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Long-term effect of 2 intensive statin regimens on treatment and incidence of cardiovascular events in familial hypercholesterolemia: The SAFEHEART study

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KEYWORDS:
Familial hypercholesterolemia;
Atorvastatin;
Rosuvastatin;
Long-term prognosis

BACKGROUND: Maximal doses of potent statins are the basement of treatment of familial hypercholesterolemia (FH). Little is known about the use of different statin regimens in FH.

OBJECTIVES: The objectives of the study were to describe the treatment changes and low-density lipoprotein cholesterol (LDL-C) goal achievement with atorvastatin (ATV) and rosuvastatin (RV) in the SAFEHEART cohort, as well as to analyze the incidence of atherosclerotic cardiovascular events (ACVEs) and changes in the cardiovascular risk.

METHODS: SAFEHEART is a prospective follow-up nationwide cohort study in a molecularly defined FH population. The patients were contacted on a yearly basis to obtain relevant changes in life habits, medication, and ACVEs.

RESULTS: A total of 1939 patients were analyzed. Median follow-up was 6.6 years (5–10). The estimated 10-year risk according the SAFEHEART risk equation was 1.61 (0.67–3.39) and 1.22 (0.54–2.93) at enrollment for ATV and RV, respectively ($P < .001$). There were no significant differences at the follow-up: 1.29 (0.54–2.82) and 1.22 (0.54–2.76) in the ATV and RV groups, respectively ($P = .51$). Sixteen percent of patients in primary prevention with ATV and 18% with RV achieved an LDL-C <100 mg/dL and 4% in secondary prevention with ATV and 5% with RV achieved an LDL-C <70 mg/dL. The use of ezetimibe was marginally greater in the RV group. One hundred sixty ACVEs occurred during follow-up, being its incidence rate 1.1 events/100 patient-years in the ATV group and 1.2 in the RV group ($P = .58$).

CONCLUSION: ATV and RV are 2 high-potency statins widely used in FH. Although the reduction in LDL-C levels was greater with RV than with ATV, the superiority of RV for reducing ACVEs was not demonstrated.

Introduction

Heterozygous familial hypercholesterolemia (FH) is a codominant autosomal disorder with a prevalence around 1:250 cases worldwide, making it by far the most common genetic condition causing premature morbidity and mortality from atherosclerotic cardiovascular disease.[1] Although lipid-lowering therapy (LLT) has shown a reduction in coronary and total mortality in patients with FH and LLT has improved in recent years, most patients with FH do not reach an optimal therapeutic level of low-density lipoprotein cholesterol (LDL-C) and, therefore, continue to have a high risk of premature atherosclerotic cardiovascular events (ACVEs).[2–4]

Little is known about the use of different statins and the achievement of LDL-C goals in patients with FH. National registries are a valuable source to provide this key information, necessary to improve models of health care, family cascade screening, the education of physicians and patients, and to help define priorities in therapeutic guidelines and health planning policies.[5,6] The SAFEHEART study (Spanish Familial Hypercholesterolemia Cohort Study), a national registry of patients with FH was designed to improve the knowledge of this disease in Spain.[7,8]

The objective of this study was to describe the changes in the treatment and achievement of LDL-C goals with potent statins such as atorvastatin (ATV) and rosuvastatin (RV) used alone or in combination with Ezetimibe in the SAFEHEART cohort from inclusion until the last follow-up, as well as to analyze the incidence of cardiovascular events and changes in the estimated risk in the FH population treated with 2 intensive statin regimens.

Methods

Design and population

SAFEHEART is a prospective nationwide cohort study, open, multicentric with long-term protocolized follow-up in

a molecularly defined FH population with participation from primary and specialized care.[7] The recruitment of families with FH began in 2004 and the end date for reporting events was January 2019. This study was approved by the ethics committee of the Fundación Jiménez Díaz Hospital in Madrid and all the subjects gave their written informed consent. The objectives of treatment were defined according to the hyperlipidemia guidelines.[9] These guidelines were used to inform, educate, and train participating physicians and include patients and families in this registry.

