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An Observational, Prospective, Open-Label, Multicentre Evaluation of Aliskiren in Treated, Uncontrolled Patients

A Real-Life, Long-Term, Follow-Up, Clinical Practice in Italy

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Abstract

Introduction: The addition of the direct renin inhibitor aliskiren is demonstrated to improve blood pressure (BP) control rate and reduce progression of organ damage in treated hypertensive patients in clinical trials with a relatively short follow-up period.

Aim: The objective of this study was to assess the effectiveness, safety and tolerability of aliskiren as an add-on antihypertensive therapy in high-risk, treated, hypertensive patients, who were not controlled with concomitant treatment with at least two antihypertensive drugs under 'real-life' conditions, during a planned observation and treatment period of at least 12 months in Italy.

Methods: Clinical data were derived from medical databases of treated, uncontrolled, hypertensive patients followed by specialized physicians operating in different clinical settings (hospital divisions or outpatient clinics) in Italy. Aliskiren was added to stable antihypertensive treatment, including at least two drug classes (independently of class or dosage) and unable to achieve BP control. Follow-up visits for measuring clinic BP levels and collecting data on drug safety and tolerability were planned at time intervals of 1, 6 and 12 months. At each predefined follow-up visit, aliskiren could be up-titrated from 150 to 300 mg daily if BP control was not achieved.

Results: From May 2009 to June 2011, a total of 1186 treated, uncontrolled, hypertensive patients (46.3% female, aged 65.2 ± 11.7 years, mean duration of hypertension 13.2 ± 9.3 years, mean clinic BP levels 156.5 ± 15.9/90.3 ± 9.5 mmHg) were enrolled. Systolic and diastolic BP levels were 141.1/82.4, 134.9/79.8 and 133.6/78.9 mmHg at 1-, 6- and 12-month follow-up visits, respectively ($p < 0.0001$ vs baseline for all comparisons). These effects were consistent in all predefined subgroups, including those with left ventricular hypertrophy, renal disease, diabetes mellitus, coronary artery disease or cerebrovascular disease. Reduced levels of microalbuminuria were also reported, without affecting other renal and

electrolyte parameters. Overall, compliance to study medication was high (93.0%), with a very low proportion of patients experiencing adverse events leading to drug discontinuation (3.6%).

Conclusions: In this observational, prospective, open-label, multicentre study, we reported the 12-month clinical effectiveness, safety and tolerability of adding aliskiren to treated, uncontrolled, hypertensive patients in a 'real-life' setting in Italy. This strategy leads to a significantly improved BP control rate and low incidence of drug-related side effects or discontinuations.

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Keywords: hypertension, high blood pressure, antihypertensive therapy, direct renin inhibitors, aliskiren, renin-angiotensin system.

Introduction

Uncontrolled hypertension remains a major problem for healthcare systems, being strictly related to an elevated burden of cardiovascular morbidity and mortality in both Western and developing countries.[1] Randomized controlled clinical trials have demonstrated the clinical benefits obtained by lowering blood pressure (BP) to normal values (i.e. BP levels below 140/90 mmHg or below 130/80 mmHg in high-risk hypertensive patients with diabetes mellitus or renal disease, respectively, in terms of reduced incidence of major cardiovascular events and better cardiovascular outcomes, independently by age and presence of concomitant diseases.[2-4] Despite this solid evidence in favour of achieving effective and sustained BP reductions, recent international surveys and observational studies have consistently reported a persistently low rate of BP control in treated hypertensive patients, particularly in those at high or very high cardiovascular risk.[5-8]

Over the last years, clinical trials have systematically tested and consistently demonstrated the clinical efficacy, safety and tolerability of combination strategies based on the use of drugs inhibiting the renin-angiotensin system (RAS), including ACE inhibitors or angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]), with either diuretics or calcium-channel blockers (CCBs), or both.[9-11] On the basis of these findings, an extensive use of combination therapies with these antihypertensive drug classes has been prompted to provide additional BP-lowering efficacy and better BP control in treated hypertensive patients, compared with different monotherapies or combination therapies based on β-adrenoceptor antagonists (β-blockers) and diuretics.[12,13] Despite this evidence, an acceptable BP control rate in the general population is far from being achieved.

More recently, aliskiren, a direct renin inhibitor (DRI), which selectively antagonizes the cleavage from angiotensinogen to angiotensin I by blocking the active site of the renin enzyme,[14,15] has been evaluated in randomized controlled clinical trials on top of antihypertensive strategies in high-risk patients with hypertension.[16] Several national registries have confirmed the clinical benefits of adding aliskiren in treated hypertensive patients at high cardiovascular risk in a setting of 'real-life' practice.[17,18] However, these surveys had a relatively short follow-up period, thus limiting the potential implications for daily clinical practice. In addition, the preliminary analysis of the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints) trial[19] have raised doubts and uncertainties on the clinical safety of this drug combined with either ACE inhibitors or ARBs in high-risk patients with diabetes and renal disease. This latter trial does not seem to confirm the available evidence (and clinical practice) of the potential benefits derived from adding aliskiren to any other RAS blocking agent, CCB or diuretic, in terms of effective BP reduction and control.

This analysis was undertaken to evaluate the long-term effectiveness, safety and tolerability of adding aliskiren 150–300 mg daily in treated hypertensive patients with uncontrolled BP in a setting of 'real-life' clinical practice among specialized physicians operating in hospital divisions and outpatient clinics during a 1-year follow-up period in Italy.

