Two-Year Outcomes of Patients Treated With Aliskiren Under Clinical Practice Conditions: Non-Interventional Prospective Study

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The authors investigated the long-term effectiveness and safety of aliskiren (ALIS) with particular attention on its association with dual blockade of the renin-angiotensin system (RAS). The open, prospective 3A Registry (N=8723) in Germany assigned patients in a 4:1:1 ratio to ALIS, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), or non-RAS drugs. Patients taking ALIS compared with those taking ACE inhibitors/ARBs or non-RAS had more comorbidities and risk factors, were taking more antihypertensive agents, and had higher blood pressure (BP) values at entry. At 2 years, BP reduction from baseline was similar in all groups (mean, −20.5/−9.9 mm Hg). A total of 2.3% of patients died, 0.5% had myocardial infarction, 0.6% had stroke, 2.9% were hospitalized, and 5.5% had any event (not significant between groups). ALIS alone or combined with another RAS inhibitor was well tolerated and effective in lowering BP in typical unselected patients with hypertension. Given the methodical limitations of the design, the study cannot be used to confirm or refute safety concerns for dual RAS blockade as suggested by the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) trial. *J Clin Hypertens (Greenwich).* 2016;18:647–654. © 2015 Wiley Periodicals, Inc.

The renin-angiotensin-aldosterone system (RAS) plays a pivotal role in the regulation of fluid balance and blood pressure (BP), and RAS blockade is an established principle in the treatment of hypertension.[1] Further, RAS inhibition exerts a renoprotective effect independent of BP reduction.[2] Three drug classes are available that inhibit the RAS at various stages, namely angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and the direct renin inhibitor aliskiren (ALIS), which controls the RAS directly at the point of activation.[3] ALIS has been extensively investigated in randomized controlled trials as monotherapy and in various free and single-pill combinations.[4–7] However, the drug is less well documented with regard to its effectiveness and safety under clinical practice conditions.[8–10]

Particular interest has been given to the combination of ALIS with an ACE inhibitor or ARB, ie, dual RAS blockade, as ALIS was expected to block the compensatory rise of plasma renin activity (PRA) induced by RAS inhibitors acting downwards in the cascade. Although recent results of both the Valsartan in Acute Myocardial Infarction Trial (VALIANT)[11] and the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)[12] showed no clinical benefits of the combination of effective doses of an ACE inhibitor and ARB, the combination with ALIS could probably offset potential deleterious effects of compensating renin activation—a well-known risk factor for cardiovascular and renal events[13,14]—and exert substantial renoprotective effects.[15] Against this background, the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) was studying ALIS on top of ACE inhibitor or ARB therapy in optimally treated patients with type 2 diabetes and renal impairment compared with a placebo add-on. However, the active-treatment group experienced an increase in renal complications, hyperkalemia, and hypotension over 18 to 24 months of follow-up.[16] There was also a slight increase in cardiovascular events (death or stroke) in the ALIS group; however, the US Food and Drug Administration (FDA) did not reach a definite conclusion regarding an actual link between these drugs and death or stroke.[17] Nonetheless, the described events led to early termination of the study in 2011 as recommended by the Data and Safety Monitoring Board.

The 3A Project is one of the largest contemporary registries documenting management of unselected patients with hypertension by primary care physicians.[18,19] As it documents predominantly ALIS over the long term, it provides the largest and most current dataset on the utilization and effects of the drug in clinical practice. Here, we report the 2-year outcomes of unselected patients with hypertension treated with various antihypertensive regimens. Particular focus was put on the effectiveness and safety of ALIS without other RAS inhibitors and in combination with other RAS blockers (ALIS plus an ACE inhibitor/ARB),

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including the outcomes of the drug in a patient population similar to ALTITUDE.

