Original article

Angiotensin II receptor blockers versus angiotensin-converting enzyme inhibitors in patients with stable coronary artery disease: Prevalence, correlates, and prognostic impact (from the CORONOR study)

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ABSTRACT

Background: In international guidelines for patients with stable coronary artery disease (CAD), angiotensin-converting enzyme inhibitors (ACE-I) are recommended while angiotensin II receptor blockers (ARB) are proposed as an alternative in case of intolerance. There are no real-life data on the frequency and correlates of ARB use in this setting.
Methods: We studied 3363 outpatients included in a prospective registry on stable CAD (the CORONOR study) and receiving an ARB or an ACE-I at inclusion.
Results: Altogether, 944 patients received an ARB (28.1%). Factors positively and independently associated with ARB use versus ACE-I use were a history of hypertension, the absence of prior myocardial infarction, age, female gender, estimated glomerular filtration rate <60 ml/min/m^2, and left ventricular ejection fraction $\geq$40%. In the whole study population, the hazard ratio (HR) for the combined endpoint (cardiovascular death, myocardial infarction, stroke) of patients with ARB use was 0.95 (0.69–1.31) ($p = 0.765$) (patients with ACE-I use as reference). Similar results were observed when the analysis was restricted to a propensity-matched cohort: HR = 0.91 (0.62–1.34) ($p = 0.632$).
Conclusions: Our study shows that a significant proportion of stable CAD patients are treated with ARB rather than with ACE-I in modern practice. Several correlates of ARB prescription were identified. Our results suggest that patients receiving ARB have similar outcome than patients receiving ACE-I.

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Introduction

Secondary medical prevention is a key issue for patients with stable coronary artery disease (CAD). According to current guidelines, angiotensin-converting enzyme inhibitors (ACE-I) are recommended for patients with stable CAD, especially in case of coexistent hypertension, diabetes mellitus, left ventricular dysfunction, or chronic kidney disease [1,2]. When ACE inhibition is indicated but not tolerated, angiotensin II receptor blockers (ARB) are proposed as an alternative [1,2], although it is acknowledged that there are no clinical outcome studies showing a beneficial effect of ARB in stable CAD [2]. However, practice patterns for CAD patients have been shown to vary considerably [3], and there are limited recent real-life

data in the literature on the prevalence of ARB use (rather than ACE-I) in stable CAD populations. Furthermore, the determinants of ARB use in stable CAD have not been specifically investigated. The present analysis was designed to address these questions in the CORONOR study, a registry on stable CAD [4]. We also investigated, using propensity score matching, the outcome of patients receiving ARB versus those receiving ACE-I.

Materials and methods

Study population

The CORONOR (Suivi d'une cohorte de patients COROnariens stables en région NORd-pas-de-Calais) study was a multicenter study that enrolled 4184 consecutive outpatients with stable CAD between February 2010 and April 2011 [4,5]. The patients were included by 50 cardiologists from the region of Nord Pas-de-Calais in

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France during an outpatient visit. Patients were considered eligible if they had evidence of CAD defined by at least one of the following: previous myocardial infarction (MI) (more than 1 year previously), previous coronary revascularization (more than 1 year previously), and/or obstruction of ≥50% of the luminal diameter of at least one native vessel on coronary angiography. The sole exclusion criterion was hospitalization for MI or coronary revascularization within the past year.

Study design

A case record form, which contained information regarding demographic and clinical details of the patients, was prospectively completed at initial visit. During the outpatient visit, the investigators reviewed the current treatment and entered in the case record form the treatment that would be prescribed afterwards.

Two-year clinical follow-up was performed at outpatient visits or by contacting the general practitioner as well as the patient himself. In case of any hospitalization during the follow-up period, hospital records were reviewed for evidence of clinical events. We collected data on death, MI, and stroke. All events were adjudicated blindly by two investigators and by three investigators in case of disagreement. The cause of death was determined after a detailed review of the circumstances of death according to prespecified definitions [4]. The primary endpoint was a composite of cardiovascular death, MI, or stroke. Components of the primary endpoint were also studied separately.