Methods

Methodology of the Study

This is an observational, prospective, open-label, multicentre study to assess effectiveness, safety and tolerability of aliskiren in a setting of 'real-life' practice of high-risk patients with hypertension not controlled with concomitant treatments, including at least two other antihypertensive drugs.

The study conformed to the Declaration of Helsinki and its subsequent modifications, and confidentiality on the demographic and clinical data was carefully preserved.

Study Centres

There were 45 sites involved in the study, of which 44 sites actively enrolled patients and were thus included in the present

analysis. All centres have a practice for the clinical management of high-risk patients and were distributed across the Italian territory. A full list of centres and investigators is reported in Supplemental Digital Content (SDC), http://links.adisonline.com/HBZ/A3.

Involved Physicians

Physicians operating in different clinical settings (hospital divisions or outpatient clinics) and who provided information on at least one outpatient treated with the study drug (aliskiren) at the recommended dosages, participated in the present analysis.

According to Italian national regulatory rules for aliskiren prescriptions,[18] from the time of the study enrolment to conclusion, all investigators included in the present analysis had to be specialized physicians with proven experience in treating hypertensive patients with high cardiovascular risk and operating in centres with experience in the clinical management of hypertension and cardiovascular and renal diseases, including cardiologists, diabetologists, nephrologists and specialists in internal medicine.

Acceptance of the study invitation placed physicians under no obligation, and physicians were entitled to drop out of the survey at any stage. Physicians included in the study did not receive any compensation or benefits for their participation.

Inclusion and Exclusion Criteria

The main inclusion criteria were: (i) written informed consent, signed by each patient included in the present study; (ii) men or women aged over 18 years; and (iii) known history of diagnosed and treated hypertension, not controlled with concomitant antihypertensive drug treatments.

The main exclusion criteria were: (i) proven intolerance to the study drug; (ii) concomitant use of ciclosporin; (iii) drugs inhibiting P-glycoprotein (verapamil, quinidine); (iv) presence of acute illness; and (v) any concomitant mental, neurological or physical disorders that may have affected acceptance of study participation or the written consent signature.

Drug Prescriptions

In Italy, at the time when this study was ruled out, prescriptions of aliskiren had to be filled by specialized physicians, only when a standard treatment, including at least two antihypertensive drug classes (independent of the dosage), failed to normalize BP levels in treated, uncontrolled, hypertensive patients (BP levels above 130/80 mmHg).[18] These BP thresholds had been fixed due to the concomitant presence, beyond uncontrolled hypertension, of signs of hypertension-related organ damage (i.e. left ventricular hypertrophy or proteinuria) or associated clinical conditions (i.e. diabetes, myocardial infarction, stroke and heart failure).[18]

All clinical data were locally collected into a specific clinical case report form, which was designed to collect information on prescribing physicians, drug prescriptions and treated patients. The entire data collection was completed by involved physicians on-site and then delivered to the data collection centre.

Study Design

At baseline, all patients with treated uncontrolled hypertension received a first prescription of aliskiren at the recommended dosage of 150 mg daily. This dosage could be up-titrated to 300 mg daily in those hypertensive patients not achieving the recommended BP goals (BP <130/80 mmHg) during the predefined follow-up visits. Follow-up visits for evaluating antihypertensive efficacy (measure of clinic BP levels) and collecting data on safety (incidence of major cardiovascular events), adherence (number of tablets taken) and tolerability (incidence of drug-related side effects or discontinuations) were planned at predefined time intervals (1, 6 and 12 months). At each follow-up visit, assessment of microalbuminuria was also suggested (although not mandatory) to evaluate the effects of aliskiren as add-on therapy on a marker of renal organ damage.

Aims of the Study

The primary aim was to assess the clinical effectiveness, safety and tolerability of adding aliskiren 150–300 mg daily as antihypertensive therapy under 'real-life' conditions in high-risk patients not controlled with concomitant treatment, including at least two antihypertensive drugs, during a planned observation and treatment period of at least 12 months.

Secondary aims were to evaluate (i) systolic and diastolic BP levels and control in different groups of hypertensive patients, who were stratified according to age class (i.e. <50, 50–64, 65–74 and ≥75 years); (ii) systolic and diastolic BP levels and control in different groups of hypertensive patients, who were stratified according to presence or absence of concomitant cardiovascular risk factors, organ damage or associated clinical conditions; (iii) changes in pulse pressure levels in different age groups of hypertensive patients; (iv) patients' compliance and adherence to the tested drug (aliskiren), defined as proportions of tablets taken (all, >75%, 50%, <25%); (v) changes from baseline of several clinical parameters, including renal (sodium,

potassium, creatinine, blood urea nitrogen) and glucose (fasting glucose levels and glycosylated haemoglobin) parameters; (vi) prevalence of microalbuminuria and/or creatinuria in those patients with available clinical data during the predefined follow-up visits; and (vii) changes from baseline of concomitant treatments.

Blood Pressure Measurements and Control

Clinic BP levels were measured according to current recommendations provided by European guidelines.[20,21] According to these recommendations, the average of three BP measurements in the seated position was considered as the reference value and then reported in the electronic case report form. Physicians did not receive any specific indications on which device to be used for measuring clinic BP levels and how to report measured BP values in the form; thus, they were free to report these values with or without decimals.