PATIENTS AND METHODS

Registry Design and Description

The 3A Registry is a prospective, observational, multicenter cohort study. It was initiated in August 2008 by the Institut für Herzinfarktforschung in Ludwigshafen, Germany. Physicians in the primary care setting (mainly family physicians and cardiologists) throughout Germany were eligible for participation, if they were responsible for the initiation or modification of antihypertensive therapy of their patients. The study was performed in agreement with German regulations (German Drug Law). The choice of drugs and treatment patterns was the sole responsibility of the treating physician and not stipulated by the protocol. The study materials were approved by the Medical Ethical Committee, Mainz, Germany. The registry has been published in Clinicaltrials.gov under NCT01454583 and in the German Association of Research-Based Pharmaceutical Companies (VfA) database.[20]

In the first recruitment round, about 900 physicians enrolled nearly 15,000 patients (which formed the basis for the current analysis), and in the second round, about 70 nephrologists enrolled an additional 1000 patients.

Patients and Schedule

Patients were eligible to participate if they met the following criteria: (1) age 18 years or older, (2) known (prevalent) or newly diagnosed (incident) arterial hypertension, (3) newly initiated or modified treatment for hypertension, (4) ability and willingness to attend follow-up visits, and (5) provided written informed consent. Physicians were requested to include eligible patients in a consecutive manner into the study to avoid selection bias. The only exclusion criteria were participation in a randomized controlled clinical trial or foreseeable problems in attending follow-up visits.

Since one of the aims of the registry was to collect information about the use of the new compound ALIS, patients were categorized into three groups in a targeted 4:1:1 ratio: (1) treatment with the direct renin inhibitor ALIS, or (2) an ACE inhibitor or ARB, or (3) agents not blocking the RAS (non-RAS). These drugs were to be administered as monotherapy or in addition to an existing drug regimen (combination therapy), upon the discretion of the treating physicians. Each site was requested to enroll 12 patients in a consecutive manner. This sequential, stratified recruitment aimed at reducing sampling bias.

BP measurement was performed with the standard devices available at the physicians' office (manual sphygmomanometers or semiautomated devices), which, according to German legislation, must carry a calibration stamp. Further, the guidance for measuring BP (eg, sitting patient under resting conditions, repeat measurements) had to be followed.[21]

Objectives

The registry aimed mainly at the following: characterization of consecutive patients with arterial hypertension in outpatient care; identification and characterization of treatment with ALIS; assessment of adherence to therapy; documentation of adverse events, in particular cardiovascular events; efficacy of the different BP-lowering therapies; prevalence and prognostic impact of renal dysfunction; and evaluation of health-economic impact.

Data Collection and Entry

Data were collected during the baseline visit and the follow-up visits after 1 and 2 years using electronic case record forms (eCRFs) using an SSL-secured Internet connection. Measures of quality control included automated plausibility checks during data entry, queries provided by the data manager after review of the data, and on-site monitoring with source data verification in 10% of the patients.

Parameters

Detailed sociodemographic and clinical parameters (risk factors, comorbidities) were collected at baseline, as were data on hypertension history and BP, cardiac medication, and available laboratory values. At the follow-up visits after 1 and 2 years, current antihypertensive medication, BP levels, and laboratory values were documented. In addition, physicians were to report all deaths and cardiovascular events. To avoid underreporting, they received a list with tick boxes on deaths (sudden cardiac death, other cardiovascular, malignancy, other), cardiac events (myocardial infarction [MI], percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG], application of an implantable cardioverter-defibrillator), or stroke events. To assess chronic kidney disease (defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), the Modification of Diet in Renal Disease Study (MDRD) formula was used.[22]

Adverse Events

Outcome data of specific events were reported using the eCRF for all patients as described above. In addition, a detailed follow-up of adverse events (AEs) and serious AEs (SAEs) was performed for Novartis products due to legal reasons (sponsor's obligation) using separate paper forms. A consistency check was performed by Novartis for the outcome events (death, MI, PCI, CABG, stroke, and hospitalization) by comparing the AE form and the data in the eCRF. To avoid bias, data from these AE forms were not reconciled with the electronically reported event data but were analyzed and reported independently. Thus, the AE report in this paper refers exclusively to patients receiving ALIS. For each patient, only AEs were analyzed with an onset date before the (planned) 2-year follow-up or the date of death.

