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Francisco Freire Barbas de Albuquerque

Inibidores da PCSK9 no tratamento de doenças cardiovasculares: uma revisão narrativa

PCSK9 Inhibitors in the Treatment of Cardiovascular Diseases: A Narrative Review

março, 2019

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PCSK9 Inhibitors in the Treatment of Cardiovascular Diseases: A Narrative Review

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Faculdade de Medicina da Universidade do Porto, 11/03/2019

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PCSK9 Inhibitors in the Treatment of Cardiovascular Diseases: A Narrative Review

Inibidores da PCSK9 no tratamento de doenças cardiovasculares: Uma revisão narrativa

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Abstract

Cardiovascular diseases are a main cause of morbidity and mortality worldwide and its prevention is a major concern in current practical guidelines. Reduction of low-density lipoprotein cholesterol (LDL-c) plasma levels lower than 70 mg/dL in patients with established cardiovascular disease, sometimes cannot be achieved, despite maximum-tolerated statin dose. The proprotein convertase subtilisin/kenin 9 inhibitors have recently emerged and showed an incremental reduction in LDL-c levels in this patient setting and a reduction of major adverse cardiovascular events have been clearly established. Several randomized controlled trials regarding the clinical effects of evolocumab, alirocumab and bococizumab have been published in the latest years and some of them are described in this article. Physicians might be looking towards a very useful lipid-lowering therapy for high cardiovascular risk patients.

Key words: PCSK9 inhibitors**,** Evolocumab, Alirocumab, Bococizumab

Resumo

As doenças cardiovasculares são uma causa importante de morbimortalidade em todo o mundo e a sua prevenção constitui um assunto importante nas *guidelines* práticas atuais. A redução dos níveis plasmáticos de lipoproteínas de colesterol de baixa densidade (c-LDL) abaixo de 70 mg/dL em doentes com doença cardiovascular estabelecida, por vezes, não consegue ser alcançada, apesar da dose máxima tolerada de estatinas. Os inibidores proproteina convertase subtilisina/kenina 9 (PCSK9) emergiram recentemente mostrando uma redução adicional nos níveis de c-LDL neste grupo de doentes, assim como redução inequívoca nos eventos cardiovasculares major. Vários ensaios clínicos randomizados centrados nos efeitos clínicos do evolocumab, alirocumab e bococizumab têm sido publicados nos últimos anos e estando alguns deles são descritos neste artigo. A comunidade médica poderá estar a olhar em direção a uma terapêutica de redução lipídica muito útil em doentes com elevado risco cardiovascular.

Palavras-chave: Inibidores PCSK9**,** Evolocumab**,** Alirocumab**,** Bococizumab

Abbreviations Table		
Designation	**English**	**Portuguese**
3-hidroxi-3-methyl-glutaril-CoA	HMG-CoA	HMG-CoA
Absolute risk reduction	AAR	RRA
Acute coronary syndrome	ACS	SCA
High-sensitivity C reactive protein	hs-CRP	PCR-as
Cambridge Neuropsychological Test Automated battery	CANTAB	CANTAB
Cardiovascular diseases	CVD	DCV
Confidence interval	CI	IC
Coronary heart disease	CHD	DAC
Everyday cognition tool	ECog	ECog
Hazard ratio	HR	HR
LDL-cholesterol	LDL-c	c-LDL
LDL receptor	LDLR	RLDL
Major adverse limb events	MALE	EAMM
Major adverse cardiovascular events	MACE	EACM
Myocardial infarction	MI	EAM
Number needed to treat	NNT	NNT
Number	n	n
Percent atheroma volume	PAV	VAP
Peripheral artery disease	PAD	DAP
Proprotein convertase subtilisin/kenin 9	PCSK9	PCSK9
Total atheroma volume	TAV	VAT

Introduction

Cardiovascular diseases (CVD) remain a leading cause of morbidity and mortality worldwide [1]. Secondary CVD prevention is crucial in our society since more patients survive their first episode of cardiovascular event and are at higher risk of recurrence [2, 3].

In this review, among the treatment targets and goals for CVD prevention, the author will focus only in hypercholesteremia. LDL-cholesterol (LDL-c) is a well-established and modifiable risk factor for CVD. Currently, an LDL-c goal of less than 70 mg/dl is recommended in very high-risk patients. To achieve these plasma levels, not only a lifestyle modification but also medical treatment is required [2].

Statins remain the first-line drug for lipid management in patients with atherosclerotic CVD by inhibiting 3-hidroxi-3-methyl-glutaril-CoA (HMG-CoA) reductase [4]. Although these drugs are safe, some patients experience adverse events or are intolerant to them, or do not achieve LDL-c goals despite maximum tolerated statin-dose [5]. In either case, the second line therapy available is ezetimibe, a cholesterol absorption inhibitor, which not only provides an additional reduction in LDL-c levels when associated to a statin, but also significantly reduces major adverse cardiovascular events (MACE) [6].

Even with an optimized regimen, some patients still do not reach their LDL-c goals. To accomplish that, a novel class of drugs, the proprotein convertase subtilisin/kenin 9 (PCSK9) inhibitors, had recently emerged [7]. Evolocumab, alirocumab and bococizumab, are the three most studied PCSK9 inhibitors [8].

PCSK9 is produced mostly in the liver and binds to LDL receptors (LDLR) on hepatic cell surface. It targets the LDLR for degradation inside hepatic cell endosome. Consequently, the LDLR is not recycled to the hepatic cell surface resulting in fewer LDLR available to capture LDL-c on plasma. Ultimately, a rise in LDL-c levels on plasma occurs [9]. Thus, when using a PCSK9 inhibitor, the LDLR is not degraded and is able to return to the cell surface. This results in a decrease in LDL-c plasma levels (figure 1). Recently, Toth PP et al. showed that PCSK9 inhibitors were associated with a significant reduction in LDL-c plasma levels compared to either placebo and ezetimibe [10].

It is important to establish if incremental reduction in LDL-c plasma levels prevents cardiovascular events and overall mortality [11].

The main goal of this narrative review is to provide a summarized description of the major randomized controlled trials regarding the efficacy and clinical effects of evolocumab, alirocumab and bococizumab on CVD.

The current report was not funded by any interested party, either governmental or industry, and the decision to carry out this review was taken exclusively by the author.

Methods

Search Strategy

This study started with a research on two data bases, Pubmed and ISI Web of Knowledge, using the queries ‘’ (evolocumab OR alirocumab OR bococizumab) AND Randomized Controlled Trial [Filter]’’, ‘’evolocumab’’ AND ‘’clinical trial’’, ‘’alirocumab’’ AND ‘’clinical trial’’, ‘’bococizumab’’ AND ‘’clinical trial’’. The search took place in November 2018 and no articles were excluded based on publication date. The aim of this search was to identify randomized controlled trials regarding evolocumab, alirocumab and bococizumab. The queries resulted in 463 articles. A flowchart showing the literature search method, as well as the resulting number of articles selected, is displayed in Figure 2.

