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FULL RESEARCH PAPER
Coronary Heart Disease

β-blocker use and risk of all-cause mortality in patients with coronary heart disease: effect modification by serum vitamin A

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Aims Blockade of β-adrenoceptors reduces sympathetic nervous system activity and improves survival in patients with heart failure with reduced left ventricular ejection fraction (HFrEF); however, any improvement in longevity among patients with coronary heart disease (CHD) but without HFrEF remains uncertain. Vitamin A has been linked to the activation of tyrosine hydroxylase, the rate-limiting enzyme in the catecholamine synthesis pathway. We investigated if vitamin A status modified the association of β-blocker use with the risk of all-cause mortality.

Methods and results A total of 4118 patients undergoing elective coronary angiography for suspected stable angina pectoris, of whom the majority had normal left ventricular ejection fraction (LVEF) were studied. Hazard ratios (HRs) of all-cause mortality comparing treatment vs. non-treatment of β-blockers according to the tertiles of serum vitamin A were explored in Cox proportional hazards regression models. During a median follow-up of 10.3 years, 897 patients (21.8%) died. The overall LVEF was 65% and 283 (6.9%) had anamnestic HF. After multivariable adjustments for traditional risk factors, medical history, and drug therapies of cardiovascular disease, β-blocker treatment was inversely associated with the risk of all-cause mortality [HR : 0.84; 95% CI (confidence interval), 0.72–0.97]. However, the inverse association was generally stronger among patients in the upper serum vitamin A tertile (HR :0.66; 95% CI, 0.50–0.86; $P_{interaction}$ = 0.012), which remained present after excluding patients with LVEF < 40%.

Conclusion In patients with suspected CHD, β-blocker treatment was associated with improved survival primarily among patients with high serum vitamin A levels.

Keywords Epidemiology • β-blocker therapy • Coronary heart disease • Mortality

Introduction

Stable angina pectoris (SAP) is a common clinical manifestation of coronary heart disease (CHD) with a highly variable long-term prognosis.[1] β-blockers inhibit the binding of endogenous catecholamines to β-adrenoceptors and are recommended in CHD for symptom relief.[2–4] The beneficial effect of β-blocker therapy on mortality is well-established in patients with symptomatic heart failure and reduced left ventricular ejection fraction (HFrEF),[5–7] i.e. left ventricular ejection fraction (LVEF) <40%[8]; however, any survival benefit in patients with stable CHD remains uncertain. While some studies in CHD patients suggest that β-blockers may increase survival,[9,10] others showed no clear clinical benefit.[11,12]

Vitamin A as retinol is a fat-soluble micronutrient generally obtained from the diet either as pro-vitamin A carotenoids from

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Key message

- Studies examining the effect of β-blocker therapy on the risk of mortality in patients with coronary heart disease (CHD) without reduced left ventricular ejection fraction (LVEF) are limited and the findings are inconclusive.
- In this large prospective cohort study based on patients with suspected CHD, among whom the majority had normal LVEF, we found that β-blocker use at discharge was associated with a decreased risk of all-cause mortality.
- The survival benefit of β-blocker use was confined to patients with concomitantly elevated serum vitamin A.
- The effect modification by serum Vitamin A was independent of traditional cardiovascular risk factors.

plant foods or retinyl esters from animal foods, and is essential for diverse physiological functions.[13] In target cells, retinol is converted to the major biologically active form, retinoic acid (RA) which binds to nuclear RA receptors (RAR) for signalling.[13] The role of vitamin A and related metabolites in the development of CHD is unclear,[13] however, we previously showed that serum vitamin A was positively associated with several cardiovascular risk factors, including hypertension and impaired renal function.[14,15] Interestingly, available evidence suggest that vitamin A metabolism is involved in the regulation of the catecholamine system and vascular function. More specifically, RA *in vitro* promotes the differentiation of catecholaminergic cells.[16] Further, retinol[17] and RA,[18] respectively, are reported to increase activity and expression of tyrosine hydroxylase (TH), the rate-limiting enzyme in the catecholamine biosynthesis pathway that regulates the tissue levels of dopamine, epinephrine, and norepinephrine.[19] In addition, RAR signalling can directly transactivate the TH transcription in human neuroblastoma cells by interacting at the promoter region of the RA responsive element sequence.[20] Others have shown that *all-trans*-RA increases nitric oxide (NO) synthesis in endothelial cells via modulating dimethylarginine dimethylaminohydrolase 2 expression.[21]

Taken together, vitamin A may influence catecholamine synthesis and endothelial function. We, therefore, explored whether circulating concentrations of vitamin A modified the association between β-blocker treatment and survival in a large cohort of patients who underwent elective coronary angiography for suspected SAP.

