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CRITICAL ANALYSIS OF THE STUDIES THAT HAVE CHANGED RECENT CLINICAL PRACTICE: DYSLIPIDEMIA.

ANÁLISE CRÍTICA DOS ESTUDOS QUE MUDARAM A PRÁTICA CLÍNICA RECENTE: DISLIPIDEMIAS.

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ABSTRACT

Ischemic events continue to occur in patients with poorly controlled risk factors, such as those with high concentrations of LDL-cholesterol or triglycerides and those with diabetes and multivascular artherosclerotic disease, in spite of treatment with statins. These patients are at risk not only for the first, but also for recurrent ischemic events, which can be fatal. The evaluation of recurrent events brings a perspective of the total burden of artherosclerotic events to which the patient is exposed and not only of the first one. Two studies using new lipid-lowering therapies addressed the reduction of cardiovascular events and also of total events, of a first event, and of subsequent events. Evolocumab, a proprotein convertase subutilisin kexin type 9 inhibitor, and icosapent ethyl, a highly purified formulation of omega-3 fatty acid, demonstrated reductions in key primary and secondary cardiovascular events, as well as in total events, first events and subsequent events in high and very high risk patients taking statins, but with a high risk of new cardiovascular events. Based on the benefits observed, these therapeutic strategies can be incorporated into clinical practice, provided they are evaluated within a risk benefit context, with an acceptable cost-effectiveness ratio.

Keywords: Risk; Dyslipidemia; Fatty Acids, Omega -3.

RESUMO

Os eventos isquêmicos continuam a ocorrer em pacientes com fatores de risco mal controlados, como os que têm concentrações elevadas de LDL-colesterol ou de triglicérides, nos que têm diabetes e doença aterosclerótica multivascular, a despeito do tratamento com estatinas. Além dos eventos iniciais, esses pacientes têm risco substancial de eventos recorrentes, possivelmente fatais. A avaliação dos eventos recorrentes traz a perspectiva da carga total de eventos ateroscleróticos a que esses pacientes estão expostos e não apenas dos primeiros eventos. Dois estudos com novas terapêuticas hipolipemiantes abordaram a redução de eventos cardiovasculares e também de eventos totais, de um primeiro evento e de eventos subsequentes. O evolocumabe, um inibidor da pró-proteína convertase subtilisina/quexina tipo 9 e o icosapenta etil, formulação altamente purificada de ácido graxo ômega 3 demonstraram reduções dos eventos cardiovasculares primários e secundários chave, bem como dos eventos totais, dos primeiros eventos e dos eventos subsequentes em pacientes de alto risco e risco muito alto que usam estatinas, mas com um risco elevado de novos eventos cardiovasculares. Pelos benefícios demonstrados, essas estratégias terapêuticas poderão ser incorporadas à prática clínica, desde que avaliadas num contexto de risco e benefício, e com um custo-efetividade aceitável.

Descritores: *Risco; Dislipidemia; Ácidos Graxos Ômega 3.*

INTRODUCTION

Despite major advances in the use of statins in the primary and secondary prevention of cardiovascular disease, ischemic events continue to occur in patients with poorly controlled risk factors, such as those with elevated LDL-cholesterol or triglyceride concentrations, in those with diabetes, multivascular atherosclerotic disease, among other situations.[1–4] In addition to the initial events, these patients have a substantial risk of recurrent, potentially fatal events. The evaluation of recurrent events brings the perspective of the total burden of

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atherosclerotic events to which these patients are exposed, and not only of the first events[5-6] From the perspective of the physician, the patient, and the healthcare system, it is not only first events that count, but also subsequent events.

We will address two recent studies that have shown reductions in cardiovascular events, early events, and subsequent events with different lipid-lowering interventions associated with classic statin treatment. Considerations regarding the findings of these studies may be part of new recommendations and may be incorporated into clinical practice.

FOURIER STUDY

Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study was a study to evaluate cardiovascular outcomes testing the efficacy and safety of evolocumab, a fully human monoclonal antibody, which acts by inhibiting the proprotein convertase subtilisin/kexin-type9 (PCSK9), which participates in LDL receptor catabolism (LDLR), binding to it and favoring its degradation. By inhibiting PCSK9, evolocumab prevents LDLR from binding to PCSK9 and allows LDLR to be recycled and capture cholesterol from circulation to the tissues, especially the liver. Thus, this drug promotes LDL-cholesterol (LDL-c) reductions in monotherapy, associated with statins with or without ezetimibe addition of the order of 50-60%.[8,9]

FOURIER[8] study was a randomized, double-blind, placebo-controlled clinical study involving 27,564 patients with cardiovascular atherosclerotic disease (coronary artery disease, stroke or symptomatic peripheral arterial disease) and LDL-c concentrations > 70 mg/dL who were on statins +/- ezetimibe. Patients were randomized to receive either evolocumab (140 mg every two weeks or 420 mg monthly) or placebo injections subcutaneously. The primary efficacy endpoint was cardiovascular death, myocardial infarction, stroke or TIA, hospitalization for unstable angina, or coronary revascularization. The key secondary endpoint was cardiovascular death, fatal or non-fatal myocardial infarction or stroke. The duration of the study (average) was 2.2 years.