Inclusion criteria

Randomized controlled trials whose primary end-point is a clinical outcome were included.

Published ad-hoc exploratory analysis of the selected trials, if considered relevant by the author, may also have been included in the report.

Exclusion criteria

Studies other than randomized controlled trials whose primary end-point is a clinical outcome were excluded. Case reports, retrospective studies, observational studies other than randomized controlled trials and systematic reviews were therefore excluded. Randomized controlled trials whose primary end-point was change in LDL-c level from baseline overtime alone, although relevant, were considered outside the scope of this review.

Major Randomized Controlled Trials

Studies involving Evolocumab

OSLER (2015)

Sabatine et al. enrolled patients that had completed a parent phase 2 or phase 3 trial of evolocumab [12-21], respectively, into one of two longer-term extension trials, designated Open-Label Study of Long-Term Evaluation against LDL Cholesterol 1 and 2 (OSLER-1 and -2) [22].

Patients were eligible if they did not have an adverse event that led to the discontinuation of a study drug during the parent trial, did not have an unstable medical condition, and were not expected to need unblinded lipid measurement or adjustment of background lipid-regulating therapy during the first 12 weeks of participation in the OSLER trials.

A total of 4465 patients were enrolled in the OSLER program (1342 patients in OSLER-1 and 3141 patients in OSLER-2)

Eligible patients were randomly assigned to receive either evolocumab plus standard therapy (n=2976) or standard therapy alone (n=1489), regardless of their study-group in the parent study. Evolocumab was administered monthly, subcutaneously, at a dose of 420mg in OSLER-1 and 140mg twice a week or 420mg monthly in OSLER-2.

The median duration of follow-up was 11.1 months.

The primary end-point was the incidence of adverse events. It occurred in 2060 patients (69.2%) in the evolocumab group and in 965 patients (64.8%) in the standard therapy group. Serious adverse events occurred in 222 patients (7.5%) in the evolocumab group and in 111 patients (7.5%) in the standard-therapy group.

The secondary end-point was the percent change in the LDL cholesterol level, which was reduced by 61% (95% CI, 59 to 63; P<0.001) in the evolocumab group compared to standard-therapy group at 12 week and was maintained over time.

An exploratory analysis showed an all cardiovascular events reduction in evolocumab group compared to standard-therapy group (Kaplan-Meier estimates at 1 year, 0.95% and 2.18%, respectively; HR=0.47; 95% CI, 0.28 to 0.78; P=0.003).

Sattar et al [23], in a post-hoc analysis regarding new-onset diabetes and glycemia in OSLER trial population, showed a similar change in both HbA1c and fasting plasma glucose over 48 weeks, in both treatment arms.

GLAGOV (2016)

In the multicenter, double-blind, placebo-controlled Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) randomized controlled trial [24], 968 patients were enrolled to receive either evolocumab 420mg monthly (n=484) or respective placebo (n=484), via subcutaneous injections, for 76 weeks. Inclusion criteria were patients greater than 18 years old and at least 1 epicardial coronary stenosis of at least 20% on coronary angiography and had a target vessel suitable for imaging with less than 50% visual obstruction. In addition, patients also required to have been treated with a stable statin dose for at least 4 weeks and to have an LDL-c level of 80 mg/dL or higher, or between 60 to 80 mg/dL with 1 major or 3 minor cardiovascular risk factors.

The primary efficacy end-point was the nominal change in percent atheroma volume (PAV) and the secondary efficacy end-point was the nominal change in normalized total atheroma volume (TAV), both measured by intravascular ultrasonography (IVUS) and calculated as the value at 78 weeks minus the value at baseline, respectively, in evolocumab group (n=423) and placebo group (n=423).

PAV did not change in placebo group (0.05%, P=0.78 compared with baseline) and decreased by 0.95% in the evolocumab group (P<0.001 compared with baseline; between-group difference, -1.0% [95% CI, -1.8% to -0.64%]; P<0.001).

TAV did not change in placebo group (-0.9mm3, P=0.45 compared with baseline) and decreased by 5.8mm3 in evolocumab group (P<0.001 compared with baseline; between-group differences, -4.9mm3 [95 CI, -7.3 to -2.5]; P<0.001).

The prespecified subgroup analysis of change in PAV from baseline to week-78 follow-up showed treatment differences favoring the use of evolocumab.

FOURIER (2017)

In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition with Elevated Risk (FOURIER) study [(11)], a randomized, double-blind, placebo-controlled, multinational clinical trial, 27564 patients between 40 and 85 years who had clinically evident CVD and fasting LDL-c level of at least 70 mg/dL or non-HDL-c level of at least 100 mg/dL while they were taking optimized regimen of lipid-lowering therapy with statins, with or without ezetimibe, were assigned to receive either evolocumab (140mg every 2 weeks or 420 mg monthly, subcutaneously) (n=13784) or matching placebo (n=13780). The median duration follow-up was 2.2 years.

The primary end-point was a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization, which occurred in 1344 patients (9.8%) in evolocumab group and in 1563 patients (11.3%) in placebo group (HR 0.85; 95% CI, 0.79 to 0.92; P<0.001).

The secondary end-point was the composite of cardiovascular death, stroke or myocardial infarction, which occurred in 816 patients (5.9%) in evolocumab group and 1013 patients (7.4%) in placebo group (HR 0.80; 95% CI, 0.73 to 0.88; P<0.001).

Despite this significantly risk reduction of 15% in primary end-point and 20% in secondary end-point, an exploratory analysis of each outcome individually showed that evolocumab had no statistical significant effect on cardiovascular death (P=0.62), death from any cause (P=0.54), hospitalization for unstable angina (P=0.89) and cardiovascular death or hospitalization for worsening heart failure

(P=0.82), compared to placebo. Yet, myocardial infarction was reduced 27% (P<0.001), stroke was reduced 21% (P=0.01) and coronary revascularization was reduced 22% (P<0.001) in the evolocumab group when compared to placebo.

Regarding lipid data, the mean percentage reduction in LDL-c level with evolocumab was 59% (95% CI, 58 to 60; P<0.001). This reduction was sustained over time and neutralizing antibodies did not develop in any patient.

After FOURIER trial had been published, several post-hoc exploratory analysis emerged and brought some relevant results regarding different subgroups in FOURIER trial population.

