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Conceptual Paper

The Research of Outcome: Investigating Results of New Technologies in Medicine

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In 1972, during my straight surgical internship at Michael Reese Hospital in Chicago, I was introduced to Cardiac Surgery from Stanley K. Brockman, a former trainee at the Mayo Clinic and teaching staff at Vanderbilt. He frequently repeated: "the only difficult thing of Cardiac Surgery is to get into the position of doing it". In the following years at the Cardiac Surgery of the University of Padova (Italy) I realized that the most difficult thing for a surgeon was the wisdom of performing the "correct surgery at the correct time" according to patient's frailty (Figure 1) and to the available alternative therapies.

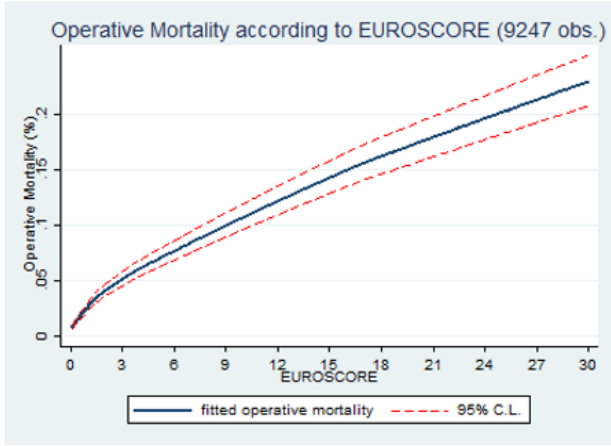

Figure 1

Naively I thought surgery was essentially a manual job suited to my skilled hands, however in 1977 I read a paper of Eugene Blackstone [1] that changed my expectations from those of a simple craftmanship to a scientific discipline that, through mathematical and statistical models, allowed to make predictions of the probability of a prosthetic poppet escape and of the correct timing of of prosthesis replacement. I was not prepared to it from the high school of my youth. Arthur Benjamin [2] has requested that Statistics and Probability be at the apex of mathematical training also in the USA, because much more related to human real life than calculus.

In 1979 I had the opportunity to spend a research fellowship with Eugene H. Blackstone at the University of Alabama and I was trained in the technology of the "Research of Outcome", learning the use of confidence limits, logistic and hazard models, propensity score analysis and bootstrap bagging of multivariable selection.

Back home I started to collect the data on 10000 valvular operations which I used in many of the papers I published or coauthored. I wrote in "Basic" my own "logit" routine and my own "text editor" and devoted much time to the study of statistic and programming.

I don't recommend it and advise you that spend too much time learning these technologies could distract from the main issue and skill of our, potentially deadly, invasive maneuvers [3].

The invitation to write this paper is due to some appreciation of my last contribution to the "Research of Outcome" concerning the fate of patients operated on with the Standard Biocor mitral valve [4]. This paper, judged as potentially acceptable from the editor of JTCVS, was finally refused because I was unable to provide echo data: this was indeed a fault because porcine valves are at risk of calcification, therefore my paper rested in a drawer. Nonetheless monitoring of prostheses degeneration is just one of the purposes of prospective studies: the main purpose is to verify our ability to cure, that depends from the overall operative strategy. For this reason I had joined my data with those of the nearby University of Verona, were the use of the Standard Biocor Valve was initially started on 1989 from prof. Dino Casarotto, so to cover the whole range of 20 years. The paper, dated 2010, was published in 2017 on request of a free publisher.

In the research of outcome we should be able to identify the mode and causes of death, but this is seldom possible and it is also biased from a disease-linked prejudice of the physician who compiles the death certification. A valid alternative is to measure the ability to restore in our patients a life expectation similar to the one of the general population matched for age, sex and race. Success may be graphically certified by inclusion of general population survival curves within the 95% or 70% confidence limits of our patients survival (roughly analogous to the familiar 2 and 1 standard deviations used in comparing continuous data). In the international arena the comparison requires a "neutral benchmark": to this purpose an easily available standard is the one offered from US survival data.