Conventional BP control was regarded as clinic BP values below 140 mmHg for systolic and/or below 90 mmHg for diastolic BP levels; at the same time, strict BP control was defined as systolic/diastolic BP levels below 140/90 mmHg for non-diabetic patients and below 130/80 mmHg for diabetic patients.[20,21]

Definition of Risk Factors, Markers of Organ Damage and Clinical Conditions

Obesity was defined as a body mass index more than 30 kg/m^2.[22] The presence of hypercholesterolaemia was defined on the basis of the following diagnostic criteria: serum total cholesterol values exceeding 220 mg/dL and/or history of use of lipid-lowering drugs.[23] Diabetes was defined in the presence of blood glucose levels exceeding 126 mg/dL and/or by use of antidiabetic drugs.[24]

Presence of hypertension-related organ damage was reported by involved physicians, rather than clinically assessed at either local or central level. Thus, definition of markers of organ damage was based on recommendations derived from currently available clinical guidelines.[20] In particular, left ventricular hypertrophy was defined by an echocardiographically assessed left ventricular mass indexed to the body surface area greater than 125 g/m^2 in men and 110 g/m^2 in women. Carotid atherosclerosis was defined as an average intima-media thickness exceeding 0.8 mm. Microalbuminuria was defined by a urinary albumin excretion rate between 30 mg and 300 mg/24 hours. These examinations, performed during the study period, were not mandatory nor requested by study protocol and were requested on the basis of physicians' judgement, according to the principles of Good Clinical Practice.

Ischaemic heart disease (prior myocardial infarction) was generally defined according to the presence during the referred acute phase of two of the following three items: (i) symptoms (e.g. chest pain) lasting longer than 15 minutes; (ii) transient increase in serum concentrations of enzymes or markers indicating cardiac damage; and (iii) ECG changes typical of myocardial ischaemia (new persistent ST-segment elevation or pathological Q waves in two contiguous leads).[25,26] The diagnosis of ischaemic heart disease could also include other coronary events, for example acute coronary syndrome, recurrent angina and coronary revascularization, as listed in the case-report form.[27] Non-fatal stroke was defined as a neurological deficit with sudden onset and persistence of symptoms for more than 24 hours or leading to death with no apparent causes other than vascular ones.[28] Transient ischaemic attack was defined as a neurological event with the signs and symptoms of stroke, lasting for a short period of time (typically between 2 and 30 minutes).[29]

Safety Monitoring

According to the National Decree (219/2006), the involved investigators were responsible for registering and reporting adverse reactions to the appropriate health authorities.

Being aliskiren therapy under intensive monitoring for innovative drugs, according to the health authorities requirements, all adverse reactions (serious/non-serious/listed/unlisted) had to be reported to *Agenzia Italiana del Farmaco* (AIFA). In addition, all serious adverse events had to be reported to local Drug Safety Units within 24 hours from investigator's awareness.

Statistical Analysis

The statistical analysis was performed by an external, independent source (MB). Continuous variables were expressed as mean ± standard deviation and were compared by Student's t-test for paired data. Discrete variables, expressed as numbers and percentages, were compared by Pearson's chi-square test. Statistical analyses were performed with the R Program (R Foundation for Statistical Computing, Vienna, Austria).

Since the sample size was not specifically computed to detect a between-group difference for a particular variable, statistical tests were applied to assess only relevant differences among groups by using a value of $p < 0.01$. This level of significance may also permit to reduce the false discovery rate due to multiple comparisons performed in the present analysis.

Results

Population Distribution and Follow-Up Visits

From May 2009 to June 2011, a total of 1186 hypertensive patients were included in the present study. Among these, 1159 (97.7%) attained the follow-up visit at 1 month, 1074 (90.6%) at 6 months, and 996 (84.0%) at 12 months or at the end of the observation. Overall, a high proportion of enrolled patients (n = 975; 82.2%) completed the final observation. Among those who did not complete the study (n = 211; 17.8%), the main reasons for interruption were: lost to follow-up (n = 105; 49.8%); adverse events (n = 37; 17.5%); consent withdrawals (n = 33; 15.6%); unsatisfactory therapeutic efficacy (n = 21; 9.9%); abnormal laboratory values (n = 4; 1.9%); patients' own circumstances or decisions (n = 4; 1.9%); death due to non-cardiovascular causes (n = 3; 1.4%); administrative reasons (n = 3; 1.4%); and abnormal results of non-cardiovascular test (n = 1; 0.5%).

At the end of the follow-up period, 1180 (99.5%) patients received at least one dose of the study drug and were thus included in the safety population analysis, whereas 938 (791%) patients were included in the per-protocol population analysis. The main reasons for the exclusion from the per-protocol analysis were: patients who did not complete the entire study follow-up (n = 211; 17.8%); patients without at least one post-baseline assessment (n = 27; 2.3%); patients who received the study drug for the first time, whose treatment was started after 7 days from baseline (n = 16; 1.3%); patients who did not use the study drug, also excluded from the safety population (n = 6; 0.5%); and patients who were not controlled with at least two antihypertensive drugs (n = 2; 0.2%).