Giugliano RP et al [25] compared the outcomes of evolocumab in 2 subgroups: patients with baseline LDL-c level of less than 70 mg/dL versus levels greater than 70 mg/dL and patients receiving a maximal-potency background statin versus submaximal statin therapy. The authors found that evolocumab reduced the risk for the primary end-point by 20% (HR, 0.80; 95% CI, 0.60-1.07) in patients with an LDL-c level of less than 70 mg/dL and by 14% (HR, 0.86; 95% CI, 0.73-0.89) in patients with a LDL-c level of at least 70 mg/dL, with no evidence of treatment effect modification by baseline LDL-c (P=0.65 for interaction).

Likewise, evolocumab reduced either primary and secondary end-point in both background statin therapy subgroups, with no evidence of treatment effect modification owing to intensity of background statin therapy (P=0.71 for interaction).

Sabatine MS et al [26], examined the cardiovascular efficacy and safety of evolocumab by baseline diabetes status. A total of 11031 (40%) had diabetes and 16533 (60%) did not have diabetes at baseline. When analyzing the placebo group alone, patients with diabetes were at significantly greater risk for the primary end-point (HR 1.26, 95% CI 1.13-1.40, p<0.0001) and secondary end-point (HR 1.40, 95% CI 1.23-1.60, p<0.0001), than those without diabetes. Moreover, evolocumab significantly reduced the primary and secondary end-point in patients with and without diabetes at baseline, compared to placebo. Nevertheless, the absolute risk reduction tended to be greater in patients with diabetes (ARR 2.7%, 95% CI 0.7-4-8) when compared to those without diabetes (ARR 1.6% (95% CI 0.1-3.2)).

The authors also found that the risk of new-onset diabetes in patients without diabetes at baseline was not increased with the use of evolocumab, nor did it worsen the glycaemia.

Bohula EA et al [27], explored the effect of evolocumab stratified by baseline high-sensitivity C reactive protein (hs-CRP) level.

The analytic cohort was composed of 27495 patients of the trial population, categorized into 3 subgroups: 7981 patients with a low-baseline hsCRP level (<1 mg/dL), 11177 with an intermediate hsCRP (1-3 mg/dL) and 8337 with a high hsCRP (>3 mg/dL).

First, among the 13740 patients assigned to placebo arm in FOURIER trial, the higher the baseline hsCRP levels were, the greater the rates of cardiovascular events were. Second, the relative risk reduction with evolocumab versus placebo for both the primary and secondary end-points was consistent across baseline hsCRP strata. Yet, the ARR for primary and secondary end-points with evolocumab tended to be the highest in those with baseline hsCRP level >3 mg/dL, with a number needed to treat (NNT) for the primary end-point of 38 in those in this stratum versus 56 in those with the lowest baseline hsCRP levels. Even among patients achieving very low LDL-c concentrations (<20 mg/dL) 1 month after randomization, the adjusted event rate was as greater as the higher the baseline hsCRP levels were.

Bonaca MP et al [28] stratified the study population according to symptomatic peripheral artery disease (PAD). A total of 3642 (13.2%) had a history of symptomatic lower extremity PAD at baseline of whom a total of 2137 patients had concomitant prior myocardial infarction (MI) or prior stroke and 1505 patients had no history of neither MI nor stroke.

When analyzing placebo arm alone, patients with PAD had significantly higher rates of both the primary and secondary end-point in comparison with patients without PAD. Likewise, patients with PAD and concomitant MI or stroke had higher rates of CV events than those without. Nevertheless, patients with PAD and no prior MI or stroke, still had higher rates of CV death, MI or stroke than patients with prior MI or stroke and no symptomatic PAD (10.3% versus 7.6%; adjusted HR, 2.07; 95% CI, 1.42-3.01; P=0.0001). Last, patients with symptomatic PAD had higher rates of major adverse limb events (MALE).

In terms of MACE, in patients with PAD evolocumab reduced primary end-point by 21% (2.5-year Kaplan Meier rate, 13.3% versus 16.8%; HR, 0.79; 95% CI, 0.66-0.94; P=0.0098) and secondary end-point by 27% (9.5% versus 13.0%; HR, 0.73; 95% CI, 0.59-0.91; P=0.0040) compared to placebo. This reduction was consistent even in patients with PAD without prior MI or stroke.

Furthermore, LDL-c lowering with evolocumab reduced the risk of MALE by 42% in the overall population (0.27% versus 0.45%; HR, 0.58; 95% CI, 0.38-0.88; P=0.00093; ARR, 0.18%).

Last, when looking at the composite of MACE or MALE in patients with PAD and no prior MI or stroke, evolocumab resulted in an ARR at 2.5 years of 6.3% yielding NNT of 16.

Sabatine MS et al [29] analyzed the effects of evolocumab by severity and extent of coronary artery disease. The patients were stratified based on the number of prior MIs (more than 2 versus less than 2), the timing of prior MIs (less than 2 years versus more than 2 years) and the presence of residual multivessel coronary disease defined as $\geq$ 40% stenosis in $\geq$ 2 large vessels.

When analyzing the placebo arm alone, both the primary and secondary end-point were significantly higher in all strata.

When considering the benefit of evolocumab versus placebo, regarding timing of prior MI, evolocumab reduced primary end-point by 20% (HR, 0.80, 0.71-0.91) in those with a more recent MI versus 5% (HR, 0.95) in those without. This result was consistent in the rest strata, where evolocumab reduced the primary end-point by 18% in those with multiple prior MIs (HR, 0.82, 0.72-0.93) and 21% (HR 0.79, 0.69-0.91) in those with multivessel disease.

Table 1 and 2 provide a compilation of the available data from the original articles regarding hazard ratios, absolute risk reductions and number need to treat with respect to primary and secondary end-point of the FOURIER trial population.

EBBINGHAUS (2017)

The Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) study [30], assessed the cognitive function from a subgroup of patients from the FOURIER trial, using the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Patients were enrolled previously to the first dose administration in FOURIER trial. The inclusion criteria were the ones described previously in FOURIER trial. Patients were excluded if any condition could confound the study results, such as dementia or any cognitive impairment. A total of 1974 patients were enrolled.

The primary end point was the score on the spacial working memory strategy index of executive function (scores range from 4 to 28, with lower scores representing more efficient use of strategy and planning).

The three secondary end points were working memory, episodic memory and psychomotor speed.

The primary analysis population included 1204 patients, out of the total 1974, who had baseline CANTAB assessment before or on the day of the first dose of evolocumab (n=586) or placebo (n=618) and had at least one follow-up CANTAB assessment. This analysis was a noninferiority comparison of the mean change in the primary end point from baseline over time. The median duration of follow-up was 19.4 months in the primary analysis population.

