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Total Burden of Events

A New Standard Stressing the Positive Impact of Inflammation Modulation*

François Roubille, MD, PhD,^a Fabien Huet, MD, MSc,^a Claire Duflos, MD, PhD^{b,c}

In this issue of the *Journal*, Everett et al. (1) reported a subanalysis of CANTOS (Canakinumab Thrombosis Outcomes Study) investigating the impact of canakinumab on the total number of cardiovascular events, including recurrent events collected after a first event, in 10,061 patients with stable coronary artery disease (prior myocardial infarction [MI]).

Atherosclerosis is often considered primarily as an accumulation of inflammatory cells (primarily macrophages) beneath the endothelium, and progress with the further accumulation of cells, connective-tissue elements, lipids, and debris through immunological and inflammatory activation (2). Inflammation could be not only involved in “chronic” phenomena, but could also participate in acute events, especially through destabilization of atherosclerotic plaques. Despite optimal medical management (including guidelines-guided drugs and control of risk factors), cardiovascular patients continue to present recurrent clinical outcomes, the so-called “residual” risk, that could be—at least in part—due to vascular inflammation.

Over the last 2 decades, both basic studies and clinical trials have provided evidence for the potential benefits of fighting inflammation in atherosclerosis, having very specific targets including canakinumab (an anti-interleukin-1 β antibody) in the CANTOS trial or on contrary nonspecific targets, including the well-known drugs methotrexate and colchicine. Whereas methotrexate failed to provide beneficial effect in CIRT (Cardiovascular Inflammation Reduction Trial) (3), colchicine has been shown to exert beneficial effects in COLCOT (Colchicine Cardiovascular Outcomes Trial) (4).

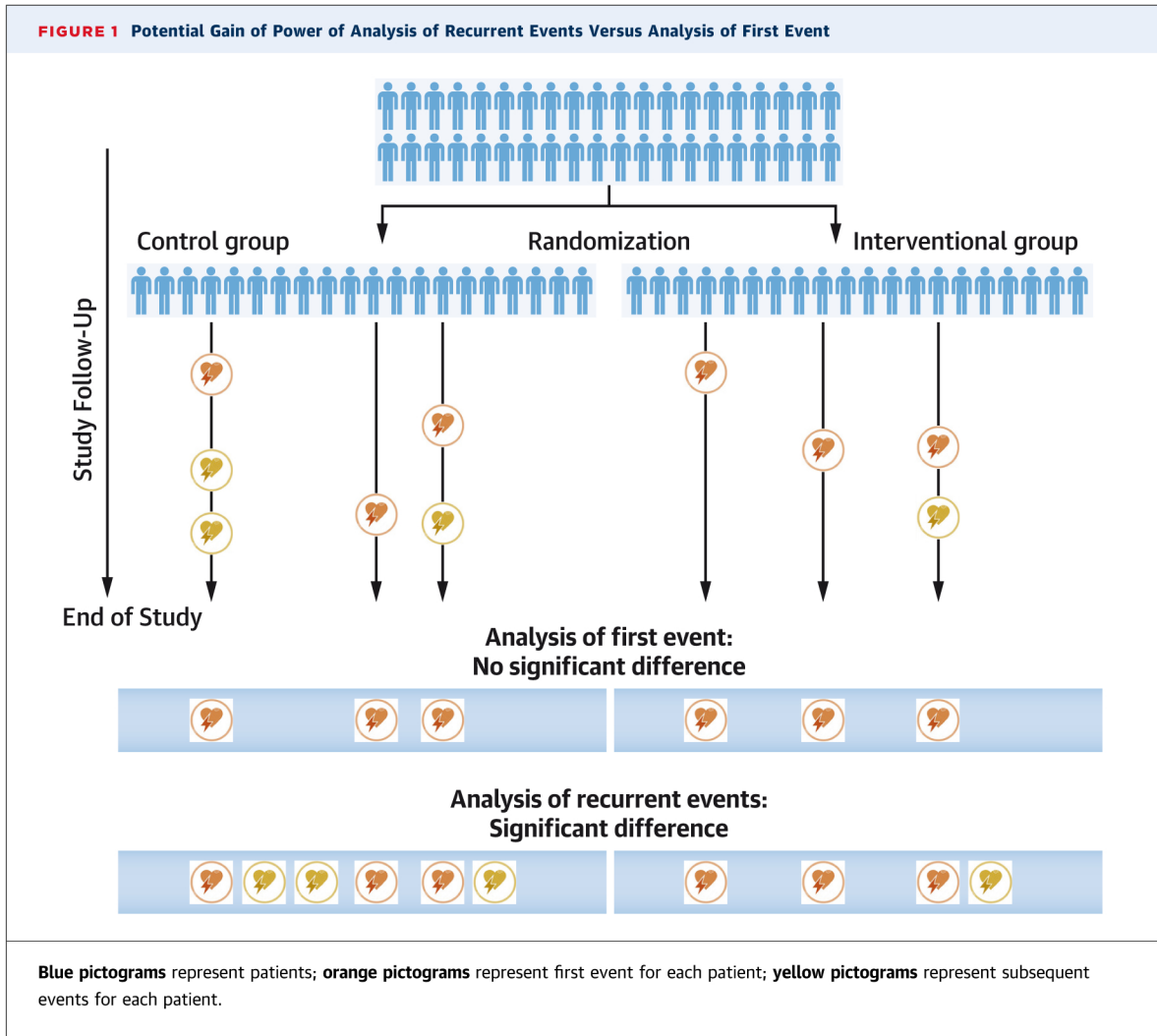
Despite a slightly higher incidence of fatal infections in the CANTOS study, canakinumab led to a 15% lower risk of a first major adverse cardiovascular event: a composite of nonfatal MI, nonfatal stroke, coronary revascularization, and cardiovascular death (5). Here, this new analysis provides important information: all of the doses used are effective at reducing events. This is not consistent with the initial analysis, and many limitations acknowledged by the authors have to be taken into consideration. Nevertheless, this is crucial information, especially as the LoDoCo2 (Colchicine in Patients with Chronic Coronary Disease) trial and new subanalyses of the COLCOT (NCT02551094) trial are soon to be published. Indeed, this new post hoc analysis corroborates the available data and reinforces the positive impact of immunomodulation/anti-inflammatory intervention to reduce cardiovascular events in patients with coronary artery disease. In case of positive results, this type of approach should be considered in the management of patients in daily practice.