The coordinating center of the SAFEHEART study managed the follow-up of the patients. The patients were contacted on a yearly basis by using a standardized telephone survey to obtain relevant changes in life habits, medication, and the appearance of cardiovascular events. The definitions of previous and incident ACVEs have been previously reported.[10]

Variables

In addition to the aforementioned demographic and clinical variables, age, classic cardiovascular risk factors, physical examination, and LLT were included. The lipid profiles were determined in venous blood samples in a centralized laboratory.[7] The serum concentration of LDL-C was calculated using the Friedewald formula. The DNA was isolated from whole blood using standard methods, and the genetic diagnosis of FH was performed as previously described.[11] Cardiovascular risk was defined by the SAFEHEART risk equation (SAFEHEART-RE).[10] The classification of LLT was defined as previously reported[4]: maximal statin dose as ATV 40 to 80 mg/d or RV 20 to 40 mg/d which was considered high-intensity statin doses; maximal combined therapy as maximal statin dose plus ezetimibe 10 mg/d; and maximal LLT as any LLT expected to produce at least a 50% reduction in LDL-C baseline levels. The classification of LLT intensity, in terms of potency, has been previously reported.[12,13]

Incident ACVEs during follow-up was defined as the occurrence after enrollment of the first one of the following: fatal or nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, coronary revascularization, peripheral artery revascularization, and cardiovascular death (any death related to cardiovascular disease or derived of cardiovascular therapeutic procedures not described in the previous definitions).

Statistical analysis

The statistical analysis was carried out with the STATA program, version 12.0 (Stata Corporation, College Station, TX). A descriptive analysis was carried out to report the number of cases and percentages for the qualitative variables, the mean, and the standard deviation for the quantitative variables that followed a normal distribution and the median and interquartile range for the quantitative variables that did not follow a normal distribution. Comparisons of proportions between the qualitative variables were carried out using the chi square test and the binomial test to compare the proportion observed in each treatment group with the value of the total population. The mean comparisons of the quantitative variables were analyzed with the Student's *t*-test for independent data, and the medians comparisons were analyzed with the Mann-Whitney *U*-test for independent data. The incidence rate of cardiovascular events was calculated as the quotient in which the numerator is the number of observed events and the denominator is the time at risk for the event. The time at risk was the sum of the follow-up time of patients who do not have an event plus the sum of the time until the event appears in the patients in which the event occurs. The incidence rate was expressed as the number of events per 100 patient-years. A value of $P < .05$ was considered statistically significant.

Results

A total of 4870 subjects were enrolled, 3601 with genetic diagnosis of FH and 1269 nonaffected relatives. The analysis in this study was made with 1939 patients with FH, after excluding homozygous subjects, younger than 18 years, without complete follow-up, those who did not receive LLT at the last follow-up, took a statin different from ATV or RV, or were in treatment with inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) (Fig. 1). The median follow-up time was 6.6 years (5–10 years). Three hundred patients changed during the follow-up from ATV to RV and 46 patients from RV to ATV. All of them were treated with the last drug until the last contact and always, continuously, for more than half of the follow-up.

The main characteristics of the cohort are described in Table 1. It is interesting to point out that only statistically significant differences were found between the ATV group and the RV group in the following variables: use of statins at maximum dose (71% and 81% in the ATV and RV groups, respectively, $P < .001$), use of added ezetimibe (65% and 77% in the ATV and RV groups, respectively, $P < .001$), use of maximum combined treatment (53% and 66% in the ATV and RV groups, respectively, $P < .001$), and maximum LLT (88% and 81% in the ATV and RV groups, respectively, $P < .001$). Likewise, 505 patients in the ATV group (47%) and 252 in the RV group (29%) were managed in primary care ($P < .001$). Regarding the lipid parameters, statistically significant differences were found in LDL-C levels [128 mg/dL (107–152) and 123 mg/dL (104–146) in the ATV and RV groups, respectively; $P < .005$] and TG levels [82 mg/dL (64–116) and 93 mg/dL (70–129) in the ATV and RV groups, respectively; $P < .001$].