According to this distribution, clinical data on BP levels and control have been analysed in those patients included in the per-protocol population who had valid data for these parameters at the time of predefined follow-up visits. At the same time, general clinical characteristics, distribution of major risk factors, adherence and compliance to drug prescriptions, data on safety and tolerability of the study drug have been evaluated in those patients included in the safety population.

General Characteristics

The general characteristics and the distribution of major cardiovascular risk factors in the overall population sample (safety population) are reported in table I. A total sample of 1180 adult hypertensive patients (mean age 65.2 ± 11.7 years, 99.5% Caucasian) was analysed. This population was almost equally distributed between male (53.7%) and female (46.3%) individuals. About one-third of the patients was aged between 50–64 years (n = 373; 31.6%); another third was relatively older (aged between 65–74 years: n = 394; 33.4%). The remaining

Table I. General characteristics in the overall study population and in gender subgroups. Data presented as mean ± SD unless otherwise stated

Parameter	Overall population (n = 1180)
Gender [n (%)]	
Male	634 (53.7)
Female	546 (46.3)
Race [n (%)]	
Caucasian	1174 (99.5)
Others (Black, Asian, others)	6 (0.5)
Age (y)	65.2 ± 11.7
Height (cm)	165.5 ± 9.2
Weight (cm)	80.5 ± 15.8
Systolic BP (mmHg)	156.5 ± 15.9
Diastolic BP (mmHg)	90.3 ± 9.5
Heart rate (beats/min)	72.3 ± 10.4
Fasting glucose (mmol/L)	6.62 ± 2.2
HbA_{1c} (%)	6.63 ± 1.3
Sodium (mmol/L)	139.9 ± 3.8
Potassium (mmol/L)	4.2 ± 0.5
BUN (mmol/L)	8.1 ± 3.5
Creatinine (umol/L)	95.5 ± 45.0
Cardiovascular risk factors [n (%)]	
Smoking	109 (9.2)
Family history of premature cardiovascular disease	450 (38.1)
Dyslipidaemia	484 (41.0)
Obesity	323 (27.4)
Diabetes mellitus	402 (34.1)
Markers of organ damage [n (%)]	
Left ventricular hypertrophy[a]	794 (67.3)
Renal disease (creatinine increase)[b]	126 (10.7)
Microalbuminuria	119 (10.1)
Concomitant clinical conditions [n (%)]	
Coronary heart disease	131 (11.1)
Myocardial infarction	107 (9.1)
Cerebrovascular disease	122 (10.3)
Congestive heart failure	68 (5.8)

a Diagnosis of left ventricular hypertrophy was based on ECG or echocardiogram examinations.

b Diagnosis of renal disease was based on estimated glomerular filtration rate ≤60 mL/min.

BP = blood pressure; **BUN** = blood urea nitrogen; **HbA_{1c}** = glycosylated haemoglobin.

proportions of enrolled patients included both young (aged <30–49 years: n = 136; 11.5%) and very elderly individuals (aged ≥75 years: n = 277; 23.5%).

Hypercholesterolaemia was the most frequent concomitant cardiovascular risk factor in this hypertensive population (41.0%), followed by family history of premature cardiovascular disease (38.1%), diabetes (34.1%), obesity (27.4%) and smoking habit (9.2%). Among markers of organ damage, left ventricular hypertrophy was reported in more than half of the patients (67.3%), whereas microalbuminuria was documented in a relatively small proportion of the patients (10.1%), when available. With regard to associated clinical conditions, coronary artery disease (11.1%), previous myocardial infarction (9.1%), cerebrovascular disease (10.3%) and renal disease (defined as increased creatinine serum levels) or proteinuria (10.7%) were almost equally reported, with the only exception of congestive heart failure, which was relatively rare in this population (5.7%), as expected. The distribution of concomitant cardiovascular risk factors, markers of organ damage and associated clinical conditions, stratified by age class, is reported in table SI, SDC.

Blood Pressure Levels during the Follow-Up Period

Systolic and diastolic BP levels during the observational period were reported in figure 1. At 1-month follow-up visits, systolic and diastolic BP levels were reduced from 156.7 mmHg to 141.1 mmHg, and from 90.6 mmHg to 82.4 mmHg, respectively ($p < 0.0001$ vs baseline for both comparisons). During the follow-up period, systolic and diastolic BP levels were 134.9/79.8 and 133.6/78.9 mmHg at 6- and 12-month follow-up visits, respectively ($p < 0.0001$ vs baseline for both comparisons). Thus, at the end of the observational period (1 year), the average systolic/diastolic BP reductions were −23/−12 mmHg ($p < 0.0001$ for trend). Greater reductions were observed for systolic than for diastolic BP levels; in particular, systolic BP levels were −15.7, −21.6 and −23.1 mmHg at 1-, 6- and 12-month follow-up visits, respectively.

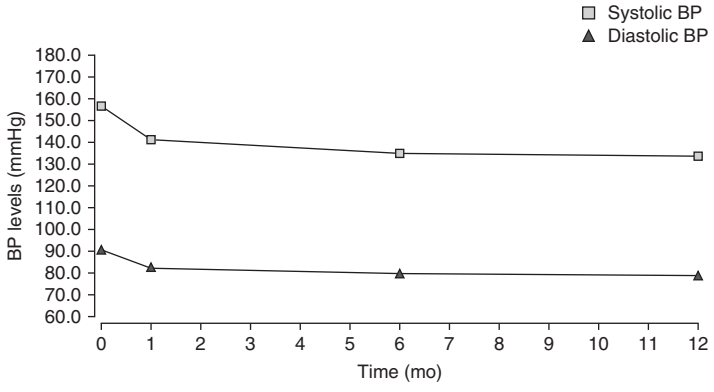

Fig. 1. Systolic and diastolic blood pressure (BP) levels at predefined time intervals (1, 6 and 12 mo) after the addition of aliskiren 150–300 mg daily to standard antihypertensive therapy including at least two antihypertensive drug classes (n = 938).