THE TOTAL BURDEN OF EVENTS: A NEW STANDARD

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Everett et al. (1) provide an analysis of recurrent events of this composite outcome. The first

FIGURE 1 Potential Gain of Power of Analysis of Recurrent Events Versus Analysis of First Event



advantage of this method is its clinical interpretation. The patients included in the trial completed follow-up, and in case of a clinical event, they had been asked to remain on their assigned treatment for the duration of the trial, which is a crucial point. The initial but also the subsequent events were collected and adjudicated. A patient with recurrent events could be hospitalized for a nonfatal MI, a second MI, and then a stroke, and could finally die. This is a complex clinical situation with heavy consequences. The treatment under study might not only reduce the time until a primary clinical event, such as MI, but also reduce its consequences over time, such as, for example, progression to heart failure and therefore the risk of in hospital readmission, making its interest even stronger. In the classical analysis—either survival or logistic model—the efficacy is estimated by measuring the first occurrence of the event only, although the recurrent events are also serious for the patient, the society, and the health system. In a world of health care cost-limitation policy, reducing the

number of clinical events after initial hospitalization is a highly relevant challenge. However, one should note that a usual drawback of composite outcomes is that in clinical practice, the weight of clinical events considered separately is not similar (6). Certainly, from the physician’s point-of-view, the frequent event “coronary revascularization” is not a serious event when compared to stroke or—obviously—death. Now, this drawback may be magnified when analyzing recurrent outcomes. In the CANTOS trial, of the 2003 first serious cardiovascular events, 36% were MI, 30% coronary revascularization, 23% cardiovascular death, and 11% stroke. Above all, of the 1,414 subsequent serious cardiovascular events, two-thirds were revascularization (whereas only 17% were MI, 15% cardiovascular death, and 4% stroke): the clinical translation of these findings is not so easy, as this event is more and more represented and a bit over-estimated. Can we consider that all revascularizations represent the same burden on the patient or on the health system? By continuing this reflection on the

burden, should we not even consider other components, like serious adverse events in the composite outcome, allowing for a straightforward estimation of the risk-benefit balance? Another potential drawback of this composite outcome is that death is a competing component for other components of the composite outcome: when a patient dies, she or he cannot present recurrent events after that, and is therefore considered a “not so bad outcome” despite presenting the worse outcome.

The second advantage of this method is that taking into consideration all events could be a way to reach a higher statistical power under certain conditions met during follow-up of patients and during statistical analysis (Figure 1). First, there should not be too many cases of discontinuation of the drug (7). Importantly, in the present study, the adherence remained high after a first cardiovascular event, as 73% of all patients who survived their first event remained adherent to study medication. Second, in the case where it is challenging to determine which events are truly discrete events after the first event, a blind assessment of outcomes would ensure conservative analyses, and a well-chosen sensibility analysis would explore the range of plausible estimates. Luckily, even if not met, these conditions would bias the results toward the null hypothesis, preventing an overestimation of the benefit-risk balance. Third, the correct models should be chosen for the statistical analysis. Analysis methods for count data are well known; the most classical is the Poisson regression (8), but the negative binomial regression (used by the authors) is very frequently preferred for its larger ability to cope with overdispersion (9). These 2 models can be easily improved to fit data with overrepresentation of patients with zero events, which is frequent in biomedical data. Moreover, in case of high

variability of follow-up durations, the inclusion of an offset allows for modeling rates rather than counts. Similarly, sample size estimations can be proposed following the same principles (10). Such analyses are therefore more frequently used, with roughly 100 clinical trials indexed each year in Medline since 2015 (REDUCE [IASD System II to REDUCE Elevated Left Atrial Pressure in Patients With Heart Failure], CARMELINA [Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus], IMPACT-HF [Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure], BACE [Azithromycin during Acute Chronic Obstructive Pulmonary Disease Exacerbations Requiring Hospitalization]). A Multi-center, Randomized, Double-Blind, Placebo-controlled Trial], and so on). Thus, methodological tools are available to adequately design, conduct, and analyze recurrent events, as the authors have done here.

In conclusion, the approach by the authors is appealing and should probably be considered as the preferred primary analysis in clinical research (and then included in the analysis plan from the start), although some limitations should not be discarded, especially the difficult clinical meaning. Regarding the impact of immunomodulation in patients with coronary artery disease, confirmation is needed from similar analyses, especially the COLCOT trial, which remains the other large trial supporting this hypothesis, and other results are awaited for colchicine including the LoDoCo2 trial (11).

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