Figure 2 shows the evolution between the time of enrollment in the SAFEHEART study and the time of the last follow-up in the ATV or RV treatment in the studied cohort.

It is important to highlight the considerable change that all monotherapies and combined therapies have undergone, highlighting the very important numerical increase of patients treated with coadministration of RV and ezetimibe: 200 patients at the time of enrollment (10%) and 675 patients at the time of the last follow-up (35%) ($P < .001$).

Table 2 shows the potency of lipid-lowering treatment used at inclusion and at the time of the last follow-up in the ATV and RV groups expressed in potency terms. Although the potency of the treatment in this population did not strictly follow a normal distribution and, therefore, was expressed as a median, values are given here as means because it may be more informative. In both groups, the potency increased during the follow-up, going from 6.7 ± 1.6 to 7.1 ± 1.4 in the ATV group ($P < .001$) and from 6.9 ± 1.4 to 7.5 ± 1.2 in the RV group ($P < .001$).

Regarding the risk of developing a cardiovascular event estimated by the SAFEHEART-RE, Table 3 shows how in the inclusion, the estimated 10-year risk was 1.61 (0.67–3.39) and 1.22 (0.54–2.93) in the groups ATV and RV, respectively ($P < .001$), meaning there were no significant differences between the 2 groups at the time of the last follow-up: 1.29 (0.54–2.82) and 1.22 (0.54–2.76) in the ATV and RV groups, respectively ($P = .51$).

Regarding the achievement of LDL-C goals, 16% of patients in primary prevention in the ATV group and 18%