Statistical analysis

Continuous variables were described as the mean ± standard deviation. Categorical variables were presented as absolute numbers and percentages. Baseline characteristics and cardiovascular treatments were compared by using the χ^2 test or the Fisher's test for categorical variables and the Student unpaired t test for continuous variables as appropriate. A logistic regression was used to determine factors associated with ARB use rather than ACE-I use. Variables with a p-value <0.05 in univariate analysis were entered into the final model. Cumulative event rates were estimated using the Kaplan–Meier method. Cox proportional hazard analyses were performed to calculate hazard ratios (HR) and 95% confidence intervals (CI). The proportional hazards assumption was tested visually using Kaplan–Meier curves and by examining a plot of −ln[−ln(survival time)] against the ln(time). Because of differences in key characteristics according to ARB use versus ACE-I use at baseline (Table 1), we calculated a propensity score, using the *psmatch2* routine, including as covariates: age, sex, hypertension, diabetes mellitus, prior myocardial infarction, prior coronary artery bypass surgery, prior hospitalization for heart failure, left ventricular ejection fraction, estimated glomerular filtration rate, heart rate, antiplatelets, and statins. We first performed a regression adjustment with the propensity score as a continuous variable. Then, using propensity scoring, patients with ARB use were one-to-one matched, using the single nearest-neighbor method, with patients with ACE-I use to obtain groups with similar baseline characteristics. All statistical analyses were performed with the STATA 14.0 software® (STATA Corporation, College Station, TX, USA). Statistical significance was assumed at a p-value <0.05.

Results

The baseline characteristics of the 4184 patients included in the CORONOR study have been reported previously [4]. There was a wide prescription of secondary prevention drugs: antiplatelet therapy (96.4%), β-blockers (79.4%), statins (92.2%). Antagonists of the renin–angiotensin–aldosterone (RAA) system were prescribed

Table 1
Baseline characteristics of the study population.

	All patients			Propensity-matched population		
	ARB ($n=944$)	ACE-I ($n=2419$)	p-Value	ARB ($n=836$)	ACE-I ($n=836$)	p-Value
Age, years ± SD	70.1 ± 10.3	65.4 ± 11.9	<0.0001	70.3 ± 10.2	70.4 ± 10.8	0.861
Men	69	81.7	<0.0001	68.7	71.2	0.263
Time since CAD diagnosis, years ± SD	7.7 ± 6.2	7.3 ± 6.2	0.069	7.7 ± 6.2	7.4 ± 6.2	0.226
Smoking						
- No	44	33.3		44.2	45.9	
- Previous	49.3	53.6	<0.0001	49.6	45.6	0.096
- Current	6.7	13.1		6.2	8.5	
Familial history of CAD	25.6	28	0.162	25.4	24	0.533
History of hypertension	82.5	57	<0.0001	83.3	83.9	0.742
Diabetes mellitus	38.8	30.5	<0.0001	39.6	38.8	0.726
Prior MI	51.7	70.1	<0.0001	51.2	52.6	0.557
Prior coronary angiography	99.5	99.2	0.503	99.4	98.9	0.285
Multivessel CAD	59	58.5	0.791	59.1	60.6	0.528
Prior coronary revascularization	84.4	86.6	0.102	84	85.3	0.456
Prior BMS implantation	46.8	56.3	<0.0001	47	52.6	0.02
Prior DES implantation	29.2	24.5	0.005	28.5	27.5	0.663
Prior coronary bypass	21.5	20.8	0.669	21.7	20.8	0.676
Atrial fibrillation at inclusion	7.4	7.3	0.889	7.7	8.4	0.640
Prior stroke	7.9	8	0.943	8.5	9.1	0.666
Prior aortic or peripheral intervention	8.7	9	0.795	9	10.4	0.321
Prior hospitalization for HF	6.8	8.6	0.075	7.4	7.1	0.777
Heart rate, bpm ± SD	66.9 ± 11.6	66.2 ± 11.9	0.093	67 ± 11.6	67.1 ± 12.2	0.838
eGFR, ml/min/1.73 m² ± SD	73.1 ± 24.1	80.9 ± 24	<0.0001	73.1 ± 24	72.8 ± 22.8	0.835
eGFR <60 ml/min/1.73 m²	28.8	17.8	<0.0001	28.7	28.1	0.786
LVEF, % ± SD	58.7 ± 10.3	56.1 ± 11.1	<0.0001	58.6 ± 10.5	58.2 ± 10.4	0.462
LVEF <40%	4.4	7.3	0.002	4.8	4.4	0.726
Antiplatelet drugs	95.2	96.9	0.016	95	96.2	0.188
β-Blockers	78.1	83	0.001	77.6	81.2	0.070
Statins	90.5	94.2	<0.0001	89.7	91	0.362

Data are percent values or mean ± standard deviation (SD).
ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; BMS, bare metal stent; DES, drug eluting stent; MI, myocardial infarction; HF, heart failure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.