Data Entry and Analysis

Continuous variables are summarized with descriptive statistics (absolute numbers, means, standard deviations, or medians, with 25th and 75th percentile as appropriate). All summaries are presented on available data. Categorical data are presented as number and percentage of patients in each category. Four treatment classes were analyzed: ALIS without an ACE inhibitor or ARB vs an ACE inhibitor or ARB vs ALIS plus an ACE inhibitor or ARB (ie, dual RAS inhibition) vs non-RAS drugs (eg, β-blockers, calcium channel blockers). Descriptive analyses on AEs/SAEs were performed for the following two treatment classes: ALIS without ACE inhibitors/ARBs vs ALIS plus an ACE inhibitor/ARB (ie, dual RAS inhibition). Comparisons between treatment classes were performed by chi-square test for categorical variables or Kruskal-Wallis test for continuous measures.

A number of subgroups were analyzed (ie, by presence/absence of diabetes mellitus, chronic kidney disease, previous cardiovascular events, and an ALTITUDE-like condition, defined as a combination of diabetes mellitus and eGFR 30–59 mL/min/m^2). No Bonferroni adjustments were made for multiple comparisons. Events were documented without the date, and analyzed separately or, if appropriate, in combination (eg, major adverse cardiovascular and cerebrovascular events [MACCEs]). Percentages were calculated on the basis of patients with data for each respective parameter (ie, no percentages for missing values are provided).

In addition, Kaplan-Meier (KM) curves were generated for a 730-day period disregarding any covariates or adjustments (all patients in a medication class account for the gradient of corresponding KM curve, regardless of their count or intensity of confounders). Therefore, curves must not receive any isolated interpretation without obeying the results from the multiple Cox proportional hazard regression model, which generates survival curves similar to KM curves. In the Cox model, however, because of the adjustment for confounders, there are no unique estimations of the survival curves, but individual curves for each possible profile of covariates. The default profile was determined by modal or median values of the confounders. Figures refer to the following profile of a "standard patient": age 64 years, male, nonsmoker, dyslipidemia, diabetes, GFR MDRD ≥60 mL/min/1.73 m^2, no cardiovascular disease, hyper-

TABLE I. Demographic and Clinical Characteristics at Baseline

	Antihypertensive Treatment				
	Total	Aliskiren Without ACE Inhibitor/ARB	ACE Inhibitor/ARB	Aliskiren + ACE Inhibitor/ARB	Non-RAS
	8723 (100%)	3279 (37.6%)	1476 (16.9%)	2592 (29.7%)	1376 (15.8%)
Demographic variables					
Age, median, y	64.7	62.1	65.2	67.4	62.8
range, y	55–72	53–71	55–72	58–73	52–71
Women	45.9	45.9	43.6	44.1	51.7
BMI, median, kg/m^2	28.3	28.0	28.1	29.4	27.7
Risk factors, %					
Diabetes mellitus or glycated hemoglobin ≥6.5%	28.5	23.9	27.3	38.3	22.0
Microalbuminuria/proteinuria	10.4	7.8	10.4	15.8	5.0
Comorbidities, %					
Any cardiovascular disease	30.5	23.6	32.0	42.1	23.8
Coronary artery disease	20.3	15.5	22.4	27.2	16.4
Stroke	4.7	3.5	4.2	6.4	4.6
Symptomatic peripheral arterial disease	6.1	4.4	6.1	9.4	4.2
Chronic heart failure	12.9	9.9	12.9	18.6	9.2
Renal failure	8.7	6.6	7.4	14.1	4.9
Blood pressure characteristics					
Known hypertension	85.1	76.9	86.5	99.0	77.1
Duration of hypertension, y	6.8	6.1	6.6	8.0	5.6
Antihypertensive drugs, No.	2.6±1.4	2.0±1.1	2.3±1.1	3.9±1.2	1.6±0.8
Resistant hypertension, %[a]	33.2	21.0	29.5	59.9	13.9
SBP/DBP at baseline, mm Hg	155/90	158/91	154/89	159/90	152/89

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; non-RAS, antihypertensive drugs not affecting the renin-angiotensin system; SBP, systolic blood pressure. Values are presented as percentages unless otherwise indicated. [a]Resistant hypertension was defined as therapy with at least three antihypertensive drugs including a diuretic. Comparisons between treatment groups were performed by chi-square test for categorical variables or Kruskal-Wallis test for continuous measures. All *P* values from group comparisons (results of two-sided tests) were <.0001.