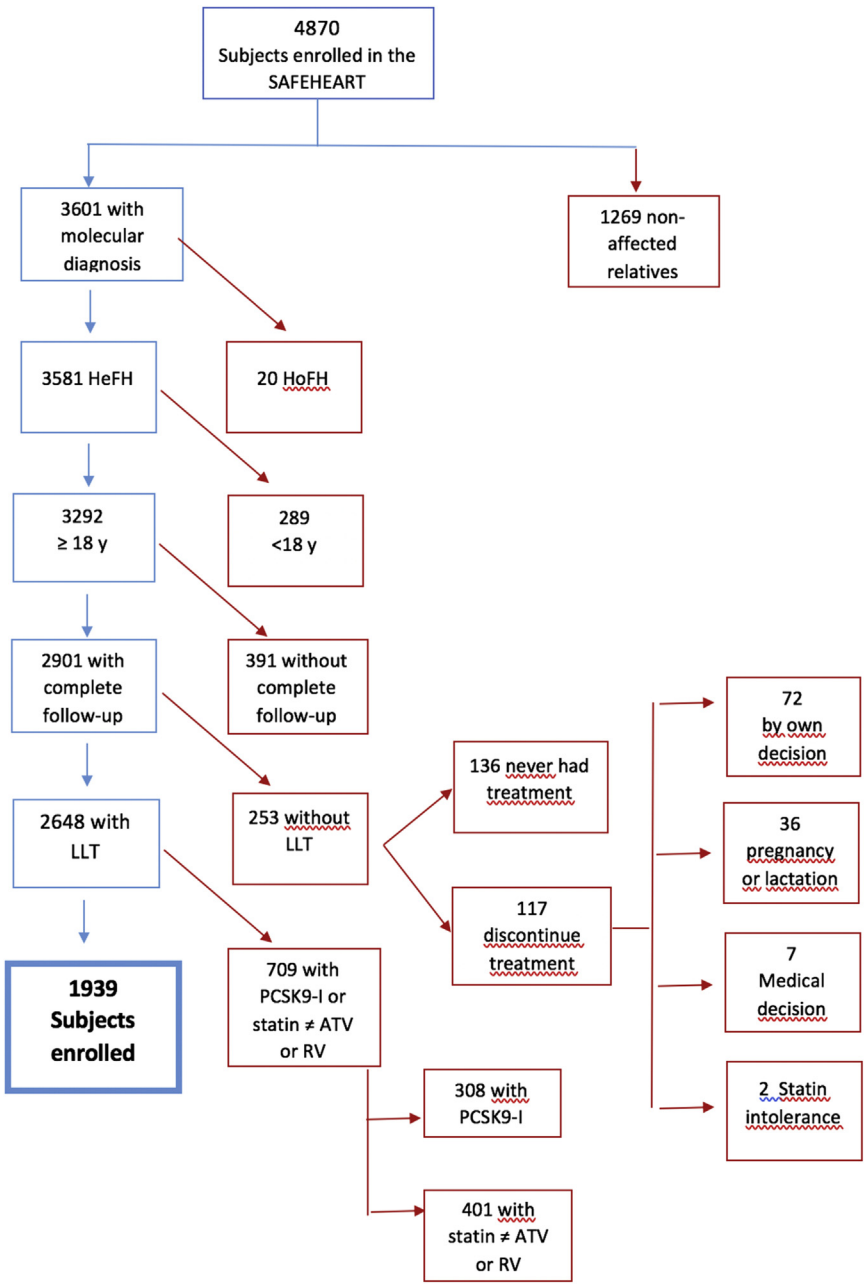

Figure 1 Flow diagram showing the recruitment of cases in the SAFEHEART registry. ATV, atorvastatin; RV, rosuvastatin; LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9; FH, familial hypercholesterolemia; HeFH, heterozygous familiar hypercholesterolaemia; HoFH, homozygous familiar hypercholesterolaemia.

Table 1 Characteristics of the SAFEHEART population treated with ATV or RV in the last follow-up

Qualitative variables; n (%)	Total	ATV	RV	*P*
n	1939	1065	874	<.001
Gender (male)	890	508 (48)	382 (44)	.08
ACVEs at enrollment	232	134 (13)	98 (11)	.35
Nonfatal ACVEs in follow-up	128	61 (6)	67 (8)	.09
Fatal ACVEs in follow-up	42	28 (3)	14 (2)	.12
Fatal or nonfatal ACVEs in follow-up	160	83 (8)	77 (9)	.42
ACVEs at enrollment or during follow-up	311	168 (16)	143 (16)	.73
Diabetes mellitus	160	93 (9)	67 (8)	.39
Hypertension	432	237 (22)	195 (22)	.97
Active smoking	291	160 (15)	131 (15)	.98
Maximal statin dose	1460	755 (71)	705 (81)	<.001
Ezetimibe	1367	692 (65)	675 (77)	<.001
Maximal combined therapy	1135	561 (53)	574 (66)	<.001
Maximum lipid-lowering therapy	1647	942 (88)	705 (81)	<.001
Patients in primary prevention	1628	897 (84)	731 (84)	.7
Patients in secondary prevention	281	148 (14)	133 (15)	.5
LDL-C<100 mg/dL in patients in primary prevention	274	140 (16)	134 (18)	.14
LDL-C<70 mg/dL in patients in secondary prevention	13	6 (4)	7 (5)	.56
Patients managed in primary care	757	505 (47)	252 (29)	<.001
Quantitative variables; median (IQR)				
Age (y)	54 (42–65)	54 (42–66)	54 (43–65)	.70
BMI Kg/m^2	25.8 (23–29)	25.7 (23–28)	26.1 (23–29)	.07
Total cholesterol mg/dL	198 (176–225)	200 (177–227)	197 (176–222)	.12
LDL-C mg/dL	125 (106–148)	128 (107–152)	123 (104–146)	<.005
HDL-C mg/dL	51 (43–61)	51 (43–61)	51 (44–60)	.95
TG mg/dL	86 (67–121)	82 (64–116)	93 (70–129)	<.001
Years on statin treatment	18 (13–26)	18 (13–26)	18 (13–26)	.71
Years on Ezetimibe treatment*	4.7 (0–11)	5.7 (0–12)	3.8 (0–11)	.08

ATV, atorvastatin; RV, rosuvastatin; ACVEs, atherosclerotic cardiovascular events; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; IQR, interquartile range.