After 48 weeks of treatment, the percentage reduction in LDL-c with evolocumab compared to placebo was 59%, falling from baseline LDL-c of 92 mg/dL to 30 mg/dL (P <0.001). Compared to placebo, evolocumab reduced the risk of the primary outcome (1,344 patients [9.8%] vs. 1,563 patients [11.3%]; RR, 0.85; 95% Confidence Interval (CI) 0.79 to 0.92; P <0.001) and the key secondary (816 [5.9%] vs. 1,013 [7.4%]; RR, 0.80; 95% CI: 0.73 to 0.88; P <0.001). Results were consistent between the subgroups analyzed, even those with baseline LDL-c in the lower quartile (median, 74 mg/dL). There were no differences in the adverse event profile between the groups, even regarding new cases of diabetes or neurocognitive events. Injection site reactions were more common with evolocumab (2.1% vs. 1.6%).

Regarding recurrent events, FOURIER also analyzed whether the inhibitor of PCSK9, evolocumab, could reduce the number of cardiovascular events in patients with stable athe- rosclerotic disease receiving statin therapy.

Thus, the purpose of this analysis[10] was to evaluate the effect of evolocumab on total cardiovascular events, given its importance to patients, physicians and the health system. A secondary analysis of FOURIER study evaluated the primary outcome as time to the first event of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization. The key secondary outcome was time to the first event of cardiovascular death, myocardial infarction or stroke. In pre-specified analysis, total cardiovascular events were assessed between the therapeutic arms.There were 2,907 first events and 4,906 total events during the study. Evolvocumab reduced total events by 18% (RR, 0.82; 95% CI: 0.75-0.90; P <.001) including both early events (hazard ratio, 0.85; 95% CI, 0.79-0.92; P <0.001) as subsequent events (RR, 0.74; 95% CI, 0.65-0.85). There were 2,192 first total events in the evolocumab group and 2,714 total events in the placebo group. For every 1,000 patients treated for three years, evolocumab prevented 22 first events and 52 total events. Reductions in total events occurred due to a reduction in the occurrence of total myocardial infarctions (RR, 0.74; 95% CI: 0.65-0.84; P <0.001), strokes (RR, 0.77; CI 95 %, 0.64-0.93; P = 0.007), and coronary revascularizations (RR, 0.78; 95% CI, 0.71-0.87; P <0.001).

The addition of PCSK9 inhibitor evolocumab to statin therapy improved clinical outcomes, with significant reductions in total cardiovascular events, by reducing the occurrence of total myocardial infarctions, strokes, and coronary revascularizations. More than twice as many events were prevented with evolocumab vs. placebo compared to the analysis that took into account only the first events. These findings point to the benefit of continued use of aggressive lipid-lowering therapies to prevent recurrence of cardiovascular events.The 2018[11] USA guideline situates the patient with recurrent events as very high risk and proposes that if after use of high-intensity statin and ezetimibe LDL-c is above 70 mg/dL, consideration should be given to the association of a PCSK9 inhibitor to further reduce LDL-c and cardiovascular events.

REDUCE-IT STUDY

REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) was another study that analyzed early and recurrent cardiovascular events using icosapent ethyl, a highly purified omega-3 fatty acid, which consists in EPA (eicosapentenoic acid) modification.In the original study,[12] the assumption for the study was that patients with high triglyceride concentrations are at increased risk for ischemic events. Icosapent ethyl, a highly purified formulation of eicosapentenoic acid, reduces triglycerides, but had not been evaluated for ischemic events. This is a multicenter, randomized, double-blind, placebo-controlled study that selected patients with established cardiovascular disease or diabetes and multiple cardiovascular risk factors, receiving statins and presenting fasting triglyceride concentrations between 135 and 499 mg/dL and LDL-c from 41 to 100 mg/dL. Eligible patients were randomized to receive 2 g of icosapent ethyl twice daily (total daily dose of 4 g) or placebo. The primary outcome was cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary endpoint was cardiovascular death, nonfatal myocardial infarction or nonfatal stroke. The study included 8,179 patients (70.7% in secondary prevention of cardiovascular events) who were followed for 4.9 years (median). The primary outcome occurred in 17.2% of patients receiving icosapent ethyl,