In terms of outcomes, the mean change from baseline over time in the primary end-point did not differ significantly between the two study groups; the raw score at baseline was 17.8 in both groups, and mean change from baseline in the score was -0.21+/- 2.62 in evolocumab group and -0.29 +/- 2.81 in placebo group ($P<0.001$ for noninferiority and $P=0.85$ for superiority). With respect to the three secondary end points, the mean change in raw scores from baseline also did not differ significantly between two study groups.

The full analysis population included the 1204 from the primary analysis population plus the 770 patients whose first CANTAB assessment occurred after the day on which the first dose of evolocumab

(n=983) or placebo (n=990) was administered. No significantly differences were observed between two study groups.

Between-group differences assessment showed no significantly differences favoring either the use of evolocumab or the use of placebo.

At the final visit, a total of 1581 patients in the EBBINGHAUS study performed retrospective self-assessments of their executive and memory function comparing current level of everyday functioning with their level at the beginning of the trial, using the Everyday Cognition tool (ECog). No significant between-group differences were observed in scores on individual domains (P=0.83 for memory domain; P=0.28 for executive functioning domain) or total score (P=0.42).

These results support either objectively (via CANTAB assessment) and subjectively (via ECog) that the use of evolocumab does not cause any cognitive impairment compared to placebo.

Studies involving Bococizumab

SPIRE (2017)

The Studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE) program for the development of bococizumab consists of two parts: the six SPIRE lipid-lowering studies and the SPIRE-1 and SPIRE-2 event-driven cardiovascular outcome trials [8, 31]. The former did not meet the inclusion criteria for this report and the last is described in this article.

The SPIRE-1 and SPIRE-2 studies are two randomized, placebo-controlled, multinational clinical trials which aim to evaluate the clinical efficacy and the safety of bococizumab. During the conduct of these two trials, the sponsor discontinued further development of bococizumab on November 1, 2016, because data from the six SPIRE lipid-lowering trial became available indicating that the drug was associated with the development antidrug antibodies that significantly attenuated LDL-c lowering over time. In addition, even among patients who were antibody negative, bococizumab was associated with a wide variation in LDL-c reduction[31]. Despite the discontinuation of bococizumab and the prematurely stop

of SPIRE-1 and SPIRE-2 trials, the unblinded data collected between October 2013 until November 2016 were analyzed and the results are described here [8].

The inclusion criteria were to have either a previous cardiovascular event or history of diabetes, chronic kidney disease, or peripheral vascular disease with additional cardiovascular risk condition or a history of familial hypercholesteremia, to have one or more additional cardiovascular risk factors and age of at least 50 years for men and 60 years for women. Patients were also required to have an LDL-c level ≥70 mg/dl or non-HDL level ≥ 100 mg/dl in SPIRE-1 and to have a LDL-c level ≥ 100 mg/dl or non-HDL ≥ 130 mg/dl in SPIRE-2. Treatment with a statin during the previous 4 weeks was a condition met in all patients.

At the time the sponsor stopped the trial a total of 16817 patients had been enrolled in SPIRE-1 trial to receive either bococizumab 150mg, twice a week, via subcutaneous injections (n=8408) or matching placebo (n=8392). A total of 10621 patients had enrolled in SPIRE-2 trial to received either bococizumab 150mg subcutaneously every two weeks (n=5312) or matching placebo (n=5309). By the time the trial was terminated, the median follow-up time was 7 months in SPIRE-1 and 12 months in SPIRE-2.

The primary end-point of the two trials was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for unstable angina requiring urgent revascularization.

In SPIRE-1 the primary end-point occurred in 173 patients each in bococizumab group and placebo group (HR 0.99; 95% CI, 0.80 to 1.22; P=0.94). In SPIRE-2 the primary end-point occurred in 179 patients in bococizumab group and in 224 patients in placebo group (HR, 0.79; 95% CI, 0.65 to 0.97; P=0.02). In the combined analysis, the primary end-point occurred in 352 patients in bococizumab group and in 397 in placebo group (HR, 0.88; 95% CI, 0.76 to 1.02; P=0.08).

In summary, bococizumab significantly reduced cardiovascular events in the higher risk patient group (SPIRE-2) but did it not in the lower risk patient group (SPIRE-1).

Studies involving Alirocumab

ODYSSEY OUTCOMES (2018)

The ODYSSEY OUTCOMES trial [32] tested whether adding alirocumab to standard high intensity statin therapy, in post-acute coronary syndrome (ACS) patients would improve their morbidity and mortality. In this multi-center, double-blind, placebo-controlled trial, the authors randomized 18924 patients, who were more than 40 years of age, had a recent ACS within 1 to 12 months prior to randomization and who had an LDL-c level more than 70 mg/dl, or non-HDL-c level more than 100 mg/dl or a apolipoprotein B more than 80 mg/dl, despite maximal intensity-statin therapy, to receive either alirocumab (n=9462) 75mg subcutaneously every two weeks or matching placebo (n=9462).

Protocol-specific dose-adjustments were performed to target an LDL-c level of 25 to 50 mg/dl and to avoid sustained levels below 15mg/dl. If patients achieved LDL-c levels above 50 mg/dL alirocumab was up-titrated from 75mg to 150mg. If patients achieved levels below 15 mg/dL in two consecutives measurements, patients were switched to placebo arm. LDL-c levels were considered acceptable between 15-25 mg/dl with alirocumab 75mg, but down-titrated if alirocumab 150mg.

Median duration of follow-up was 2.8 years.

The primary efficacy end-point was a composite of death from coronary heart disease (CHD), nonfatal myocardial infarction, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization. A total of 903 patients (9.5%) in the alirocumab group and 1052 patients (11.1%) in the placebo group (HR 0.85, 95% CI, 0.78-0.93, P<0.001) experienced the primary end-point. A prespecified subgroup analysis demonstrated the greatest benefit in those with an LDL-c level higher than 100 mg/dL at baseline (HR 0.76, 95% CI, 0.65-0.87) compared to those with LDL-c levels lower than 100 mg/dl.

The major secondary efficacy end-point included: any CHD event; major CHD event; any CV event; composite of death from any cause, non-fatal MI or non-fatal ischemic stroke; death from CHD; death from CV causes; death from any cause. The hierarchical analysis showed significant results in the first four secondary end-points, but it was stopped after the first nonsignificant P value observed in death from CHD end-point (P=0.38), in accordance with the hierarchical testing plan.

A total of 334 patients (3.5%) in the alirocumab group and 392 patients (4.1%) in the placebo group died (HR, 0.85; 95% CI, 0.73 to 0.98).