*Only patients on ezetimibe treatment.

in the RV group achieved an LDL-C <100 mg/dL and 4% in secondary prevention in the ATV group and 5% in the RV group achieved an LDL-C <70 mg/dL. Figure 3 shows the achievement of objectives in LDL-C. Nevertheless, there was an increase during follow-up in the percentage of subjects without ACVEs who reached an LDL-C under 115 and 130 mg/dL, respectively, and the increase was significant in the RV group compared with the ATV group ($P < .05$).

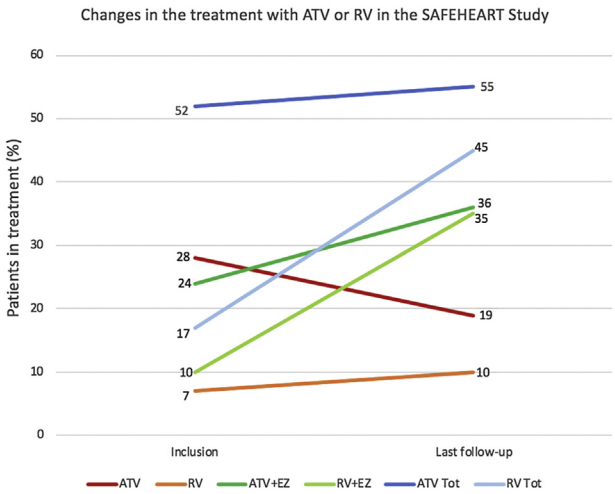

Figure 2 Changes in the treatment with ATV or RV in the SAFEHEART registry. ATV, atorvastatin; EZ, ezetimibe; RV, rosuvastatin; Tot, total.

During follow-up, a total of 160 fatal or nonfatal first incident ACVEs were recorded; 128 first nonfatal events and 42 deadly events (Table 1). The overall incidence rate of cardiovascular events was 1.15 events/100 patient-years; 1.1 in the ATV group and 1.2 in the RV group ($P = .58$). Figure 4 shows the survival curves in both treatment groups for incident ACVEs.

Discussion

This study is the first, to our knowledge, to compare the use in real clinical practice of 2 high-potency statins in patients with FH. It is a prospective long-term follow-up study analyzing the incidence of fatal and nonfatal cardiovascular events. It is well known that lipid-lowering treatment with high-potency statins in FH lowers LDL-C

Table 2 Classification of lipid-lowering treatment by potency* (mean ± SD)

Potency	Total	ATV	RV	*P*
Potency at enrollment	6.8 ± 1.5	6.7 ± 1.6	7.1 ± 1.4	<.001
Potency at follow-up	7.2 ± 1.4	6.9 ± 1.4	7.5 ± 1.2	<.001

ATV, atorvastatin group; RV, rosuvastatin group.
*Lipid-lowering therapy potency has been calculated according the method described in the study by Penning-van Beest et al[12] modified by Masana et al.[13] As a reference point, the potency of atorvastatin 40 mg is 6.

levels, a fact that is associated with a reduction in the incidence of cardiovascular events.[14] A strong recommendation for the use of high-intensity statins[15] and combined therapy with ezetimibe should be established in patients with FH,[16] with the use of ezetimibe now being well supported by IMPROVE-IT.[17] As the results of the present study show, although the reduction in LDL-C levels is greater in the group treated with RV than in the group treated with ATV, the incidence of fatal and nonfatal cardiovascular events is similar in both groups.