compared to 22% in the placebo group (hazard ratio, 0.75; 95% CI: 0.68 to 0.83; P <0.001); Key secondary event rates were 11.2% and 14.8% (hazard ratio, 0.74; 95% CI: 0.65 to 0.83; P <0.001). Additional ischemic events were also lower in patients receiving icosapent ethyl than in the placebo group, including cardiovascular death rates (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI: 0.66 to 0.98; P = 0.03). However, a higher percentage of patients in the icosapent ethyl group were hospitalized for atrial fibrillation or atrial flutter (3.1% vs. 2.1%, P = 0.004). Severe bleeding occurred in 2.7% in the icosapent ethyl group and 2.1% in the placebo group (P = 0.06). The study concluded that in patients with elevated triglycerides, despite statin use, the risk of ischemic events, including cardiovascular death, was significantly reduced among those receiving icosapent ethyl 2 g twice daily compared to those receiving placebo. In the same way as FOURIER analysis, REDUCE-IT evaluated the first events and subsequent events.[13] REDUCE-IT patients were also at increased risk for subsequent ischemic events. The aim of this study was a pre-specified analysis to determine if icosapent ethyl would also reduce the total ischemic events. In this pre-specified analysis, differences in total events were evaluated using negative binomial regression and other statistical methods. Of the 8,179 patients followed by 4.9 years (median), 1,606 (55.2%) had first primary events and 1,303 (44.8%) had subsequent primary events (including 762 second events and 541 third or more events). Icosapent ethyl reduced total primary events (61 vs. 89 per 1000 patient years for icosapent ethyl vs. placebo, respectively; RR 0.70, 95% CI 0.62-0.78, P <0.0001). Icosapent ethyl also reduced each component of the primary outcome as well as total key secondary outcomes (32 vs. 44 per 1,000 patient-years for icosapent ethyl vs. placebo, respectively, RR 0.72, 95% CI: 0.63 -0.82, P <0.0001). The study concluded that in patients treated with statins and with high triglyceride concentrations and cardiovascular disease or diabetes, icosapent ethyl substantially reduced the burden of first events, subsequent events, and total ischemic events. Guidelines recommendations for reducing cardiovascular events and subsequent events in patients with elevated triglycerides and cardiovascular disease or diabetes do not yet address the indication of icosapent ethyl for prevention of cardiovascular events. This new formulation is not available in our country either. However, results demonstrating a 25% reduction in primary outcome and even greater reductions in subsequent events may be incorporated into guidelines to reduce the burden of first events, subsequent events, and total ischemic events.

A summary of the main characteristics of these two studies that may change clinical practice is presented in Table 1.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

Table 1. Characteristics of FOURIER and REDUCE-IT studies that guide changes in clinical practice.

Characteristics	FOURIER	REDUCE-IT
Drug	Evolocumab	Icosapent ethyl
Class	Anti PCSK9 human monoclonal antibody	Highly Purified Omega 3 Fatty Acid
Dose used	140 mg every two weeks or 420 mg/month	2g 2 x a day
Administration	Subcutaneous injection	Oral use
Number of patients	27.564	8.179
Previous cardiovascular disease	CAD, stroke, PAD	CVD or Diabetes + Cardiovascular risk factors
Lipid criterion	LDL-c > 70 mg/dL	LDL-c between 41 and 100 mg/dL and TG between 135 and 499 mg/dL
Statin use	Moderate to high intensity +/- ezetimibe	Sufficient to maintain LDL-c between 41 and 100 mg/dL
Primary endpoint	CV Death, fatal or non-fatal AMI or stroke, UA (unstable angina) or myocardial revascularization (MR)	CV Death, fatal or non-fatal AMI or stroke, UA (unstable angina) or myocardial revascularization (MR)
Reduction of primary endpoint	15%	25%
NNT	66	21
Key secondary endpoint	CV Death, fatal or non-fatal AMI or stroke,	CV Death, fatal or non-fatal AMI or stroke,
Reduction of key secondary endpoint	20%	26%
NNT	66	28
Reduction of mortality	No	20%
Reduction of the total of primary events	18%	30%
Reduction of subsequent events	26%	30%

UA- Unstable angina; CV - Cardiovascular; CAD - Coronary Artery Disease; PAD - Peripheral Arterial Disease; CVD- Cardiovascular Disease; AMI- Acute Myocardial Infarction; NNT- Number Needed to Treat to reduce an Event; MR - Myocardial Revascularization.

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