High plasma levels of low-density lipoprotein cholesterol (LDL-C) have long been known to associate with a measurable increase of cardiovascular (CV) events in the general population. LDL-C lowering drugs, from the venerable statins to ezetimibe and PCSK9 inhibitors, are therefore pillars of the clinical management of patients with high LDL-C, but the magnitude of reduction of CV events in the at-risk patients remains a matter of controversy. This may sound counterintuitive for "old" drugs like statins, but the effect size of LDL-C–lowering interventions is in fact confounded by factors that range from patient characteristics and treatment duration to definitions of CV events (Gaba et al., 2023).

The March issue of the Journal of Pharmacology and Experimental Therapeutics presents a paper that fits nicely into this complex scenario (Trimarco et al., 2024). The article begins with a thoughtful analysis of reasons why the incidence of CV events varied across randomized clinical trials (RCTs) and Mendelian-type studies. According to RCTs, a satisfactory statin control of LDL-C would in fact reduce CV risk by approximately 22%–24% per mmol/dL within a year of treatment, without convincing evidence for further benefit over the subsequent years (Collins et al., 2016); in contrast, Mendelian-type studies identify a more robust 55% reduction that extends over time if LDL-C is adequately controlled (Ference et al., 2012). Such a difference does not come as a surprise, with RCTs and Mendelian studies being different in many respects; in particular, Mendelian studies randomize patients according to genotype and look at patient exposure to risk factors or treatments over a timespan that is only exceptionally contemplated by RCTs (Ference et al., 2019; Gill et al., 2020). In the settings of LDL-C and CV events, many other variables may come into play and introduce additional uncertainty around risk assessment before treatment or risk mitigation during and after treatment. Such variables include but are not limited to LDL-C levels before treatment, comorbidities, prior CV events, and the magnitude of LDL-C reduction that one intends to achieve with statins or other LDL-C–lowering agents (Hong et al., 2023). Moreover, canonical randomizations to active treatment or placebo cannot distinguish statin responders from nonresponders, producing an aggregate “statin-treated arm” that cannot adequately quantify the impact of treatment response on CV event rates. Of overarching importance is the biology of atherosclerosis and the progression of plaque from stable to unstable, which makes the duration of exposure to LDL-C or LDL-C–lowering agents two opposing determinants of clinical outcomes (Domanski et al., 2020).

How did Trimarco and colleagues (2024) unravel the tangle of all such variables and potential confounders? They conducted a retrospective population-based study by extracting data from the open electronic registry of Campania Salute Network, an initiative that archives demographic and clinical characteristics of patients referring to university- and community-based hospitals of the Campania region in Italy. One would immediately play defense here. We all know the pros and cons of retrospective studies, and we all know how incomplete and too often inaccurate registries can be for scientific purposes (Pop et al., 2019). Although the limitations of a retrospective study remain insurmountable, concerns around data quality can be dismissed in the case of Trimarco’s work, as the completeness and reliability of the Campania Network registry come as a pleasant exception to the rule. The authors then moved in multiple directions: 1) they selected statin-naive hypertensives without prior CV events, diabetes, or life-threatening and disabling comorbidities, such that statins could be evaluated in primary prevention and hence in isolation from too many competing risk factors and confounders; 2) they established a pragmatic cut off of LDL-C 100 mg/dL for identifying patients who required statins and then responded to or failed treatment; 3) they scrutinized...
data obtained over approximately 7 years of follow-up, which was longer than the longest follow-up reported by RCTs of LDL-C-lowering drugs (Wang et al., 2022); and 4) they analyzed LDL-C levels collected at least every 6 months, such that responders and nonresponders could be reliably clustered. Finally, the authors collected data from hypertensive patients who presented at baseline with an LDL-C ≤100 mg/dL and maintained that level throughout follow-up, such that CV events could be interpreted in the broader perspective of “controlled LDL-C.” In practice, the study included patients with LDL-C ≤100 mg/dL and no statin therapy (group 1, n = 140); patients who presented at baseline with LDL-C >100 mg/dL but returned to ≤100 mg/dL upon statin therapy (group 2, n = 149); and patients who failed statins and remained at LDL-C >100 mg/dL (group 3, n = 436). The three patient groups were well balanced for demographic and clinical characteristics, including type and number of antihypertensive medications per patient.