Consistent and significant systolic and diastolic BP reductions were reported in different predefined age subgroups of hypertensive patients, including elderly (aged 65–74 years) and very elderly patients (aged >75 years), as well as in young and adult individuals (see figure S1, SDC). These BP reductions were consistently reported in different high-risk hypertensive subgroups, including those with hypercholesterolaemia, diabetes, obesity, left ventricular hypertrophy, cerebrovascular disease, coronary artery disease and previous myocardial infarction (see figure S2, SDC). Systolic and diastolic BP levels were also reduced in hypertensive patients at very high cardiovascular risk, including those with congestive heart failure and renal impairment (increased serum creatinine levels).

During the follow-up period, pulse pressure was reduced by −7.5, −11.0 and −11.5mmHg at 1-, 6- and 12-month follow-up visits, respectively (figure 2). These effects were consistently observed in different age subgroups of patients, particularly in elderly (aged 65–74 years) and very elderly (aged >75 years) individuals compared with younger subjects (figure 2).

As expected, conventional BP control significantly and progressively improved after adding aliskiren on top of standard antihypertensive therapy. In particular, BP control rates showed an increasing trend from 41% at 1-month to 63% and 64% at 6-month and 1-year follow-up visits or at the end of the observation, respectively (figure 3). During the same time intervals, strict BP control rates significantly and progressively increased from 33% at 1-month to 49% and 51% at 6-month and 1-year follow-up visits or at the end of the observation, respectively (figure 3).

Consistent and significant improvements in systolic and diastolic BP control rates were also recorded in all predefined age subgroups of patients, although with several differences among groups (see figure S3, SDC). In particular, systolic BP control rates were higher in young (aged <50 years) or adult (aged 50–64 years) individuals compared with that reported in older subjects, including elderly (aged 65–74 years) and very elderly (aged >75 years) patients, who showed better diastolic BP control rates than younger ones. A high rate (more than 50% on average) of BP control was consistently reported in different high-risk hypertensive subgroups, including those

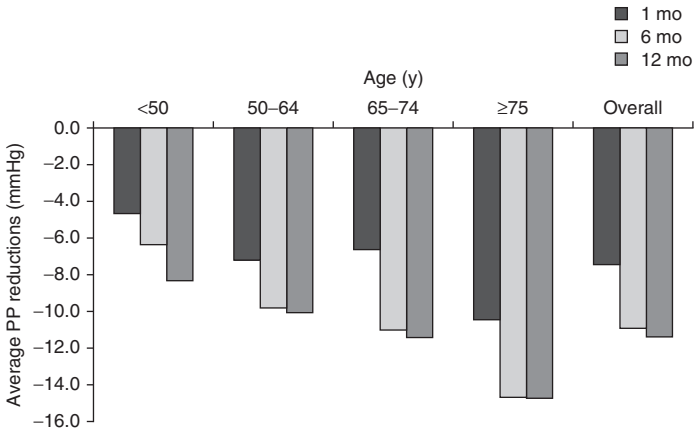

Fig. 2. Average reductions of pulse pressure (PP) levels at predefined time intervals (1, 6 and 12 mo) after the addition of aliskiren 150–300 mg daily to standard antihypertensive therapy including at least two antihypertensive drug classes (n = 938).

with hypercholesterolaemia, diabetes, obesity, left ventricular hypertrophy, cerebrovascular disease, coronary artery disease and previous myocardial infarction (see figure S4, SDC). BP control was also achieved in more than 40% of the hypertensive patients with renal impairment and in about 30% of those with left ventricular dysfunction or congestive heart failure.

Safety and Tolerability

At baseline, aliskiren was prescribed at the recommended dosage of 150 mg daily. At 1- and 6-month follow-up visits, the dosage of 300 mg daily was prescribed to more than 40% of the population (figure 4).

According to the safety population analysis, a total treatment exposure of 325 days was recorded at 1-year follow-up visit or at the end of the observation. The compliance to study treatment was persistently high during the observational period (figure 5), with 93% of patients globally compliant to prescribed antihypertensive regimen based on aliskiren.

Only a relatively small proportion of adverse events was described during the follow-up period (figure 6). Deaths were not correlated to cardiovascular causes and were not related to the study drug, as assessed by the investigators.

Renal and Glucose Parameters

Renal and glucose parameters did not show any significant differences during the follow-up period (see table SII, SDC). On the other hand, relevant changes from baseline were reported with regard to microalbuminuria and macroalbuminuria, although the limited number of available data did not allow to obtain significant differences. In fact, dosage of albuminuria was performed in about 40% of the patients at baseline and final observations and in about 30% of the follow-up visits. In these proportions, however, a marked increase of hypertensive patients who had normal renal profile at the end of the study (from 21.6% to 25.4%) was observed, as shown in figure S5, SDC. At the same time, the proportion of hypertensive patients who had microalbuminuria (11.0%) and macroalbuminuria (4.4%) at baseline observations was substantially reduced at the end of the study (7.0% and 3.2%, respectively), as illustrated in figure S5, SDC.