tension stage 2, one or two additional antihypertensive drugs, BMI 29 kg/m^2, no family history of coronary artery disease, and 6 years' duration of hypertension. Because this standard patient is a comparatively healthy one, the curves generated by the Cox proportional hazard model typically are above those generated by the KM method. Representation of estimated survival, confidence limits, and smoothing was performed in the Cox model curves in the same way as for the KM survival curves. Missing values in the temporal variables were imputed via drawing from a random distribution within the known limits (eg, previous and current follow-up). Missing values in the covariates were imputed by the overall mean. Observations with missing values for the target variables (events) were excluded from calculations and figures. *P* values ≤.05 were considered significant. All *P* values are results of two-sided tests. Statistical analysis was performed with SAS 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Patient Disposition and Characteristics

Of the original cohort of 14,113 patients with evaluable baseline visits, at 2 years, data were available for 8723 patients (61.8%). In line with the inclusion schedule, there were two thirds of patients in the ALIS groups (ALIS without ACE inhibitor/ARB, 37.6%; ALIS plus an ACE inhibitor/ARB, 29.7%), 16.9% in the ACE inhibitor/ARB group, and 15.8% in the non-RAS group.

Characteristics of patients at the inclusion visit are displayed in Table I. The mean age of patients was 64.7 years, and the ratio of men and women was similar. Risk factors and concomitant diseases were prevalent, including cardiovascular diseases (30.5%), diabetes mellitus or increased glycated hemoglobin (28.5%), or renal failure by physician diagnosis (8.7%). Patients in the non-RAS group had lower rates of risk factors and comorbidities compared with the ALIS and ACE inhibitor/ARB groups.

Hypertension

The majority of patients (85.1%) had previously known (prevalent) hypertension at entry. Notably, most patients received combination drug therapy (mean of 2.6 agents, Table I). The mean BP at entry was 155/90 mm Hg in the total cohort, but was higher in the ALIS groups (158/91 mm Hg or 159/90 mm Hg) compared with the other groups. About one third of patients met the definition of "refractory to therapy," ie, was treated with at least three different antihypertensive drugs including a diuretic.

After 2 years of treatment, BP was substantially reduced in all groups, with a relative reduction of systolic BP (SBP) between 10.4% and 12.9% and of diastolic BP (DBP) between 8.5% and 10.8% based on the value at entry. Absolute reductions are displayed in Figure 1. The rate of patients with controlled BP, defined as SBP/DBP <140/90 mm Hg, was considerably improved at 2 years compared with entry (56.1% vs 13.0%, Figure 2), and the portion of patients with hypertension stage 2 or 3 was substantially reduced.

Clinical Events

During the 2-year follow-up, 5.5% of patients in the total cohort experienced any cardiac event and 3.0% experienced MACCEs (Table II). Before adjustment, event rates differed across groups (4.9% taking ALIS without an ACE inhibitor/ARB, 4.3% taking an ACE inhibitor/ARB, 7.9% taking ALIS plus an ACE inhibitor/ARB, and 3.9% taking non-RAS agents). However, in the KM estimate of events, eg, survival free of MACCE events (Figure 3), there were no statistical differences between the four groups over time. This also held true for adjusted Cox analysis that accounted for a variety of possible confounders such as age, sex, comorbidities, and treatment modalities (Figure 4).

AEs in the ALIS Groups

In the total cohort, 7.6% of patients taking ALIS reported at least one AE, and the most frequently reported individual AEs were hypertensive crisis (0.8%), cardiac arrhythmia (0.6%), and renal dysfunction (0.6%).

The AE rate in patients taking ALIS without an ACE inhibitor/ARB was 6.2% and those taking ALIS plus an ACE inhibitor/ARB was 9.3%. In the latter group, the most frequent individual event was cardiac arrhythmia (1.0%).