In parallel with the findings of a study comparing the efficacy of both statins to reduce the progression of coronary atherosclerosis[18] and in which no significant differences were found between the 2 drugs, no differences were found in the present study when the incidence rate of cardiovascular events was analyzed. It is well known that the burden of coronary atherosclerosis is directly and proportionately related to the incidence of cardiovascular events, including coronary events.[19] This parallelism between the burden of atherosclerosis and cardiovascular events reinforces the plausibility of the findings of our study, which align with the findings of the aforementioned study. However, another recent study shows that although RV and ATV at doses of 10 and 20 mg, respectively, obtained similar reductions in LDL-C levels, RV showed that it was able to improve earlier and more robustly than ATV the image parameters related to the stability of the atherosclerosis plaques. Nevertheless, both statins significantly reduced the atheroma volume.[20] Statins, in addition to their lipid-lowering potency, have several effects independent of their lipid-lowering effect, the so-called pleiotropic effects.[21] One of these pleiotropic effects is its ability to stabilize atherosclerosis plaques, thus preventing its rupture and the appearance of subsequent cardiovascular events. Most acute coronary syndromes are secondary to the rupture of vulnerable atherosclerotic plaques. After the instabilization of an atherosclerotic plaque, a process of healing or stabilization arises. However, until this study, it was not known if there are statins that favor more than others this stabilization of the atherosclerotic plaque.

It is important to emphasize that although more than 80% patients analyzed in our study were on maximum LLT, the majority did not achieve the recommended LDL-C goals. These findings show the difficulty in reducing the LDL-C in patients with FH as they usually have high baseline LDL-C levels.[16,22] However, although the targets are not fully achieved in many patients, we can affirm that their control has improved with respect to previous data from the same cohort.[4] These results depict that a considerable number of patients with FH may be candidates to receive new medications, such as PCSK9 inhibitors. With reference to this aspect, we have recently shown that the application of SAFEHEART-RE can help make a better selection of patients with FH for the use of PCSK9 inhibitors to improve the cost-effectiveness of its use.[23]

Effective lipid-lowering therapies with statins and ezetimibe are now available as generic medications. A point of special consideration is that RV was marketed in September 2009 (ATV in October 1997) in Spain and therefore takes longer to be available as generic. Despite this delay in its availability, we can observe that the use of RV has increased considerably in patients with FH, especially in those who are managed in the specialized health care system. Furthermore, a recent study concerning cost-effectiveness of LLT in patients with FH involved in a national detection program has shown that the use of ATV and RV with or without ezetimibe is cost-effective.[24]

When applying the SAFEHEART-RE equation to the patients analyzed at the time of their enrollment in the SAFEHEART registry and at the time of the last follow-up, no significant differences were found in the estimated risk reduction between these 2 moments between the group that used ATV and the group that used RV.

Table 3 Ten-year cardiovascular risk in the SAFEHEART cohort with ATV/RV

Risk	Total	ATV	RV	*P*
Ten-year SAFEHEART-RE risk at enrollment	1.54 (0.64–3.39)	1.61 (0.67–3.39)	1.22 (0.54–2.93)	<.001
Ten-year SAFEHEART-RE risk at follow-up	1.27 (0.54–2.76)	1.29 (0.54–2.82)	1.22 (0.54–2.76)	.51

ATV, atorvastatin group; RV, rosuvastatin group; SAFEHEART-RE, SAFEHEART risk equation; IQR, interquartile range.
Median (IQR).