Methods

Study data

A total of 4166 patients undergoing coronary angiography for suspected SAP during 2000–04 at two university hospitals in Western Norway were studied. Among these patients, 2573 (61.8%) were included in the Western Norway B Vitamin Intervention Trial (WENBIT) (ClinicalTrials.gov Identifier: NCT00354081 (10 December 2020)).[22] Patients with missing data on serum vitamin A were excluded, resulting in a total of 4118 subjects eligible for the final analyses. The study protocol fulfilled the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Medicines Agency, and the Norwegian Data Inspectorate. All study participants provided written informed consent.

Baseline variables

Each patient provided information about medical history, and cardiovascular disease (CVD) risk factors through self-administered questionnaires/interviews, which were subsequently checked against hospital records, as previously reported.[22] Diabetes mellitus was classified by self-reports and/or fasting plasma glucose ≥7.0 mmol/L and/or non-fasting plasma glucose ≥11.1 mmol/L, and/or HbA1c ≥6.5%. LVEF and smoking status were determined as previously described.[23] Baseline revascularization procedures were performed with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

Angiographic evidence of coronary artery disease

Coronary angiograms were performed by trained cardiologists. Prevalence of coronary artery disease (CAD) was defined by the presence of lesions with ≥50% diameter stenosis in any epicardial coronary arteries, i.e. left descending artery, circumflex artery, or right coronary artery (RCA) or any of their main branches. The extent of significant CAD was scored 1–3 by aggregating the number of stenotic arteries.[23] Presence of left main-stem artery stenosis was classified as double- or as triple-vessel disease, if RCA was non-stenotic or stenotic, respectively.

Biochemical analyses

Blood samples were collected by study personnel prior to or immediately after angiography and stored at -80°C until analysis in 2007. Previous reports have described the biochemical analyses for relevant clinical indices.[14,15] In addition, serum vitamin A as *all-trans* retinol was analysed by liquid chromatography/tandem mass spectrometry at BEVITAL AS, Bergen, Norway (www.bevital.no (15 September 2020).[24]

Endpoints and follow-up

Study patients were followed from enrolment until death or throughout 2012. Information on fatal events was obtained from the Cause of Death Registry at Statistics Norway (www.ssb.no/en). Details on the collection and classification of endpoints have been described previously.[14,22,23]

Statistical methods

Continuous variables are presented as medians (5th–95th) percentiles, and categorical variables are reported as counts (percentages). Differences in baseline characteristics between β blockers treatment

vs. non-treatment at discharge were assessed with unadjusted linear or logistic regression.

Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality associated with β-blockers use vs. no-use, where latter was set as reference. Model 1 was adjusted for age, sex, and angiographic extent of CAD. Covariates in the multivariable-adjusted model (Model 2) additionally included CVD risk factors, such as hypertension, diabetes mellitus, smoking, estimated glomerular filtration rate (eGFR), LVEF, and medical histories, such as anamnestic heart failure (HF), atrial fibrillation, and previous acute myocardial infarction (AMI). A third model (Model 3) consisted of Model 2 with the addition of CVD medications including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and loop or thiazide diuretics. Since experimental data have suggested that *all-trans*-RA may influence vasodilation by upregulating asymmetrical dimethylarginine (ADMA) metabolizing enzyme,[21] we additionally included ADMA in an extended model. Treatments after baseline coronary angiography (none, medications only, PCI, and CABG) had negligible impact on the risk estimates and thus were not included in the final model.

To assess the effect-modification by serum vitamin A, patients were grouped according to vitamin A tertiles and the potential interaction with β-blocker use on all-cause mortality was tested by including product terms to the respective Cox models. Statistical analyses were performed using SPSS 25 SPSS Inc., IBM, NY, USA.