Finally, the treatment was safe and well tolerated. The most frequent adverse event, which was rare, was local site-injection reactions (3.8% in alirocumab group versus 2.1% in placebo group, $P<0.001$).

Table 3 provides a compilation of the studies previously described and summaries of their major findings.

Limitations

Several limitations regarding original studies described here should be considered.

GLAGOV trial examined the effects of disease progression only on patients presenting for a clinically indicated coronary angiography and focused only on atheroma volume and did not characterized the effects on atheroma morphology [(24)].

The major limitation of FOURIER trial is the relatively short follow-up period compared to other lipid-lowering trials [(11)].

Post-hoc analysis of FOURIER trials are not truly randomized controlled trial, once the results are interpreted in a post-randomization subgroup stratification. Even with adequate multivariable adjustment, residual confounding may remain.

In SPIRE program, the major limitation was the prematurely stop of the trial and discontinuation of the drug. Besides, the differences in baseline LDL-c levels and follow-up duration between SPIRE-1 and -2 populations also constitute a limitation.

In ODYSSEY OUTCOME trial, whether the safety and efficacy of alirocumab were influenced by the blinded dose-adjustment strategy, which was designed to mitigate the occurrence of very low levels of LDL-c constitutes a major limitation. Like in FOURIER trial, this trial cannot predict longer-term safety of treatment with a PCSK9 inhibitor [(32)].

A limitation in all these trials is the infrequent use of ezetimibe, for which cardiovascular efficacy is established.

Conclusions

CVD are a major problem in our society and many efforts are being made to attenuate this issue [1,2,3]. Reduction of LDL-c has been proven to reduce overall mortality, but some patients still cannot achieve current LDL-c goals [2]. PCSK9 inhibitors might be an important therapeutic weapon in this setting.

Evolocumab, alirocumab and bococizumab all proved to produce an incremental reduction on LDL-c plasma levels in patients already taking statins and ezetimibe [10]. However, the last drug was not able to maintain its effects overtime because of development of antidrug antibodies which led to its discontinuation [31]. Still, an analysis made with available data from the SPIRE-1 and 2 trials before its ending, showed no benefits of bococizumab in MACE reduction compared to placebo in SPIRE-1 and combined SPIRE-1 and 2 analysis, but a significant reduction was observed in SPIRE-2 population [8,31].

The GLAGOV trial demonstrated for the very first time a regression of atherosclerotic plaque in patients using evolocumab compared to placebo when added to a statin background [24]. Yet, whether if incremental LDL-c level reduction and plaque regression using evolocumab would prevent MACE was still uncertain.

Following this, FOURIER trial showed a significant reduction in the composite end-point of major CV death, MI, stroke, hospitalization for unstable angina or coronary revascularization, but not on all-cause mortality [11]. Importantly, these benefits came with no offsetting neurocognitive impairment, as demonstrated in EBBINGHAUS trial, or other adverse events [22,30].

Subgroup analysis of FOURIER trial demonstrated that patients with baseline diabetes, hs-CRP baseline level >3 mg/dL, baseline PAD, more than two MI, prior MI less than two years and multivessel residual coronary disease would benefit the most from evolocumab use [26-29]. Give the currently high cost of the drug [33], such finding shall be taken into consideration regarding which patients would benefit the most from drug's clinical potential.

Alirocumab showed a significant reduction in MACE comparing to placebo, similarly to FOURIER trial. This benefit was more pronounced among patients who had an LDL-c baseline level of at least 100 mg/dL, like in SPIRE-2 trial population. This drug also had an impact on overall mortality [32].

To conclude, evolocumab and alirocumab, consistently lowered LDL-c and reduced MACE [11,32] with no appreciable adverse events [22,30]. Alirocumab showed a reduction in overall mortality [32].

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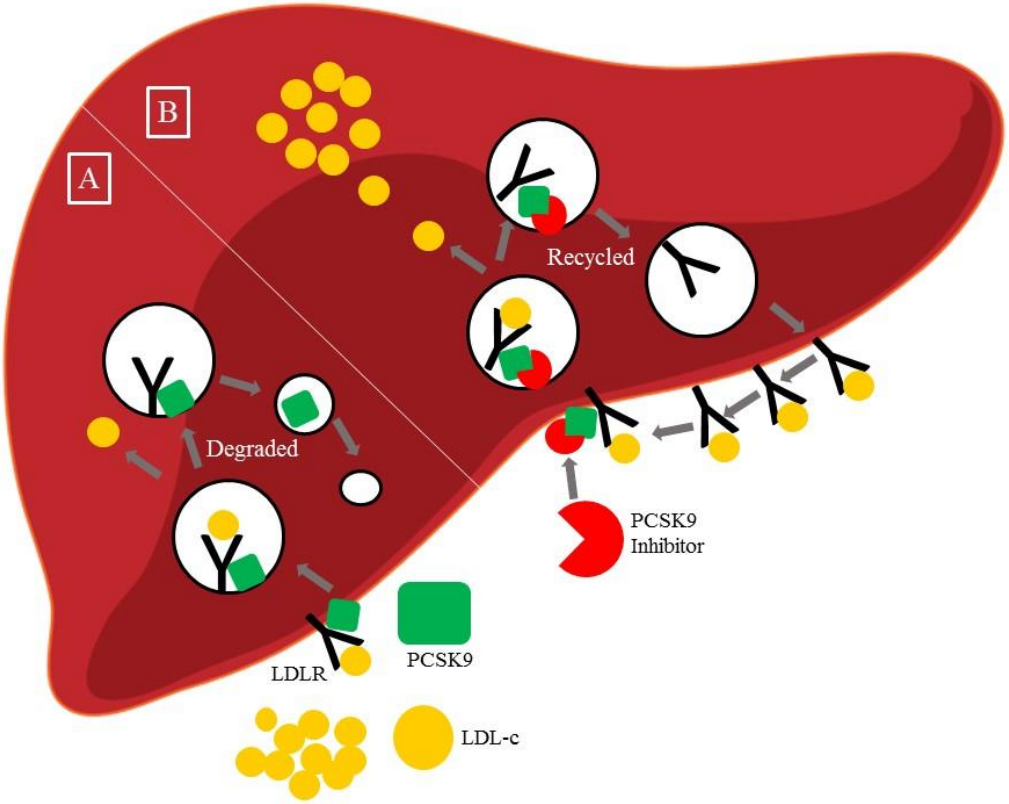
Figure caption

Figure 1. PCSK9 Inhibitors mechanism of action: A) PCSK9 binds to LDL-receptors and targets them for degradation; B) PCSK9 Inhibitors allow LDL-receptor recycling to hepatic cell surface.