Concomitant Antihypertensive Therapies

Distribution of concomitant drug classes in the safety population is reported in table II. At baseline, ARBs were the most frequently prescribed antihypertensive drugs (59.5%), followed by CCBs (53.1%), β-blockers (48.1%), ACE inhibitors (32.1%) and diuretics (24.7%), with an average number of antihypertensive drugs of 2.88 ± 0.94. With the only exception of ARBs, prescriptions of all these drug classes were reduced at the end of the follow-up period after the addition of aliskiren to standard antihypertensive therapy, with an average number of antihypertensive drugs of 2.85 ± 0.99 at 12 months.

Discussion

The results of this 'real-life' experience with aliskiren confirm the antihypertensive effectiveness, safety and tolerability

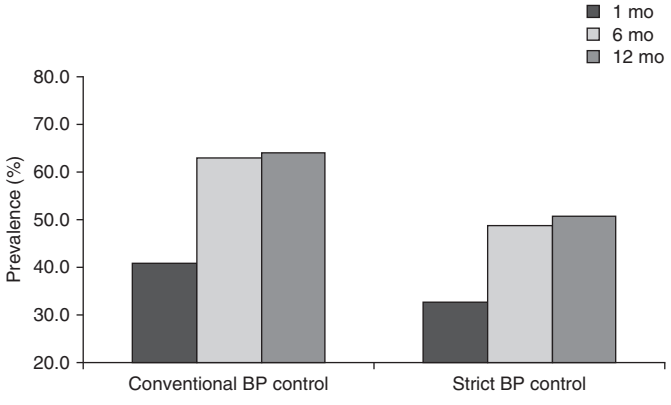

Fig. 3. Prevalence of patients achieving the predefined blood pressure (BP) goals in the per-protocol population (n = 938). Conventional BP goals were defined by the presence of systolic/diastolic BP below 140/90 mmHg. Strict BP goals were defined by the presence of systolic/diastolic BP below 140/90 mmHg for non-diabetic patients and below 130/80 mmHg for diabetic patients.

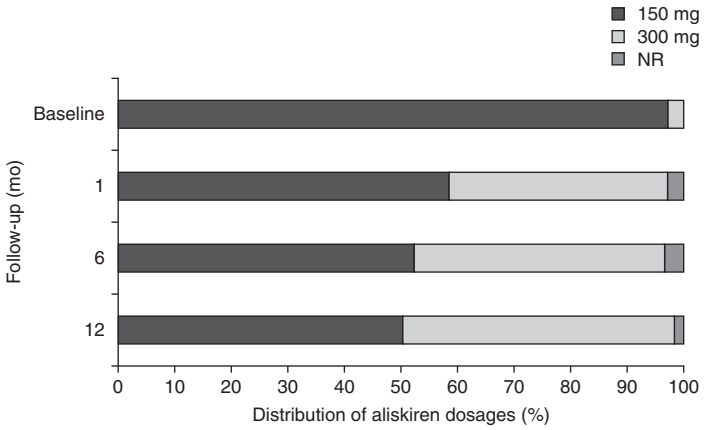

Fig. 4. Distribution of different dosages of aliskiren at predefined time intervals (baseline, 1-, 6- and 12-month follow-up visits) in the safety population (n = 1180). **NR** = not reported.

profile of aliskiren. In fact, the addition of aliskiren to standard antihypertensive therapy in a 'real-life' setting of clinical management of hypertension and high cardiovascular risk during a relatively long-term (1-year) follow-up period provided robust evidence that DRI is highly effective in terms of BP control and it is also very well tolerated and safe. Our findings may have relevance for the clinical management of high-risk patients with hypertension and other co-morbidities, especially in view of the conclusions of several recent observational studies aimed at evaluating the clinical effects of the same drug in a setting of 'real life'.[17,18,30]

The first study was an observational survey that included 11 511 Italian hypertensive patients, and retrospectively analysed clinical data derived from an institutional web-based drug monitoring system on the use of aliskiren on top of antihypertensive therapy, including at least two drugs, during a 6-month follow-up period.[18] The results of this analysis are consistent with our findings. In this population, in fact, the use of aliskiren as add-on therapy was associated with rapid and significant systolic and diastolic BP reductions at 1-month follow-up visits and with persistent and significant BP reductions during an average observational period of 6 months.[18] In addition, an extremely low incidence of side effects and only three serious (non-fatal) adverse events were recorded, and no major cardiovascular events or deaths have been reported.[18] This may have clinical relevance, in view of the fact that in this analysis only drug-related adverse events have been collected, whereas in the present study all serious adverse events were reported and analysed. Finally, both studies reported a substantial reduction of the prescriptions of all concomitant antihypertensive drug classes.