Ancillary Analysis of Subgroups of At-Risk Patients

In subgroups of patients with high cardiovascular risk (diabetes mellitus, chronic kidney failure, manifest cardiovascular disease, diabetes mellitus combined with eGRF 30–59 mL/min/1.73 m^2 [ALTITUDE-like condition]), overall event rates were substantially increased compared with the overall population. The unadjusted

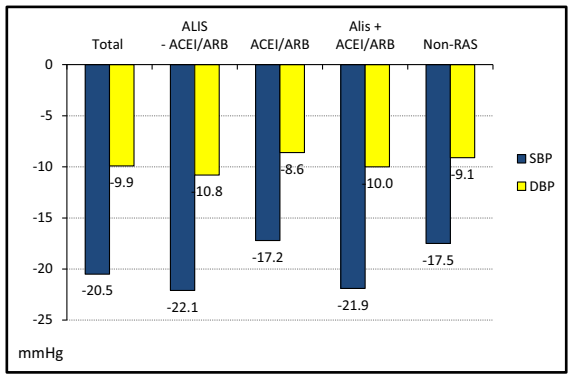

FIGURE 1. Blood pressure reduction after 2 years compared with follow-up. ALIS indicates aliskiren; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAS, renin-angiotensin system; SBP, systolic blood pressure; DBP, diastolic blood pressure.

event rates for patients taking ALIS plus an ACE inhibitor/ARB were higher compared with those taking ALIS without an ACE inhibitor/ARB. However, after Cox adjustment for confounders, there were no differences in event rates between these two ALIS groups.

The AE rate in patients with ALIS without ACE inhibitor/ARB was 6.2% and with ALIS plus an ACE inhibitor/ARB was 9.3%. In patients with an ALTITUDE-like condition, the AE rate in patients with ALIS without an ACE inhibitor/ARB was 13.0% and with ALIS plus an ACE inhibitor/ARB was 16.5%, with renal dysfunction being the most frequent event (3.6% and 3.5%, respectively).

DISCUSSION

According to the present study in a large, diverse population of hypertensive patients, long-term therapy on ALIS with or without other RAS inhibitors was generally well tolerated, effective in lowering elevated BP, and was not associated with new or unexpected safety signals under clinical practice conditions.

Observational data in this setting are all the more of interest, as ALIS in the absence of outcome trials has not been recommended as first-line therapy in guidelines on the treatment of hypertension,[21,23] nor in guidance documents of the National Institute for Health and Care Excellence (NICE)[24] in the United Kingdom or the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) in Germany.[25] Therefore, it could be assumed that the drug is used in special populations, such as patients with difficult to treat hypertension, or those intolerant of/not responding to antihypertensives of other classes. It was not clear, however, what type of patients receive the drug, and how they respond to