Figure 2. Flowchart showing literature search method n, number of articles.

Figures



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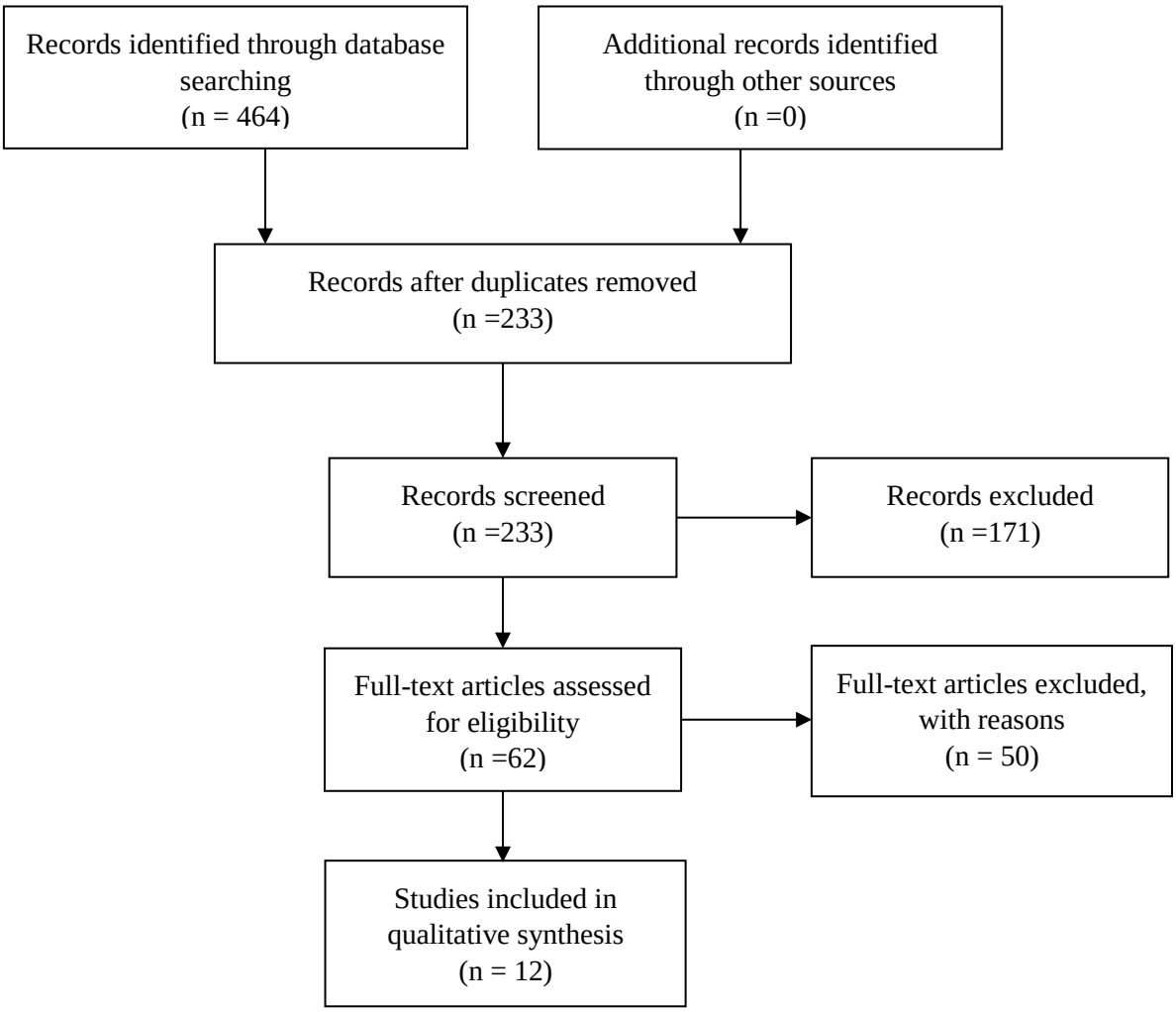

Tables

Table 1. Primary and secondary end-point Hazard Ratios by FOURIER trial subgroup population

Outcome	Hazard Ratio (95% CI)																
	Total population	Subgroup population															
		PAD		hs-CRP			High-risk features						Diabetes		LDL-c		Statin Therapy	
		w	wo	<1 mg/dL	1 to 3 mg/dL	>3 mg/dl	MI < 2y	MI > 2y	>2 MI	< 2 MI	w/ RMD	wo/ RMD	w	wo	<70 mg/dL	>70 mg/dL	Maximal dose	Submaximal dose
Primary End-point	0.85 (0.79-0.92)	0.79 (0.66-0.94)	0.86 (0.80-0.93)	0.82 (0.70-0.95)	0.93 (0.83-1.05)	0.80 (0.71-0.90)	0.80 (0.71-0.91)	0.95 (0.85-1.05)	0.82 (0.72-0.93)	0.92 (0.84-1.02)	0.79 (0.69-0.91)	0.93 (0.85-1.02)	0.83 (0.75-0.93)	0.87 (0.79-0.96)	0.80 (0.60-1.07)	0.86 (0.79-0.92)	0.86 (0.79-0.92)	0.85 (0.78-0.93)
Secondary end-point	0.80 (0.73-0.88)	0.73 (0.59-0.91)	0.81 (0.73-0.90)	0.81 (0.66-0.99)	0.87 (0.75-1.02)	0.73 (0.63-0.85)	0.79 (0.67-0.94)	0.92 (0.84-1.02)	0.79 (0.67-0.94)	0.84 (0.74-0.96)	0.70 (0.58-0.84)	0.89 (0.70-1.00)	0.82 (0.72-0.93)	0.78 (0.72-0.93)	0.70 (0.48-1.01)	0.81 (0.73-0.89)	0.78 (0.66-0.92)	0.81 (0.72-0.90)

Abbreviations: MI, myocardial infarction; PAD, peripheral artery disease; RMD, residual multivessel disease (defined as stenosis >40% in >2 large vessels); hs-CRP, high-sensitivity C-Reactive Protein; w, with; wo, without; y, years

Table 2. Primary and secondary end-point Absolute Risk Reduction (ARR) and respective Number Needed to Treat (NNT) by FOURIER trial subgroup population