The second study was an observational survey that included 1695 Belgian hypertensive patients, and retrospectively tested the effectiveness of aliskiren for the clinical management of hypertension during a 6-month follow-up period.[17] This survey, which included hypertensive patients in whom previous antihypertensive therapies failed or were not tolerated, described a similar proportion of outpatients achieving the recommended BP control (about 56%) with a good tolerability profile and high adherence to the tested drug.[17] Proportions of patients attending follow-up visits were substantially different from baseline to last observations, although the analysis provided detailed information regarding different reasons for drug discontinuations or withdrawals from the study protocol.[17]

All these reports are consistent with our findings, which report an effective, rapid and persistent BP-lowering efficacy, substantial reductions of the prescriptions of all concomitant antihypertensive drugs and a good tolerability profile provided by an aliskiren-based strategy in the clinical management of hypertension and high cardiovascular risk. Our findings, however, are also consistent with large and comprehensive meta-analyses, which included all randomized controlled clinical trials to evaluate the clinical effects of an aliskiren-based antihypertensive strategy, both as monotherapy or combination therapy, compared with placebo or active treatment (i.e. ACE inhibitors, ARBs, calcium-channel blockers and thiazide diuretics).[31,32] These meta-analyses, in fact, demonstrated not only the BP-lowering efficacy, but also the good tolerability profile of this strategy, which was similar to that of active treatment and comparable with that of placebo.[31,32] Other surveys, such as the Aliskiren Canadian Hypertension Registry (ANCHOR), are currently evaluating the effectiveness, safety and tolerability of aliskiren in 'real-life' practice.

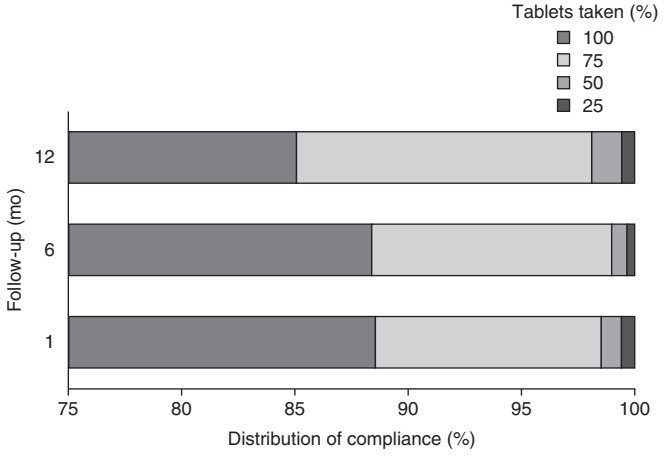

Fig. 5. Compliance to prescribed antihypertensive therapy based on aliskiren at predefined time intervals (baseline, 1-, 6- and 12-month follow-up visits) in the safety population (n = 1180). The compliance was assessed as proportions of tablets taken for any enrolled patients.

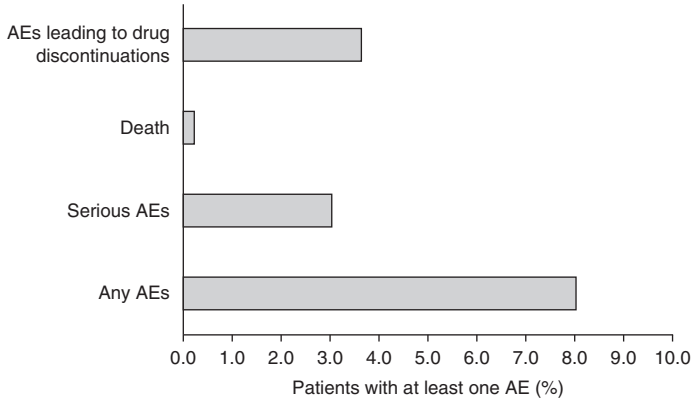

Fig. 6. Prevalence of patients with at least one adverse event (AE) in the safety population (n = 1180) during the planned observational period.

Several other aspects of our study deserve to be discussed. First, the addition of aliskiren to standard antihypertensive therapy induced a rapid and persistent improvement of BP control in high-risk hypertensive patients. At 1-month follow-up visits, about 40% of previously uncontrolled treated hypertensive patients achieved BP goals after adding low-dose aliskiren; this proportion increased to more than 60% at intermediate follow-up and was maintained at the end of the study, when about half of the patients were treated with full-dose aliskiren. This may have potential clinical advantages when approaching treated uncontrolled hypertensive patients, in view of the rapid and sustained achievement of BP goals.

The antihypertensive effectiveness of aliskiren was consistently reported in all subgroups of hypertensive patients, independently by age or concomitant presence of cardiovascular risk factors, markers of organ damage or associated clinical conditions. Indeed, in the present analysis BP levels were significantly and persistently reduced, particularly for systolic BP, in all age classes, including elderly (aged 65–74 years) and very elderly (aged ≥75 years) individuals. In particular, in these latter age groups, marked and significant BP reductions were reported (–25/–11 mmHg, on average), thus leading to a very high proportion (>60%) of elderly or very elderly patients who achieved the predefined BP targets. In addition, in these subgroups of elderly patients, aliskiren-based therapy induced greater reductions of pulse pressure than that observed in adult or young individuals. These findings are consistent with and substantially extend previous observations[33] that demonstrated the antihypertensive efficacy, safety and tolerability of aliskiren-based therapy in elderly patients with predominantly isolated systolic hypertension compared with placebo. In view of the well known complexity of achieving recommended BP goals in elderly populations, particularly for systolic BP, our results may be considered of potential clinical relevance for improving the clinical management of elderly patients with isolated systolic hypertension or with treated uncontrolled hypertension.

