Potenziale impatto dello studio REPRIEVE nella gestione clinica della prevenzione delle malattie cardiovascolari nelle persone che vivono con HIV.

Potential impact of the REPRIEVE study on clinical management of cardiovascular disease prevention in person living with HIV.

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Riassunto

Sebbene la sopravvivenza delle persone che vivono con HIV (PLWH) sia incrementata con l'introduzione della terapia antiretrovirale (ART), il rischio di eventi cardiovascolari rimane un problema di grande rilievo. Mentre sono disponibili dati solidi sull'impiego delle statine nei soggetti con rischio cardiovascolare elevato (CVR), è presente una limitata letteratura in merito ai soggetti con rischio basso-moderato. Lo studio REPRIEVE è andato a valutare i benefici dell'impiego di pitavastatina 4 mg in quest'ultima categoria di pazienti, evidenziando una riduzione significativa degli eventi cardiovascolari nel gruppo di soggetti sottoposti a trattamento rispetto al placebo. La popolazione dello studio appare eterogenea, ma include specificamente pazienti tra 40 e 75 anni. Sono stati arruolati anche pazienti classicamente esclusi dagli studi, quale soggetti con epatite C cronica, utilizzatori di alcol e droghe, persone con patologia psichiatrica. È stato valutato solamente l'impatto della pitavastatina, mentre le altre statine non sono state oggetto di studio. Concludendo, appare auspicabile estendere l'uso delle statine anche nelle PLWH a rischio cardiovascolare basso-moderato, ricordando sempre di ottimizzare anche tutte le altre condizioni che concorrono al rischio.

Abstract

Although survival of people living with HIV (PLWH) increased with the introduction of antiretroviral treatment (ART), cardiovascular risk remains a major problem. While there is scientific evidence of the benefit of the use of statins in subjects with high cardiovascular risk (CVR), there is limited literature about low-moderate risk cases. The REPRIEVE study evaluated the benefits of the use of pitavastatin 4 mg in this group of patients, with a significant reduction in cardiovascular events in the group undergoing treatment compared with placebo.

The study population appears heterogeneous but only includes patients between 40 and 75 years. Also, the study enrolled PLWH who are classically excluded from clinical trials, including those with chronic active hepatitis C infection, alcohol or drug users, and persons with psychiatric conditions.

Only the impact of pitavastatin was evaluated, while the other statins were not included in the study. In conclusion, it seems desirable to extend the use of statins also in person living with HIV (PLWH) at low-moderate CVR, always remembering to optimize all the other conditions that contribute to the risk.

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With the start of antiretroviral therapy (ART), the survival of people living with HIV (PLWH) has increased, and HIV has become a chronic disease with a longer life expectancy.

Currently, the greatest risk factor related to HIV remains cardiovascular risk, particularly related to accelerated atherosclerosis and coronary artery disease. Although total mortality in HIV patients has fallen in the last 10 years, cardiovascular mortality has increased significantly over the same period (1). The most important cardiovascular risk (CV) prevention strategies in PLWH have been included in the October 2023 EACS guidelines (2), the main reference in the European setting, and include: advice on diet and lifestyle, eventually ART modification if 10-year cardiovascular diseases CVD risk ≥ 10%, smoking cessation, optimization of blood pressure value, introduction of acetylsalicylic acid

75-150 mg if very high/high CVD risk, early detection and therapy for diabetes mellitus and treatment for hypercholesterolemia and dyslipidemia. The guidelines encourage the use of the Systematic COronary Risk Evaluation named SCORE2 (40-69y) or SCORE2-OP (>70y) (3) as the principal tool for CV risk estimation in primary prevention in "apparently healthy people", while version 11 of the guidelines (from October 2021) recommended the use of Framingham equation, but also the atherosclerotic cardiovascular disease (ASCVD) score (4) is frequently used to estimate the cardiovascular risk.

Although the underlying mechanisms that drive excess CV risk remain unclear, the interaction between traditional CV risk factors and residual inflammation/immune activation is considered to impact significantly on the increased CV risk in PLWH. So, while there are clear indications in subjects that these scores indicate high cardiovascular risk, in low-moderate risk patients the situation remains hazier, without a specific indication in the cardiovascular disease prevention guidelines.