Outcome	ARR (NNT)															
	Total population	Subgroup population														
		PAD		hs-CRP			High-risk features						Diabetes		LDL-c		Statin Therapy	
		w	wo	<1 mg/dL	1 to 3 mg/dL	>3 mg/dl	MI < 2y	MI > 2y	>2 MI	< 2 MI	w/ RMD	wo/ RMD	w	wo	<70 mg/dL	>70 mg/dL	Maximal dose	Submaximal dose
Primary End-point	1.5% (67)	3.5% (29)	1.6% (63)	1.6% (63)	1.8% (56)	2.6% (38)	3.4% (29)	0.8% (125)	3.7% (27)	1.3% (77)	3.6% (28)	1.2% (83)	2.7% (37)	1.6% (63)	2.3% (43)	1.5% (67)	1.8% (56)	1.5% (67)
Secondary end-point	1.5% (67)	3.5% (29)	1.4% (71)	0.8% (125)	2.0% (50)	3.0% (33)	2.9% (34)	1.0% (100)	2.6% (38))	1.7% (59)	3.4% (29)	1.3% (77)	2.0% (50)	2.0% (50)	2.1% (48)	1.4% (71)	1.8% (56)	1.8% (56)

Abbreviations:ARR, absolute risk reduction; MI, myocardial infarction; NNT, number needed to treat; PAD, peripheral artery disease; RMD, residual multivessel disease (defined as stenosis >40% in >2 large vessels); hsCRP, high-sensitivity C-Reactive Protein; w, with; wo, without; y, years

Table 3. Some of the major studies on clinical outcomes of PCSK9 Inhibitors and summaries of their conclusion

Study	n	Intervention	End-point	Major Findings
OSLER (2015)	4465	EVO SC plus SOC (420 mg Q1M) vs. SOC alone in OSLER-1 EVO SC (140mg Q2W or 420mg Q1M) plus SOC vs. SOC alone in OSLER-2	Incidence of adverse events	Adverse events were reported more frequently in the EVO group EVO group had a significantly lower rates of all cardiovascular events than did the patients in the SOC group No differences between groups regarding glycaemia and new onset-diabetes
GLAGOV (2016)	968	EVO SC (420mg Q1M) vs. PLA	Nominal change in PAV and nominal change in TAV	EVO significantly reduces PAV and TAV compared with PLA
FOURIER (2017)	27564	EVO SC (140mg Q2W or 420 Q1M) vs. PLA	Primary end-point: CV death, MI, stroke, hospitalization for UA or CR Secondary end-point: CV death, MI, stroke	EVO significantly reduced both the primary and secondary end-point compared to PLA EVO did not reduce all-cause mortality compared to PLA EVO was equally effective in reducing MACE in patients with LDL-c <70mg/dL vs >70mg/dL and maximal statin dose vs submaximal statin-dose EVO significantly reduced MACE in patients with and without diabetes EVO reduced MACE across hsCRP strata with greater ARR in patients with higher-baseline hsCRP levels EVO significantly reduced MACE and MALE with greater ARR in patients with PAD versus without EVO significantly reduced MACE in patients closer to their most recent MI, with multiple prior MI or with multivessel CAD with greater ARR in this subgroup of patients
EBBINGHAUS (2017)	1974	EVO SC (140mg Q2W or 420 Q1M) vs. PLA	Score on the spacial working memory strategy index of executive function	No differences between groups regarding cognitive function
SPIRE (2016)	27438 total 16817 in SPIRE-1 10621 in SPIRE-2	BOCO SC (150mg Q2W) vs. PLA	Composite of CV death, non-fatal MI, non-fatal stroke or hospitalization for UA requiring urgent revascularization	BOCO did not significantly reduced MACE in SPIRE-1 BOCO significantly reduced MACE in SPIRE-2 BOCO did not significantly reduced MACE in the combined groups
ODYSSEY OUTCOMES (2018)	18924	ALI SC (75 or 150 mg Q2W) vs PLA	Composite of CHD disease, nonfatal MI, fatal or non-fatal IS, or UA requiring hospitalization	ALI significantly reduced MACE ALI reduced overall mortality

Abbreviations:ALI, alirocumab; ARR, absolute risk reduction; BOCO, bococizumab; CAD, coronary artery disease; CHD, coronary heart disease death; CR, cardiac revascularization; CV, cardiovascular; EVO, evolocumab; IS, ischemic stroke; MACE, major adverse cardiovascular events; MALE, major adverse limb events; MI, myocardial infarction; PAD, peripheral artery disease; PAV, percent atheroma volume; PLA, placebo; Q1M, every one month; Q2W, every two weeks; SC, subcutaneous; SOC, standard of care; TAV, normalized total atheroma volume; UA, unstable angina; hsCRP, high-sensitivity C-reactive protein

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ANEXO

Normas de Publicação da Revista Portuguesa de Cardiologia

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- Com espaço duplo, margens de 2,5 cm e páginas numeradas.
- Não deverão exceder 5.000 palavras, contadas desde a primeira à última página, excluindo as tabelas.
- Consta de dois documentos: primeira página e manuscrito
- O manuscrito deve seguir sempre a mesma ordem: a) resumo estruturado em português e palavras-chave; b) resumo estruturado em inglês e palavras-chave; c) quadro de abreviaturas em português e em inglês; d) texto; e) bibliografia; f) legendas das figuras; g) tabelas (opcional) e h) figuras (opcional)-

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Título completo (menos de 150 caracteres) em português e em inglês.

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O resumo, com um máximo de 250 palavras, está dividido em quatro partes: *a)* Introdução e objectivos; *b)* Métodos; *c)* Resultados e *d)* Conclusões.

Deverá ser elucidativo e não inclui referências bibliográficas nem abreviaturas (excepto as referentes a unidades de medida).

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O resumo e as palavras-chave em inglês devem ser apresentados da mesma forma.

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Deverá conter as seguintes partes devidamente assinaladas: *a)* Introdução; *b)* Métodos; *c)* Resultados; *d)* Discussão e *e)* Conclusões. Poderá utilizar subdivisões adequadamente para organizar cada uma das secções.

As abreviaturas das unidades de medida são as recomendadas pela RPC (ver Anexo II).

Os agradecimentos situam-se no final do texto.

Bibliografia

As referências bibliográficas deverão ser citadas por ordem numérica no formato 'superscript', de acordo com a ordem de entrada no texto.

As referências bibliográficas não incluem comunicações pessoais, manuscritos ou qualquer dado não publicado. Todavia podem estar incluídos, entre parêntesis, ao longo do texto.

São citados abstracts com menos de dois anos de publicação, identificando-os com [abstract] colocado depois do título.

As revistas médicas são referenciadas com as abreviaturas utilizadas pelo Index Medicus: List of Journals Indexed, tal como se publicam no número de Janeiro de cada ano. Disponível em: http://www.ncbi.nlm.nih.gov/entrez/citmatch_help.html#JournalLists.

O estilo e a pontuação das referências deverão seguir o modelo Vancouver 3.