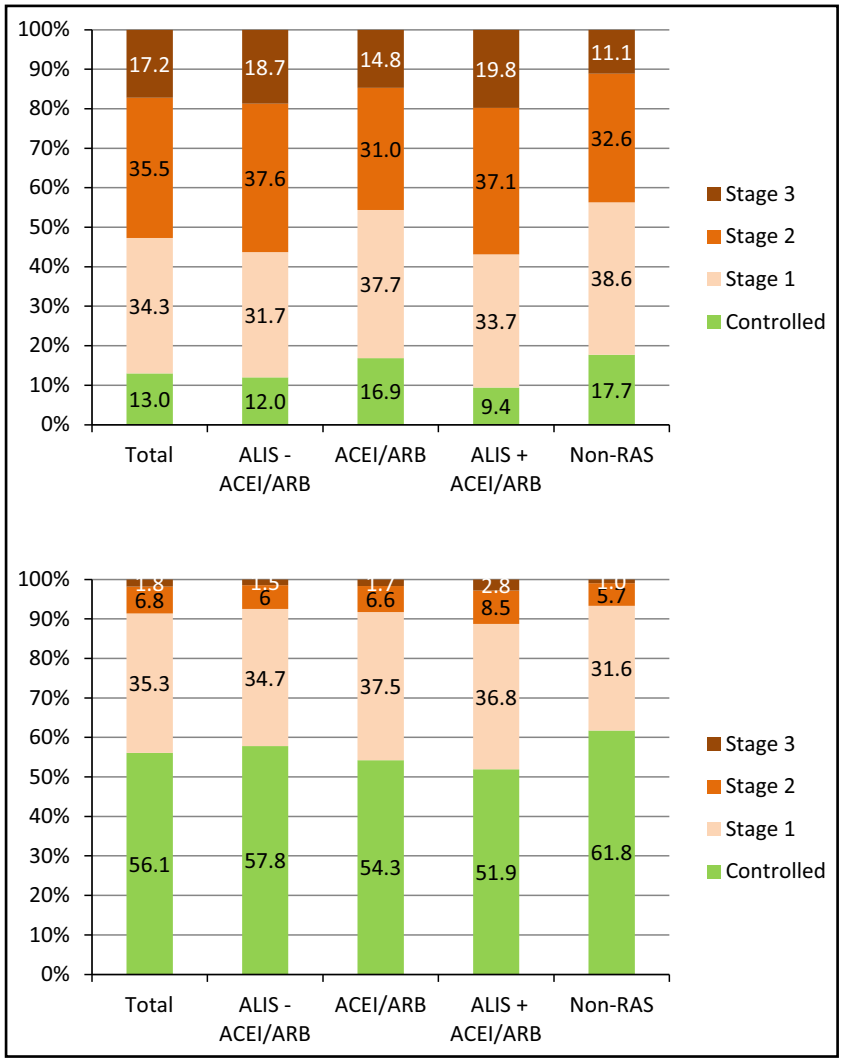

FIGURE 2. Blood pressure control status at baseline (top) and after 2 years (bottom). Controlled blood pressure: <140/90 mm Hg. Stage 1: mild hypertension, 140–159/90–99 mm Hg. Stage 2: moderate hypertension, 160–179/100–109 mm Hg. Stage 3: severe hypertension, ≥180/≥110 mm Hg. ALIS indicates aliskiren; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAS, renin-angiotensin system.

TABLE II. Clinical Events at 2 Years

	Antihypertensive Treatment				
	Total	Aliskiren Without ACE Inhibitor/ARB	ACE Inhibitor/ARB	Aliskiren + ACE Inhibitor /ARB	Non-RAS
Patients, No.	8723	3279	1476	2592	1376
Any event[a]	484 (5.5)	160 (4.9)	64 (4.3)	206 (7.9)	54 (3.9)
MACCE	266 (3.0)	89 (2.7)	36 (2.4)	102 (3.9)	39 (2.8)
Death	199 (2.3)	70 (2.1)	25 (1.7)	74 (2.9)	30 (2.2)
Myocardial infarction (nonfatal)	47 (0.5)	14 (0.4)	11 (0.7)	18 (0.7)	4 (0.3)
PCI	69 (0.8)	19 (0.6)	13 (0.9)	32 (1.2)	5 (0.4)
CABG	20 (0.2)	7 (0.2)	2 (0.1)	8 (0.3)	3 (0.2)
Stroke	56 (0.6)	18 (0.5)	4 (0.3)	23 (0.9)	11 (0.8)
Hospitalization for hypertension	253 (2.9)	79 (2.4)	32 (2.2)	122 (4.7)	20 (1.5)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MACCE, major adverse cardiac and cerebrovascular event; non-RAS, antihypertensive drugs not affecting the renin-angiotensin system. Values are presented as number (percentage). [a]Any event including death, myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), stroke, or hospitalization. Comparisons between treatment groups were performed by chi-square for categorical variables or Kruskal-Wallis test for continuous measures. All *P* values are results of two-sided tests.

therapy. According to the present study, patients in the ALIS groups compared with those in the ACE inhibitor/ARB and non-RAS groups were sicker (and more often difficult to treat), as they had higher rates of comorbidities and risk factors, took more antihypertensive agents, and had higher BP at inclusion.[18] This is in line with the preferred use of ALIS in comorbid and high-risk patients, partly stipulated by prescription guidelines, which has also been reported in Canadian and Italian registries.[8,26]

Treatment with ALIS-based therapy led to substantial reduction of BP in the long term and to BP control rates similar to the other groups. These findings correspond with the substantial BP-lowering effect of ALIS in monotherapy and its combinations with other drug classes as reported in randomized controlled trials.[27]