Starting from this premise, Grinspoon et al (5) published the outcome of Phase 3 Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), evaluating the benefit of pitavastatin therapy in the population of HIV patients with low-moderate cardiovascular risk, according to the American Heart Association and the American College of Cardiology Pooled Cohort Equation risk calculator and based on the value of LDL cholesterol. They enrolled a total of 7769 participants in antiretroviral therapy, who were assigned in a 1:1 ratio to receive oral pitavastatin calcium (at a dose of 4 mg per day) or an identical placebo. All patients were aged between 40 and 75 years, with CD4 count > 100 cells per cubic millimeter. The primary outcome was the occurrence of a major adverse cardiovascular event; secondary outcomes were a composite of a major adverse cardiovascular event or death from any cause; individual components of the primary outcome; death from any cause; LDL and non–high-density lipoprotein (non-HDL) cholesterol; targeted safety events, including incident diabetes mellitus; liver injury; and myalgia, muscle weakness, or myopathy of grade 3 (inability to perform social activities) or grade 4 (disabling) or treatment-limiting. The trial evidenced in the pitavastatin group versus placebo a significant reduction in the risk of a major adverse cardiovascular event and a lower level of LDL cholesterol. The pitavastatin group showed however, a higher rate of incident diabetes (5.3% of PWH on pitavastatin vs 4.0% on placebo) and muscle-related symptoms (2.3% vs 1.4% respectively). The trial was stopped early for efficacy and concluded that no unexpected safety concerns had been reported. One of the strengths of the study is the wide heterogeneity of the patients enrolled, with 65.2% non-White and 31.1% female, but unfortunately the age range was quite restrictive, excluding especially the very old subjects. Extending the study to PLWH older than 75 years, who present a higher risk of acute cardiovascular events than general population, would provide an extra element in the decision to use statins in primary prevention in elderly patients, in which even for the general population there are only partial data (6).

In addition, the study concerns only one of the available statins, pitavastatin. As also described in the study, the choice of such a drug was carried out mainly because it does not present pharmacological interactions with ART. In the literature, there is now numerous consolidated data on the effectiveness of pitavastatin, which with a dose of 4 mg reduces LDL-C by about 40-49%, equivalent to atorvastatin 20 mg in this effect (7). In addition, as also mentioned in the study in analysis, the degree of reduction is consistent with that observed in a study of rosuvastatin involving older persons (median age, 66 years) with no HIV infection but who had increased C-reactive protein levels without elevated LDL cholesterol levels (8). Likely, other statins may also have similar effects to that described in the REPRIEVE study on patients with low-moderate cardiovascular risk because the mechanism of action is the same, that is reduction of immune activation and inflammation in persons with HIV infection and reduction of LDL-cholesterol levels. However, this assumption must be confirmed in subsequent studies, also because pitavastatin in some European states, including Italy, is currently not prescriptible with payment exemption, unlike other commonly used statins and therefore its use would represent an important expense for the patients.

Finally, as also highlighted in recent editorial by Matthew S. Freiberg (9), one of the strong points of the article is the enrollment of participants with

HIV infection who are classically excluded from clinical trials, including those with chronic active hepatitis C infection, those who use alcohol or drugs, and those with psychiatric conditions, although the low proportion of patients presenting with these conditions makes it difficult to draw conclusions about the benefits of the use of pitavastatin in these categories of patients.

Apart from lipid-lowering CVD risk reduction, there is also considerable interest in the modulation of inflammation to reduce the risk for CVD among PLWH. A substudy of the REPRIEVE trial investigated the presence of immune activation and inflammation, involving coronary computed tomography angiography (CTA) and immune phenotyping in a sample of 755 participants. The study showed that PLWH with low-moderate risk of cardiovascular disease have a significant prevalence of coronary plaque associated with inflammation and immune activation markers and, importantly, coronary plaques were found in 30% of participants with a very low ASCVD risk (<2.5%) (10).

The evidence of benefit from statin treatment in PLWH extends the recommendation of statin in low-moderate CV risk, but this is strongly discordant with the actual routine clinical management of lipid-lowering therapy as many more than half of the patients with a clear indication were untreated (11) (12). It is hard to understand why, despite HIV patients being considered at high risk of CV events, they generally still tend to be largely under-treated for CV prevention.

The findings from REPRIEVE suggest extending the statin use in PLWH, routinely applying a model for CVD risk estimate; in Italy the SCORE2 is probably appropriate, considering that HIV is a risk enhancer, particularly in PLWH with delayed ART initiation, prolonged HIV viremia, low CD4 cells count, hepatitis co-infection, or metabolic syndrome.

In conclusion, the REPRIEVE trial lays the foundations for subsequent studies aimed at definitively clearing the use of statins even in patients with low-moderate cardiovascular risk. It is important to reiterate, as also highlighted by international guidelines, that cardiovascular risk is defined as multifactorial.

Providing dietary advice (also about avoiding or reducing alcohol consumption, avoiding drug use and smoking cessation) and optimizing lifestyle, ART, blood pressure value and optimizing the therapeutic management of diabetes are all major goals in patient management as well as the introduction of the statin and must be carried out simultaneously for a better benefit on cardiovascular risk. ■

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