Perioperative mortality: an emergent global public health problem

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Noncardiac anesthesiologists are now aware that perioperative mortality is a relevant problem. A recent large European Cohort Study (EUSOS) identified a crude mean inhospital mortality rate of 4.0% (range 1.2–21.5%) in patients undergoing noncardiac surgery in 498 hospitals across 28 European nations [1]. According to recent data, over 230 million major surgical procedures are undertaken annually in 56 countries, and we can therefore estimate that more than 10 million patients die every year worldwide in the perioperative period and more than 20 million suffer serious perioperative complications. High-risk patients constitute a large proportion of patients undergoing surgical procedures, and the size of this cohort is expected to increase in the coming years, reflecting the aging population and the improvement in therapeutic options for patients with multiple and advanced medical conditions.

Cardiac anesthesiologists, especially those leading postoperative intensive care units, have always been aware that a relevant proportion of patients die within few days or weeks after surgery and have attempted to reduce perioperative mortality over the years. This process was facilitated by the significant medical and technical advances seen in cardiology, cardiac surgery, and other related specialties. Noncardiac perioperative medicine would benefit from the same improvements (implement better care of patients on the basis of the results of large clinical studies). Therefore, a similar transition is also immediately necessary in anesthesiological culture, and cardiac anesthesiologists have the capability to lead this process.

So far, no relevant actions have been taken by the medical community to counteract the healthcare problem of perioperative mortality. Despite a clear scientific trend toward the use of large randomized trials to understand and ameliorate perioperative care, a small number of randomized controlled trials have been published until now [2] and a few others are ongoing (POISE-2 trial: NCT01082874, ATACAS trial ACTRN012605000557639, FENO HSR trial: NCT00621790, HSR-LEVO: NCT00994825). In contrast, medical treatment is frequently based on the current understanding of pathophysiology, as well as preclinical studies. Moreover, there is an established tendency among some authors to distrust randomized evidence and to consider other model of studies as more scientifically relevant, even though large observational non randomized studies can be only the starting point for discovery research, application research, and evaluation research; advantages of randomized trials are out of question. A cultural change should be incorporated, as randomized trials should be routinely performed in perioperative settings.

Nevertheless, these trials should meet precise methodological requirements to be considered solid, and should be transparently reported. Consolidated Standards of Reporting Trials (CONSORT) statement can be of great help for authors [3]. Large trials with a correct sample size are necessary, as in the majority of cases we study interventions that typically affect only one pathway in a multifactorial process, thus obtaining a moderate treatment effect (i.e. relative risk reductions in the range of 25%). As a matter of fact, many different events, such as infections, respiratory insufficiency, cardiac ischemic events, arrhythmias, cerebral ischemic events, thromboembolism, and renal impairment among others, can threaten surgery outcome [1]. Genesis of these events is favored by a

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plethora of pathological triggers occurring during the perioperative period [4]. Small trials, even when statistically significant, potentially mislead clinicians, presenting statistical fragility (substantial changes in *P*–values with small changes in the number of patients experiencing an event in the treatment group) [5].

Moreover, a correct randomization is mandatory, with the fundamental goal being to 'control' bias (minimizing or avoiding it). The inclusion of multiple centers increases geographic and demographic diversity and improves applicability of the results. Moreover, multicenter trials have to be judged by a large number of physicians, and this process could guarantee that only studies viewed as clinically important are undertaken [5].

It is time to improve. In the field of perioperative complications, large and solid randomized trials should be strongly advocated and promoted by the medical community. Large randomized trials are the right pathway to overcome the enormous lack of knowledge in this field. Indeed, some innovation could facilitate this process. First, national reimbursement could be assigned only to those patients randomized in at least one randomized trial. This attitude could help penalize physicians who and hospitals that do not get involved in medical research. Editorial policies should allow every participant to be listed among authors. Second, a dedicated course on methodology, taught by clinical scientists, should be introduced in universities, and obtaining postdoctoral master's degrees and specialization should be encouraged. Another important point is that bureaucracy should be simplified. Ideas from clinical scientists should be approved by an ethical committee comprising peers and patients after only a few days, so that randomization can start whenever possible. In several countries, even a trial with a simple design, such as that comparing two treatments used in everyday practice, is preceded by hundreds of pages of documentation, a several month wait for ethical committee approval, payment to a contract research organization for monitoring the study and for organizing pharmacovigilance of the study, and, finally, payment of an insurance to all patients enrolled in the study, even if all the patients included in the study benefit from the study. In fact, unsponsored phase IV randomized controlled trials are now considered in the same way as phase I–III studies, although their impact on daily practice and risk for patients are completely different. Given that it takes 1–2 years to get a grant, scientists are generally forced to delay their best ideas, agonizing under the weight of gargantuan bureaucracy and its related costs [6]. For example, despite total intravenous anesthesia with volatile agents being deemed mandatory since the publication, in 2007, of a meta-analysis suggesting a reduced mortality in patients receiving volatile anesthesia, ethical committee approval for a large trial on this has been delayed for years because of the lack of funding. Although funding was eventually provided by the Italian Ministry of Health (2011), the study is further delayed because the costs of bureaucracy multiplied 20–fold in the meanwhile.

How much would it cost to create a network of colleagues from all over the world who in 1 week would decide whether to use volatile agents or total intravenous anesthesia (TIVA) for cardiac anesthesia according to the randomization provided on the web? A virtual network represents the easiest way to get in touch with hundreds of colleagues all over the world and could simplify trial conduction. For example, centralized design and randomization, electronic case report forms, virtual conferences, and mailing contacts are transparent methods of leading a study while permitting consistent money sparing. This would allow performance of very large trials with limited funding.

Nevertheless, it should also be remembered that research costs are small when compared with the healthcare savings derived from effective treatment of perioperative complications.

To do this, we should not rely on national or international regulatory agencies that are not even aware of the thousands of clinical scientists working daily for the improvement of public health and patient care. We should probably interact directly with patient associations and politicians and explain to them that nowadays the bureaucracy and the ethical committees are slowing research-driven studies and indirectly leaving millions of patients without care.

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Conflicts of interest

There are no conflicts of interest.

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