The outcome data of this study are based on a robust number of patients that could be documented over 2 years. Overall, given the advanced age and large number of patients at high cardiovascular risk in the 3A Registry, the rate of death and major cardiovascular events was low (death, 2.3%; MI, 0.5%; stroke, 0.6%). For comparison, in the German cohort of the Reduction of Atherothrombosis for Continued Health (REACH),[28]

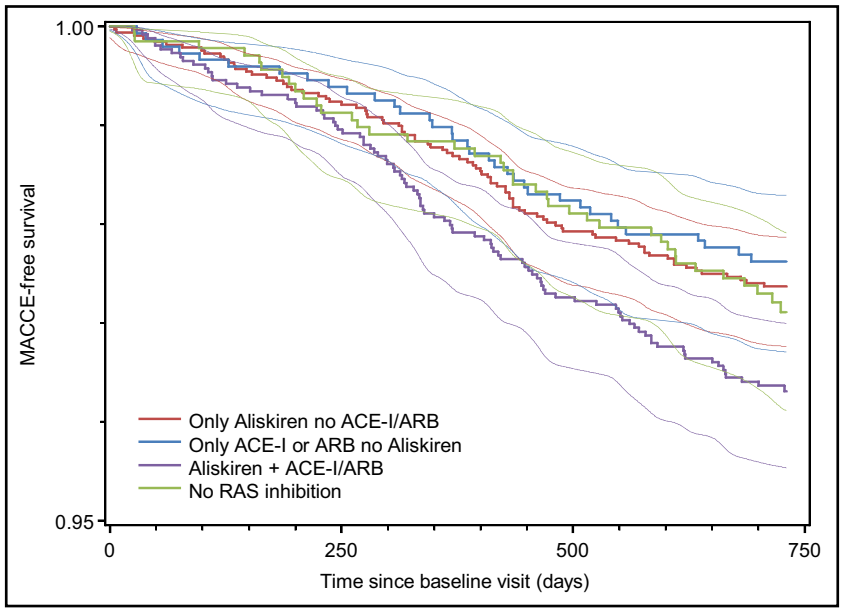

FIGURE 3. Kaplan-Meier estimate of patients with survival free of major adverse cardiac and cerebrovascular events (MACCEs) in the four treatment groups. Beside the estimated survival rates (step functions, bold lines) point-wise, two-sided 95% confidence limits are drawn as smoothed curves (thin lines). Estimation and confidence limits can be matched by equal colors. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAS, renin-angiotensin system.