Results

Baseline characteristics

The median (5th–95th) percentiles age for the 4118 patients at baseline was 62 (44–78) years, 72% were male, and the majority of our patients (72.5%) was prescribed β-blockers after angiography. The overall LVEF was 65 (40–80)% and 6.9% had anamnestic HF. As shown in *Table 1*, patients treated with β-blockers at discharge more often were male and had a higher prevalence of cardiovascular risk factors including hypertension, higher body mass index, prior AMI, and lower eGFR. Furthermore, patients prescribed with β-blockers more likely had significant coronary stenoses at angiography and lower LVEF; the latter also reflected by more use of CVD medications among patients in the β-blocker group.

Associations of β-blocker treatment with the risk of survival

A total of 897 (21.8%) patients died during a median (5th–95th percentiles) follow-up time of 10.3 (3.5–12.8) years. β-blocker treatment at discharge was associated with decreased risk of all-cause mortality in Model 1 (HR: 0.83, 95% CI, 0.71–0.97). The risk associations were essentially similar in Model 2 and 3 (*Table 2*) or additional adjusting for plasma ADMA (HR: 0.83, 95% CI, 0.72–0.97).

The risk relationships between β-blocker treatment and all-cause mortality according to serum vitamin A tertiles are presented in *Table 3*. In Model 1, among patients in the highest vitamin A tertile, β-blocker use was strongly inversely related to all-cause mortality (HR: 0.64, 95% CI, 0.50–0.83), as compared to tertile 2 (0.87, 0.66–1.14), whereas there was no association among those in the lowest vitamin A tertile (0.97, 0.75–1.26; *P* for interaction = 0.037). The results were essentially similar after multivariable adjustments (*Table 3*) or additional controlling for ADMA (data not shown).

When further exploring these analyses according to diabetes mellitus status, the overall inverse risk association of β blockers, as well as effect modification by serum vitamin A, tended to be stronger in patients with diabetes mellitus (Supplementary material online, *Table S1*).

Sensitivity analysis

Given the well-known beneficial effect of β-blockers on survival in patients with HFrEF,[5–7] we conducted a sensitivity analysis by excluding patients with LVEF <40% (159 patients) and performed analyses adjusted according to Model 3. Briefly, in patients with LVEF ≥40%, HR (95% CI) for all-cause mortality comparing β-blocker use vs no use was 0.83 (0.70–0.97). Corresponding risk estimates were 0.97 (0.74–1.27), 0.81 (0.61–1.09), and 0.68 (0.51–0.90) in the first, second, and third vitamin A tertiles, respectively.

Discussion

Principal findings

In this large prospective study of patients undergoing coronary angiography for suspected CHD, among the vast majority had preserved left ventricular systolic function, the use of β-blockers at discharge was associated with improved survival primarily among patients with elevated vitamin A concentration, even after extensive adjustment for traditional CVD risk factors, and potential confounders.

β-blockers and mortality in coronary heart disease

β-blockers are widely used to reduce heart rate and angina symptoms in patients with CHD[2,3,4]; however, their role in improving survival remains uncertain.[9–12] Nevertheless, a systematic review and meta-analysis of 26 β-blocker randomized controlled trials including 6,108 patients with SAP demonstrated an inverse association between β-blocker therapy and mortality risk when compared with no treatment.[25] The current observational study thus extends these results, and indicates that such an association may be present primarily in patients with higher serum vitamin A.

Possible mechanisms

Both RA and RAR signalling has been shown to up-regulate TH gene expression,[18,20] which catalyses the rate-limiting step in the synthesis of catecholamines.[19] Further, vitamin A as retinol was reported to increase TH activity via phosphorylation of serine 40 or serine 31,[17] which in turn would lead to an increase in catecholamine synthesis.[19] Consistent with this, vitamin A deficiency was accompanied by decreased striatal dopaminergic metabolism in mice.[26] Since β-blockers prevent the response produced by endogenous catecholamines, the effects of β-blockers are greatest when catecholamine levels are high.[2] These observations are in accordance with the hypothesis that vitamin A-dependent reactions may play a role in regulating

Table 1 Baseline characteristics of the patient population according to β-blocker therapy at discharge

