use pattern or the amount of PA during follow-up. Third, we only evaluated PA frequency levels but lacked detailed information on duration and intensity of PA. Fourth, our analysis may be limited by selection bias, i.e., patients that reported higher PA compared to sedentary counterparts may have had a healthier lifestyle or good heath, and/or better cardiorespiratory fitness, which in turn is associated with good prognosis [39]. Even though rigorous statistical adjustments were performed, the existence of residual cofounding resulting from lifestyle factors or unmeasured factors cannot be ruled out. Fifth, and importantly, we previously showed that patients treated with β-blockers had more prevalent and extensive coronary stenoses as well as lower LVEF [33]. Thus, the protective effect of PA may be stronger in β-blocker users due to more severe coronary artery disease or due to β-blocker therapy itself or combination of both. However, by excluding patients with LVEF<40% and/or prior AMI, such a bias seems less likely. Finally, due to the observational nature of this study, conclusions on causal connections cannot be drawn. Our findings could motivate RCTs to reliably determine the survival benefit from increasing PA according to β-blocker therapy, especially among subjects at higher risk of adverse events from increased SNS activity.

## 5. Conclusions

In patients with suspected stable angina pectoris, we observed an inverse association between higher physical activity and risk of all-cause mortality primarily among those prescribed β-blocker therapy.

## Author contributions

Indu Dhar: Conceptualization; Data curation, Formal analysis; Methodology; Visualization; Writing - original draft; Writing - review and editing. Gard FT. Svingen: Data curation; Investigation; Methodology; Writing - review and editing. Eva KR. Pedersen: Investigation; Writing - review and editing. Arve Ulvik: Investigation; Writing – review and editing. Espen Ø Bjørnestad: Methodology; Writing - review and editing. Simon N Dankel: Investigation; Writing – review and editing. Gunnar Mellgren: Investigation; Writing – review and editing. Ottar Nygård: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing - review and editing. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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## Data availability statement

The data underlying this article will be made available to other researchers upon reasonable request.

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## Declaration of Competing Interest

None declared.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2022.200150.

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