Revista médica: Lista de todos os autores. Se o número de autores for superior a três, incluem-se os três primeiros, seguidos da abreviatura latina et al. Exemplo:

17. Sousa PJ, Gonçalves PA, Marques H et al. Radiação na AngioTC cardíaca; preditores de maior dose utilizada e sua redução ao longo do tempo. Rev Port cardiol, 2010; 29:1655-65

Capítulo em livro: Autores, título do capítulo, editores, título do livro, cidade, editora e páginas. Exemplo:

23. Nabel EG, Nabel GJ. Gene therapy for cardiovascular disease. En: Haber E, editor. Molecular cardiovascular medicine. New York: Scientific American 1995. P79-96.

Livro: Cite as páginas específicas. Exemplo:

30. Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Mansel Dekker; 1993. P. 33.

Material electrónico: Artigo de revista em formato electrónico. *Exemplo:*

Abood S. Quality improvement initiative in nursing homes: the ANA acts it an advisory role. Am J Nurs. [serie na internet.] 2002 Jun citado 12 Ago 2002:102(6): [aprox. 3] p. Disponível em: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

. A Bibliografia será enviada como texto regular, nunca como nota de rodapé. Não se aceitam códigos específicos dos programas de gestão bibliográfica.

1. Figuras

As figuras correspondentes a gráficos e desenhos são enviadas no formato TIFF ou JPEG de preferência, com uma resolução nunca inferior a 300 dpi e utilizando o negro para linhas e texto. São alvo de numeração árabe de acordo com a ordem de entrada no texto.

- A grafia, símbolos, letras, etc, deverão ser enviados num tamanho que, ao ser reduzido, os mantenha claramente legíveis. Os detalhes especiais deverão ser assinalados com setas contrastantes com a figura.
- As legendas das figuras devem ser incluídas numa folha aparte. No final devem ser identificadas as abreviaturas empregues por ordem alfabética.
- As figuras não podem incluir dados que dêem a conhecer a proveniência do trabalho ou a identidade do paciente. As fotografias das pessoas devem ser feitas de maneira que estas não sejam identificadas ou incluir-se-á o consentimento por parte da pessoa fotografada.

Tabelas

São identificadas com numeração árabe de acordo com a ordem de entrada no texto.

Cada tabela será escrita a espaço duplo numa folha aparte.

- Incluem um título na parte superior e na parte inferior são referidas as abreviaturas por ordem alfabética.
- O seu conteúdo é auto-explicativo e os dados que incluem não figuram no texto nem nas figuras.

2. Cartas ao Editor

Devem ser enviadas sob esta rubrica e referem-se a artigos publicados na Revista. Serão somente consideradas as cartas recebidas no prazo de oito semanas após a publicação do artigo em questão.

- Com espaço duplo, com margens de 2,5 cm.
- O título (em português e em inglês), os autores (máximo quatro), proveniência, endereço e figuras devem ser especificados de acordo com as normas anteriormente referidas para os artigos originais.
- Não podem exceder as 800 palavras.
- Podem incluir um número máximo de duas figuras. As tabelas estão excluídas.

3. Casos Clínicos

Devem ser enviados sob esta rubrica.

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder 10 palavras

Os autores (máximo oito) proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.

O texto explicativo não pode exceder 3.000 palavras e contem informação de maior relevância. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.

Contêm um número máximo de 4 figuras e pode ser enviado material suplementar, como por exemplo vídeoclips.

4. Imagens em Cardiologia

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder oito palavras
- Os autores (máximo seis), proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.
- O texto explicativo não pode exceder as 250 palavras e contem informação de maior relevância, sem referências bibliográficas. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.
- Contêm um número máximo de quatro figuras.

5. Material adicional na WEB

A Revista Portuguesa de Cardiologia aceita o envio de material electrónico adicional para apoiar e melhorar a apresentação da sua investigação científica. Contudo, unicamente se considerará para publicação o material electrónico adicional directamente relacionado com o conteúdo do artigo e a sua aceitação final dependerá do critério do Editor. O material adicional aceite não será traduzido e publicar-se-á electronicamente no formato da sua recepção.

Para assegurar que o material tenha o formato apropriado recomendamos o seguinte:

	Formato	Extensão	Detalhes
Texto	Word	.doc ou docx	Tamanho máximo 300 Kb
Imagem	JPG	.jpg	Tamanho máximo 10MB
Audio	MP3	.mp3	Tamanho máximo 10MB
Vídeo	WMV	.wmv	Tamanho máximo 30MB

Os autores deverão submeter o material no formato electrónico através do EES como arquivo multimédia juntamente com o artigo e conceber um título conciso e descritivo para cada arquivo.

Do mesmo modo, este tipo de material deverá cumprir também todos os requisitos e responsabilidades éticas gerais descritas nessas normas.

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ANEXO I

DECLARAÇÃO

Declaro que autorizo a publicação do manuscrito:

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do qual sou autor ou c/autor.

Declaro ainda que presente manuscrito é original, não foi objecto de qualquer outro tipo de publicação e cedo a inteira propriedade à Revista Portuguesa de Cardiologia, ficando a sua reprodução, no todo ou em parte, dependente de prévia autorização dos editores.

Nome dos autores:

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Assinaturas:

ANEXO II

Símbolos, abreviaturas de medidas ou estatística

Designação	Português	Inglês
Ampere	A	A
Ano	ano	yr
Centímetro quadrado	cm_2	cm_2
Contagens por minuto	cpm	cpm
Contagens por segundo	cps	cps
Curie	Ci	Ci
Electrocardiograma	ECG	ECG
Equivalente	Eq	Eq
Grau Celsius	°C	°C
Grama	g	g
Hemoglobina	Hb	Hb
Hertz	Hz	Hz
Hora	h	h
Joule	J	J
Litro	L ou L	l ou L
Metro	m	m
Minuto	min	min
Molar	M	M
Mole	mol	mol
Normal (concentração)	N	N
Ohm	Ω	Ω
Osmol	osmol	osmol
Peso	peso	WT
Pressão parcial de CO_2	pCO_2	pCO_2
Pressão parcial de O_2	pO_2	pO_2
Quilograma	kg	kg
Segundo	s	sec
Semana	Sem	Wk
Sistema nervoso central	SNC	CNS
Unidade Internacional	UI	IU
Volt	V	V
Milivolt	mV	mV
Volume	Vol	Vol
Watts	W	W
Estatística:		
Coeficiente de correlação	r	r
Desvio padrão (standard)	DP	SD
Erro padrão (standard) da média	EPM	SEM
Graus de liberdade	gl	df
Média	χ	χ
Não significativa	NS	NS
Número de observações	n	n
Probabilidade	p	p
Teste «t» de Student	teste t	t test