	Non-treated (*n* = 1134)	Treated (*n* = 2984)	*P*-value
Age, years	60 (42–76)	62 (45–78)	<0.001
Male sex, *n* (%)	753 (66.4)	2208 (74.0)	<0.001
BMI, kg/m^2	25 (20–33)	26 (21–33)	<0.001
Hypertension, *n*%	398 (35.1)	1530 (51.3)	<0.001
Diabetes mellitus, *n*%	440 (38.8)	1153 (38.6)	0.92
Current smoking, *n*%	362 (31.9)	940 (31.5)	0.80
Heart failure, *n*%	79 (7.0)	204 (6.8)	0.88
Atrial fibrillation, *n*%	82 (7.2)	261 (8.7)	0.12
Prior AMI, *n*%	278 (24.5)	1381 (46.3)	<0.001
Prior PCI, *n*%	150 (13.2)	641 (21.5)	<0.001
Prior CABG, *n*%	105 (9.3)	368 (12.3)	0.01
Plasma ADMA, µmol/L	0.54 (0.41–0.80)	0.54 (0.41–0.78)	0.45
Serum vitamin A, µmol/L	2.85 (1.96–4.20)	2.81 (1.96–4.10)	0.41
eGFR, mL/min per 1.73 m^2	92 (60–112)	90 (56–110)	<0.001
Serum CRP, mg/L	1.75 (0.37–15)	1.79 (0.35–12)	0.48
LVEF, %	70 (41–80)	65(40–80)	<0.001
Total cholesterol, mmol/L	5.20 (3.70–7.4)	4.80 (3.5–7.0)	<0.001
Extent of CAD, *n* %			<0.001
No stenotic vessels	519 (45.8)	517 (17.3)	
One-vessel disease	197 (17.4)	755 (25.3)	
Two-vessel disease	179 (15.8)	740 (24.8)	
Three-vessel disease	239 (21.1)	972 (32.6)	
Treatment after baseline coronary angiography, *n*%			
None	230 (20.3)	24 (0.8)	<0.001
Medication only	470 (41.4)	1115 (37.4)	0.02
PCI	261 (23)	1091 (36.6)	<0.001
CABG	162 (14.3)	715 (24)	<0.001
Medications after angiography, *n* (%)			
Aspirin	718 (63.3)	2639 (88.4)	<0.001
Statins	709 (62.5)	2590 (86.8)	<0.001
ACEi and ARBs	324 (28.6)	994 (33.3)	0.004
Loop and thiazide diuretics	172 (15.2)	542 (18.2)	0.023

Continuous variables are presented as medians (5th–95th percentiles), and categorical variables are reported as counts (%).
ACEi, angiotensin-converting enzyme inhibitor; ADMA, asymmetric dimethylarginine; AMI, acute myocardial infarction; ARBs, angiotensin receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Table 2 Risk of all-cause mortality associated with β-blocker use at discharge

	HR (95% CI)	*P*-value
Model 1[a]	0.83 (0.71–0.97)	0.017
Model 2[b]	0.83 (0.71–0.96)	0.015
Model 3[c]	0.84 (0.72–0.97)	0.021

[a]Adjusted for age, sex, and angiographic extent of coronary artery disease.
[b]Adjusted for age, sex, angiographic extent of coronary artery disease, diabetes mellitus, hypertension, smoking, estimated glomerular filtration rate, left ventricular ejection fraction, heart failure, atrial fibrillation, and previous acute myocardial infarction.
[c]Adjusted for variable in Model 2 plus use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and loop or thiazide diuretics.

catecholamine systems, thereby explain stronger survival benefit of β-blockers among those in the upper tertile of serum vitamin A.

In addition, *all-trans*-RA is reported to increase synthesis of endothelium-derived vasodilator NO by inducing metabolism of endogenous NO synthase (NOS) inhibitor, ADMA.[21] Interestingly, β-blockers have also been suggested to enhance the bioavailability of NO and preserve NOS activity by reducing ADMA.[27] Accordingly, a meta-analysis of 1,273 patients from 16 studies demonstrated a potential beneficial effect of β-blockers on endothelial function.[28] Thus, it is plausible that the survival benefit of β-blocker use concurrent with higher vitamin A may be linked to the regulation of endothelial function. However, plasma ADMA concentrations were not different between the β-blocker treatment groups at baseline. Moreover, additional adjustment for ADMA in Model 3 did not alter our results.