We were also able to report the same long-term beneficial effects in terms of BP reductions and improved BP control in all subgroups of hypertensive patients, including those with metabolic abnormalities, obesity, diabetes, left ventricular hypertrophy or dysfunction (congestive heart failure) and coronary artery disease. In these high-risk patients, addition of aliskiren on top of an antihypertensive strategy reduced systolic/diastolic BP levels by 23/11 mmHg on average, thus leading to a significant improvement in BP control (>60%).

It should also be noted that the BP-lowering efficacy of an aliskiren-based therapy was associated with a favourable safety and tolerability profile. In the presence of high adherence to prescribed antihypertensive treatment in a 'real-life' setting of clinical management of hypertension, about 8% of the treated patients experienced drug-related adverse events, only 3% were

Table II. Distribution of previous and concomitant antihypertensive drug numbers and classes at each timepoint (safety population)

	Before start of treatment (n = 1180)	Baseline (n = 1180)	1 mo (n = 1159)	6 mo (n = 1074)	12 mo (n = 996)
Number of antihypertensive drugs (mean ± SD)	2.96 ± 0.97	2.88 ± 0.94	2.85 ± 0.93	2.87 ± 0.97	2.85 ± 0.99
Class of antihypertensive drugs [n (%)]					
ACE inhibitors	445 (37.7)	379 (32.1)	350 (30.2)	315 (29.3)	287 (28.8)
ARBs	725 (61.4)	702 (59.5)	688 (59.4)	640 (59.6)	616 (61.8)
CCBs	639 (54.1)	627 (53.1)	591 (51.0)	545 (50.7)	519 (52.1)
β-Blockers	570 (48.3)	568 (48.1)	535 (46.2)	484 (45.1)	450 (45.2)
Diuretics	300 (25.4)	292 (24.7)	280 (24.2)	244 (22.7)	243 (24.4)
Other	247 (20.9)	223 (18.9)	202 (17.4)	192 (17.9)	167 (16.8)

ARBs = angiotensin II type 1 receptor antagonists (angiotensin receptor blockers); **β-blockers** = β-adrenoceptor antagonists; **CCBs** = calcium-channel blockers.

reported to be serious, and only 3% were correlated to drug discontinuations. Deaths were not related to cardiovascular causes, nor to the tested study drug, thus confirming the good safety and tolerability profile of aliskiren reported in previous surveys performed in a 'real-life' setting.

Another aspect that should be discussed is the favourable effect reported in patients with renal impairment or albuminuria. In these patients, in fact, the use of aliskiren as add-on antihypertensive therapy not only induced effective and sustained systolic and diastolic BP reductions and improved BP control, but also reduced the proportions of patients with microalbuminuria and macroalbuminuria and increased those with normal renal excretion. Although the limited number of patients with valid clinical data on renal profile did not allow to sustain solid conclusions, our findings derived from a large database of clinical data collected in a 'real-life' setting confirmed the results of randomized clinical trials performed in diabetic patients with renal impairment and albuminuria,[34] in which aliskiren-based therapy induced significant reductions of albuminuria and improvements of urinary albumin excretion rate.

As a final consideration, the relatively high prevalence of hypertensive patients also using RAS blocking agents, such as ACE inhibitors (about 30%) and ARBs (about 60%) during the predefined follow-up period provides evidence in support of the safety and tolerability of aliskiren-based therapy in treated uncontrolled hypertensive patients. This may have clinical relevance in view of the very recent preliminary analyses of the findings from the ALTITUDE trial,[19] which reported a substantially higher risk of adverse events, mostly cerebrovascular and renal events, in patients treated with aliskiren compared with those treated with placebo on top of antihypertensive therapy including either ACE inhibitors or ARBs. This is a prospective, randomized, controlled, clinical trial, which enrolled very high-risk patients with high-normal BP levels (135/74 mmHg), diabetes, renal disease with proteinuria or previous cardiovascular events. As such, any comparison between the findings of the ALTITUDE trial[19] and the results of our study should be carefully considered, in view of the different population samples, study designs and follow-up periods.

Potential Limitations

The present study is based on a cross-sectional analysis and, as such, it can only identify associations, but it cannot provide insights on causation. The lack of case-control (placebo) design of the analysis may have at least, in part, affected our findings, mostly when relating to safety and tolerability data. The relatively small sample size of enrolled patients and distribution of involved physicians may also mean that the views expressed by respondents may not be fully representative of behaviours of the entire patient and physician community in Italy. The use of electronic support may have also limited the inclusion in this analysis only to those physicians who have an easy access to a web-based database and experience in managing electronic clinical case report forms, rather than to all physicians distributed in Italy. In most cases, dependence on physician self-reporting throughout standardized questionnaires, rather than more objective measures such as BP measurements, may also create potential biases. It should be also emphasized that, because of the inclusion criteria related to the clinical characteristics of the patients (presence of additional risk factors, organ damage, associated clinical conditions and concomitant diseases or co-morbidities), our current findings on the use of aliskiren cannot be extrapolated to the general hypertensive population.

Conclusions

In this observational, prospective, open-label, multicentre study, we reported the 12-month clinical effectiveness, safety and tolerability of adding aliskiren to standard antihypertensive strategies, including RAS blockers, in uncontrolled hypertensive patients in a setting of 'real life' in Italy. This strategy leads to a significantly improved BP control rate and low incidence of drug-related side effects or discontinuations.

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