The night of randomized clinical trials where all patients are black: a need to estimate variability in treatment effects

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The order that our mind imagines is like a net, or like a ladder, built to attain something. But afterward, you must throw the ladder away, because you discover that, even if it was useful, it was meaningless.
(Umberto Eco, The Name of the Rose, Picador Edition, Secker and Warburg, London, 1984, page 492)

In the Sixties, the few anti-thrombotic drugs available were administered following several criteria including tradition of the "School", preference of the doctor in charge, pressure of pharmaceutical companies. Epidemiology and statistics had not yet been fully developed and were not usually applied to therapeutic issues. Then, in the Seventies, clinical trials started to be organized following progressively stringent criteria (the studies had to be controlled, randomized, single or double blind, or crossover and so on) and should have involved hundreds or thousands of patients. Statistical analyses were performed by both "intention to treat" and "drug efficacy" criteria. Despite all these precautions, however, the results of different trials were not always consistent but often contrasting. Thus, meta-analysis was introduced to overcome lack of statistical power of individual studies and/or to identify a common denominator from different clinical contexts.[1,2] In subsequent years, "evidence-based" medicine was introduced to transfer the results of randomized clinical trials (RCT) and meta-analyses to everyday practice.[3,4]

Therapeutic indications included in increasingly numerous guidelines or consensus conferences derived from RCT performed on groups of patients who were seldom representative of the variability of the target disease and, even less, of the general population. Moreover, the beneficial effect of anti-thrombotic drugs ranged, at the best, between 20% and 40%: though statistically significant, such an effect could also be (but was not) read as limited to relatively small groups of "responders". As an example, out of 100 control patients with acute myocardial infarction, 10 would have suffered another infarction or died within one year; if a comparable group of 100 patients was given an anti-thrombotic drug, 3 would have benefited from the treatment ("responders"), while 7 would have not ("non-responders") and 90 would have been treated unnecessarily.[5] This result was referred to as a treatment-induced 30% reduction of the clinically relevant end-points under study.

The problem was (and still is) that we were (and are still) unable to identify *a priori* the individuals who would get a benefit from those who would not or would even be harmed by treatment. Moreover, the results of RCT were almost exclusively limited to counting the difference between control and treated groups in numbers of non-fatal events or deaths. There was no mention or studies of unaffected/surviving people in either group, nor whether the observed events were similar or different in terms of likely pathogenetic/socio-cultural/life-style variables. Pharmacogenetic studies were still far to be introduced.[6,7]

RCT and related meta-analyses still today provide estimates of average treatment effects but are less suited to understand variability or heterogeneity of patients and/or treatment effects across individuals. Indeed, applying an average result of a RCT observed in a given study popu-

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Key words: Randomized clinical trials, Individual variability, Evidence-based medicine, Personalized medicine, Antiplatelet drugs.

Contributions: The authors contributed equally.

Conflict of interest: The authors declare no potential conflict of interest.

Funding: None.

Received for publication: 9 March 2022.
Accepted for publication: 9 March 2022.

Licensee PAGEPress, Italy
Bleeding, Thrombosis and Vascular Biology 2022; 1:24
doi:10.4081/btvb.2022.24

lation to a specific patient would require an individual homogeneity that is not frequent in clinical practice.[8]

In recent years, newer machine learning methods have been proposed to address heterogeneity of treatments and to predict individual variability.[9,10] However, spurious relationships within RCT data may occur that are not generalizable to other patients. Thus, future studies on machine learning approaches are warranted.

Availability of real-life data derived from electronic health records, though based on observational studies not allowing any causal inference, might produce complementary information to overcome some RCT limitations.

In conclusion, the results generated in the past decades by RCT allowed a tremendous progress in our strategies to prevent and treat ischemic cardiovascular disease, based on strict scientific criteria. The approach that was followed, however, appeared to be more similar to a universal system with its sophisticated statistical rules, than to a system sensitive to every day clinical practice. The real needs of individual patients were largely disregarded (a kind of philosophical contrast similar to that experienced in the 19th century between Hegel's idealism and Kierkegaard's existentialism).

We should really and consistently estimate how and at what extent the effects of interventions vary across individuals to hopefully offer novel possibilities for shedding some light on the "epidemiological night" of RCT and help develop a new *individual evidence-based* medicine. Obviously, this will require new ways of thinking and organizing clinical medicine.

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