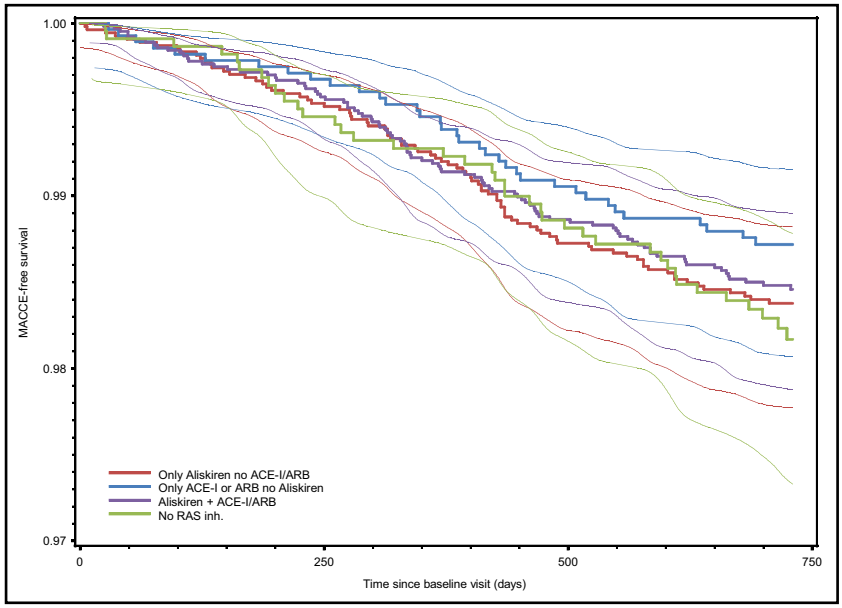

FIGURE 4. Cox regression model of patients with survival free of major adverse cardiac and cerebrovascular events (MACCEs) in the four treatment groups. Cox regression model adjustment for confounders. The figure refers to the profile of a relatively healthy "standard patient" aged 64 years, male, nonsmoker, dyslipidemia, no diabetes, glomerular filtration rate using the Modification of Diet in Renal Disease formula ≥60 mL/min/1.73 m^2, no cardiovascular disease, stage 2 hypertension, 1 or 2 additional antihypertensive drugs, body mass index 29 kg/m^2, no family history of coronary artery disease, and 6 years' duration of hypertension.

2.1% of the patients with symptomatic atherothrombotic disease and 1.5% of the patients with at least three cardiovascular risk factors had died of a cardiovascular event after 1 year.[29]

The rates for all cardiac events were higher in the ALIS plus ACE inhibitor/ARB group compared with the ALIS without ACE inhibitor/ARB group (eg, MACCE 3.9% vs 2.7% or any event 6.5% vs 4.9%). However, the impression of increased event risk in the dual RAS groups could not be substantiated in the Cox regression model that accounted for the fact that patients in this group were older and sicker compared with those in the ALIS without ACE inhibitor/ARB group. The wide confidence intervals in Figure 3 illustrate the variance and uncertainty of the results owing to the low event numbers.

Similar findings were noted in subgroups with increased cardiovascular risk such as established cardiovascular disease, diabetes mellitus,[30] or chronic kidney disease,[31] where event rates were higher than in the total population, and were also—before adjustment—higher in the ALIS plus ACE inhibitor/ARB group compared with the ALIS without ACE inhibitor/ARB group.

In a pooled analysis from nine short-term (8-week) and four longer-term (26- to 52-week) randomized controlled trials of ALIS in patients with hypertension, the safety and tolerability profile of ALIS in combination with the ARBs valsartan or losartan, or a diuretic, was similar to ALIS, ARBs, or diuretics alone.[32] In the 3A Registry, no new or unexpected safety signals for ALIS were observed. An increased risk of hypotension and hyperkalemia while taking ALIS plus ACE inhibitors/ARBs, as observed in ALTITUDE in diabetic patients,[15] was not seen in the 3A Registry. Renal dysfunction was noted in the pooled ALIS groups in 3.5% of patients, however, in contrast to ALTITUDE, with no increase in the ALIS plus ACE inhibitor/ARB group.

STUDY STRENGTHS AND LIMITATIONS

In view of methodical considerations, the registry population differs from typical randomized controlled trials in hypertension where high-risk patients are for the most part excluded. Selection bias for centers with interest or expertise in hypertension management induced by the agreement to participate is likely, but in view of the size of the registry and the inclusion schedule used, results likely apply to typical primary care patients. The study was not controlled and therefore the contribution of placebo effects is unknown. It was not possible to verify consecutive enrollment or the completeness of the information on the electronic case report form by source data monitoring in all cases. It needs to be highlighted that for 38% of patients, no follow-up at 2 years could be performed (in about 14% because of nonparticipation of the centers irrespective of the situation of the patient, and in 24% because of dropout of individual patients). It is possible that dropouts were caused by untoward effects such as tolerability issues or unsatisfactory efficacy.

Cardiovascular events were not adjudicated for ALIS, and misclassification of MI or strokes cannot be excluded. Further, underreporting of events might have

occurred. The announcement of source data monitoring (actually performed in 5% of cases) in randomly selected centers likely contributed to good data quality.

CONCLUSIONS

Under clinical practice conditions, ALIS was predominantly administered to "sicker" patients with multiple comorbidities, who are at high or very high cardiovascular risk. In patients receiving dual RAS blockade with ALIS and an ACE inhibitor/ARB there were no significant differences in death or cardiovascular events according to KM estimates or Cox regression analysis that adjusted for factors that could possibly contribute to such events. Given the methodological limitations of observational studies restricting their interpretation, the present study cannot confirm or refute safety signals from the ALTITUDE trial.

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