The contemporary Finnish series, published by Mykén [5] in 2009, reported a survival which was significantly better than ours (16% vs. 6%), but the mean age of their patients was 65 year vs. 73 years of ours: this 8 year difference of surgical intervention is obviously related to a shorter survival and to a lower rate of calcific degeneration.

The hazard parametric analysis, which in this paper utilized the Royston-Parmar model [6] instead of the more known Blackstone hazard model [7], identified three risk factors beside operative age that were independently and significantly related to shorter survival: NYHA class, male sex, pulmonary hypertension.

Parametric analysis can be easily translated into graphics and "a figure is worth 100 words". The graphics of the paper clearly show that we pay the toll of a high peri-operative hazard. The following survival slope is rather similar to the general population slope. In the most favourable risk factors scenario (female, Nyha 1-3, age ≤ 71, MPAP ≤ 35) patient survival compares to survival of the general population.

It is not so in the worst scenario, justifying the conclusions of the paper: "premature mortality is unrelated to prosthesis performance and suggest failure of the "surgical strategy of the past century".

This conclusion is shared by the rapidly evolving alternatives proposed by heart teams worldwide [8] to allow mitral valve repair as early as possible. Despite the huge progress of valvular surgery in the past century as shown by the operative mortality in our center (Figure 2), the search of alternative surgical strategies to prosthetic replacement which are offered by up to date technology is actively pursued by Gino Gerosa [9], chief of the Cardiac Surgery Department of Padova.

Finland and Italy are both founded on a public health service and committed to high quality data, nonetheless we must complain that Italian citizens and statistical data repositories oppose resistance to share individual data with researchers because of "privacy" issues and legislation [9]. The economy professor Andrea Ichino commented [10] that the scientific community in its entirety must have access to microdata to check and replicate the results. In his paper he cite my complaint of "privacy regulations that prevent our national statistical institute to share with the surgeon the death reports recorded by the certifying physicians. The investigation of the mode or cause

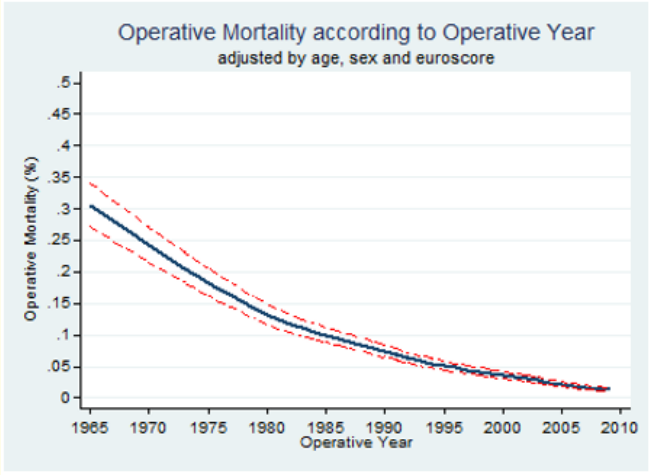

Figure 1

of death is essential to understand the risks associated with the use of new biomedical technology including valvular prostheses: it must answer the question if death was due to cardiac causes, complications of prosthesis or to cardiac unrelated disease/events".

Privacy cannot be considered an absolute good and this data would provide essential information to improve cardio-surgical therapies with positive effects for the whole nation".

In the Age of Genomics the new paradigm of medicine is offering personalized treatments for each patient, likewise modern medical statistics has the technology to evaluate of the results based on the constellation of risk factors of the individual patient.

In Italy we often rely on the "Outcome Research" produced in USA, that has predominantly private health care. Within an health system provided from the state, as in most Europe, there is a moral obligation to shear the knowledge gained during treatment of each citizen. A world recognized scientific authority as Eugene Blackstone told me that the "Institute of Medicine" in USA cleverly envisioned a "Learning Health System" to transform medicine through shared health information by 2020, but this meritorious task is still "on fieri". I share his opinion that this should be a worldwide privilege of the medical professionals.

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