It goes without saying that the limitations of a retrospective study are here to stay, but an unbiased reader cannot deny that Trimarco’s work could both incorporate some advantages of Mendelian studies and mitigate some disadvantages of RCTs. Did the results of this study reward all such efforts? The answer is more yes than no. The incidence of CV events in group 1 or group 2 was in fact significantly lower than that observed in group 3 (5.7% or 6% vs. 11.9%, corresponding to one event for every 122.5 or 115.9 patients per year, vs. one event for every 58.6 patients per year, respectively). Moreover, Cox regression of group 3 versus groups 1 and 2 in aggregate showed that an LDL-C level >100 nmol/dL was associated with an hazard ratio of 1.9 for CV events. These results clearly showed that maintaining LDL-C below 100 nmol/dL over an extended period of 7 years introduced a sizeable reduction in CV events, regardless of whether LDL-C was “controlled” by statins or by unique characteristics of normocholesterolemic patients, likely attributable to genotype, healthy lifestyle, or a combination of more factors. After all, the effect size of controlling LDL-C could be approximated to a 40% reduction in CV events, which was significantly higher than that approximated by most RCTs and nearly approached that indicated by Mendelian studies. Trimarco et al. (2024) could therefore reshape the relationship of LDL-C with CV risk and the beneficial effects of a “personalized” control of LDL-C level (Fig. 1).

There are, of course, some study weaknesses that merit consideration. By having said that the registry was reliable or at least more reliable than registries usually are, one may wonder why some data were not exploited at their best. For example, the authors report that LDL-C levels were significantly lower in groups 1 and 2 compared with group 3, but this information is more of a single shot than a dynamic representation of how LDL-C levels fluctuated at different time points of follow-up. Given that serial measurements were available, why weren’t LDL-C mean values at, for example, every 12 months reported to show how well statin responders could be distinguished from nonresponders and how quickly the responders were protected from continued exposure to high LDL-C? The lack of LDL-C temporal trends is

![Fig. 1. Conceptualization of study designs for patients with high LDL-C and risk of CV events. The upper panels show Mendelian-type studies, characterized by patients’ long-lasting exposure to a risk factor (e.g., deterioration of atherosclerotic plaques) and effective risk mitigation by statins at both early and late time points. The central panels show the canonical RCT design, characterized by patients’ shorter exposure to the risk factor and less evident risk mitigation by statins. The bottom panel shows the network registry design of Trimarco et al. (2024), in which follow-up was long and CV events were reduced if LDL-C was ≤100 nmol/dL, whether obtained with statins or reflecting patients’ baseline characteristics.](image-url)
disappointing, especially if one must believe that groups 1 and 2 shared a similar incidence of CV events and that the two groups were merged to perform Cox regressions on more solid statistical grounds. There are also some spurious data on LDL-C levels, with group 1 and both groups 1 and 2 possibly including outliers with LDL-C > 100 mg/dL at baseline or during follow-up, respectively. On a different note, a broad category of high-risk patients were excluded from the study, but data were obtained from patients whom the authors nonetheless considered as “high risk” because of hypertension. Wasn’t this a good reason for showing blood pressure trends in the three groups during follow-up? Similar concerns hold true for the prevalence of ezetimibe as a companion drug for statins in groups 2 and 3. Were the two groups balanced for ezetimibe usage, or was treatment failure in group 3 confounded by a less intense coprescription of ezetimibe?

Two more cautionary comments might be appropriate at this point. All data were from patients prescribed one of six different statins at the physician’s discretion. We will not throw fuel on the fire of unsettled issues around one statin being more active than others (Climent et al., 2021), yet this is one of those details that would make an RCT of a given statin more appealing than the present population-based analysis. On the other hand, definition of CV events was quite broad and included both nonfatal events and CV or non-CV death. The authors recognize that their study was not powered to demonstrate which event or events prevailed in one group of patients or the others, but one might also wonder if event definition was broad enough to inflate event rates and generate differences that otherwise would be difficult to see across groups.

In sum, nothing is perfect and even the work by Trimarco is not; however, an attempt to twist the field is laudable and tangible at many points. We look forward to developments along this line of insight and hope to see studies that include more patients and more controlled variables.

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