Table 3 Risk association between β-blocker use at discharge and all–cause mortality according to the tertiles of serum vitamin A

	Serum vitamin A Tertiles (μmol/L)			
	1st (<2.58)	2nd (2.58–3.10)	3rd (>3.10)	*P* for interaction
Events/*n*	331/1361	265/1388	301/1369	
Model 1[a]	0.97 (0.75–1.26)	0.87 (0.66–1.14)	0.64 (0.50–0.83)	0.037
Model 2[b]	1.08 (0.83–1.40)	0.79 (0.60–1.05)	0.64 (0.49–0.84)	0.012
Model 3[c]	1.10 (0.84–1.43)	0.79 (0.59–1.04)	0.66 (0.50–0.86)	0.012

[a]Adjusted for age, sex, and angiographic extent of coronary artery disease.
[b]Adjusted for age, sex, angiographic extent of coronary artery disease, diabetes mellitus, hypertension, smoking, estimated glomerular filtration rate, left ventricular ejection fraction, heart failure, atrial fibrillation, and previous acute myocardial infarction.
[c]Adjusted for variable in Model 2 plus use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and loop or thiazide diuretics.

Strengths and limitations

Major strengths include the large sample size, prospective design with long follow-up time, and detailed baseline clinical characteristics. Follow-up was ascertained from national health registries.

Several aspects of our study merit consideration. First, after hospital discharge, patients' compliance over time is unknown. This, however, is likely to bias results towards the null and underestimate the true associations of β-blocker treatment. Second, due to limited power, we did not examine the subtype or the dosage of β-blocker treatment used, which prevented further subgroup analysis of class effect and dose–response relationship of β-blocker therapy with all-cause mortality. Third, patients in the β-blocker group were also more likely to be treated with other medications. It has been reported that β-blockers suppress renin levels in patients receiving ACEi and diuretics.[29] Notably, treatment with *all-trans*-RA has also been suggested to reduce renin-angiotensin system (RAS) activity in rats with experimental nephritis,[30] indicating that the observed effect modification could also be related to suppression of RAS. However, controlling for ACEi/ARBs or loop/thiazide diuretics had no impact on the interactions studied. Fourth, serum retinol is a poor marker of vitamin A status,[31] and therefore, uncertainty remains whether the interactions observed are due to vitamin A status in itself or confounders. However, we performed rigorous statistical adjustment including kidney function, which is an important determinant of serum vitamin A,[15,32] and risk associations persisted. Fifth and importantly, the landmark studies of β-blocker use have demonstrated increased survival in patients with HFrEF.[5,6] However, few patients in our study had LVEF below 40% (3.9%) and excluding these patients had no major influence on the risk estimates. This may suggest that the survival benefit of β-blockers alone or concurrent with higher vitamin A could also be indicated for patients who have CHD without left ventricular systolic dysfunction. Our findings nonetheless need to be replicated in other population-based studies. Sixth, in a randomized clinical trial, β-blocker use has been demonstrated to reduce the incidence of diabetic complications.[33] Accordingly, we observed a particular beneficial association of β-blockers with mortality among the subset with diabetes mellitus, which is consistent with a previous study.[34] However, recent reports have questioned the β-blockers treatment in diabetic patients with CHD based on increased mortality risk.[35,36] The survival benefit of β blockers in very high-risk subpopulation of patients with CHD and diabetes mellitus thus requires further assessment. Seventh, we did not measure active form of vitamin A, i.e. RA, which may pose a limitation to the possible mechanisms discussed. Finally, due to the observational nature of this study, our ability to draw causal connections is limited.

Conclusions

Among patients with suspected CHD, the benefit of β-blocker treatment at discharge on mortality risk was confined to patients with higher serum vitamin A concentrations.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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Data availibility

The data will be made available to other researchers for the purpose of replicating the procedure or reproducing the results upon reasonable request.

Clinical implications

Our findings should motivate future studies on the clinical effects of β-blocker treatment according to vitamin A status to enhance precision in drug therapy.

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Conflict of interest: All authors have no conflicts to declare

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