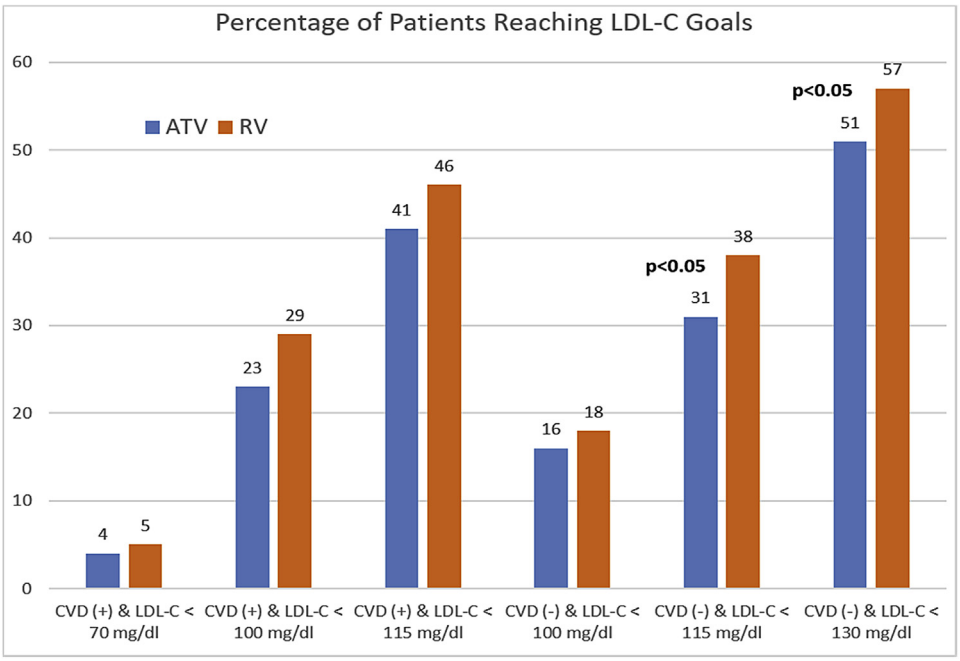

Figure 3 Goal achievement for different LDL cholesterol thresholds in FH patients with and without atherosclerotic cardiovascular disease in the atorvastatin and rosuvastatin groups. CVD (+): Patient who had a history of atherosclerotic cardiovascular disease; CVD (−): patient without history of atherosclerotic cardiovascular disease. LDL-C, low-density lipoprotein cholesterol; FH, familial hypercholesterolemia; CVD, cardiovascular disease.

The strengths and limitations of our study merit to be taken into account. The SAFEHEART study is a nationwide, long-term prospective contemporary cohort of a molecularly defined FH population. This fact makes these results as a reference because of the lack of other cohorts of similar characteristics and similar follow-up around the world. Nevertheless, the 2 groups considered for this study were not randomly assigned. Furthermore, RV was the newer drug pointed out and, although known risk factors were matched, an important limitation is that RV might have been favored for patients perceived by physicians to be at higher risk. This fact could be reflected in the greater use of RV in referral practice as compared to primary care. Another major limitation is the very small differences in LDL-C level and in risk of ACVEs between the ATV and RV groups that raise the possibility that unaccounted confounders and limited statistical power could explain the lack of differences in ACVEs.

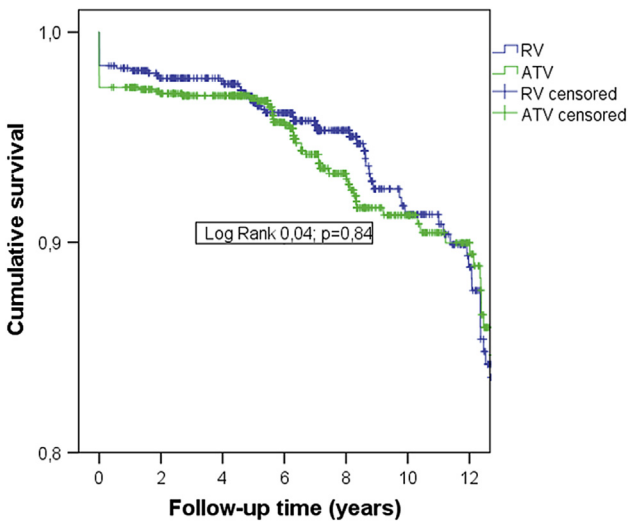

Figure 4 Survival curves for incident ACVEs in both treatment groups. ACVEs, atherosclerotic cardiovascular events.

Conclusion

ATV and RV are 2 high-potency statins widely used for patients with FH. The results of the present study show that although the reduction in LDL-C levels was greater in the group treated with RV than in the group treated with ATV, the superiority of RV for reducing ACVEs was not demonstrated.

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writing, and manuscript review. D.Z., F.F., J.F.S.M-T, J.D.M., A.G.E., J.P.M-G., R.d.A., M.M., D.M., J.M.C., L.S., M.A.B-R., R.A., P.A.B., A.M., M.J.R.J., and J.G-C. contributed to patients' enrollment and follow-up, research development, manuscript writing, and manuscript review.

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