MULTIVARIATE ANALYSIS AND OUTCOMES IN PERCUTANEOUS CORONARY INTERVENTION; FROM STATISTICS TO CATH LAB.

Fabrizio D'Ascenzo,[1] Giuseppe Biondi Zoccai,[2] Erika Cavallero,[1] Pierluigi Omedè,[1] Davide Giacomo Presutti,[1] Filippo Sciuto,[1] Enrico Cerrato,[1] Flavia Ballocca,[1] Marta Bisi,[1] Giorgio Quadri,[1] Ilaria Meynet,[1] Umberto Barbero,[1] Silvia Vicentini,[1] Mauro Gasparini,[3] Pierfrancesco Agostoni,[4] Davide Capodanno,[5] Claudio Moretti,[1] Fiorenzo Gaita[1]

1. Division of Cardiology, Department of Internal Medicine, Turin, Italy
2. Department of Medico-Surgical Sciences and Biotechnologies Sapienza University of Rome, Italy
3. Polytechnic University of Turin, Italy
4. Department of Cardiology, University Medical Center Utrecht, The Netherlands
5. Division of Cardiology, University of Catania, Italy

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ABSTRACT

High quality randomised clinical trials (RCTs) and meta-analysis represent the highest levels of evidence, but in everyday clinical practice, observational studies are often exploited as a quick and easy way to understand the performance of clinical and interventional strategies. In this setting, multivariate analyses are exploited to drive useful and independent information, but due to potentially confounding messages, should be critically appraised and used in everyday clinical practice.

Keywords: Multivariate analysis, PCI, stent.

NETWORK META-ANALYSIS, HEAD-TO-HEAD META-ANALYSIS AND RANDOMISED CLINICAL TRIALS; SHOULD OBSERVATIONAL STUDIES BE DISREGARDED?

In recent years patients, physicians and governments have been looking for the most accurate and economically sustainable combination of new drugs, diagnostics and interventional technologies in a rapidly changing economic scenario, pursuing several options in this quest, including comparative effectiveness research.[1]

Actually, from a scientific point of view, a growing bulk of new pharmacological and technological choices have been offered, especially in the cardiovascular field.[2-9] According to widespread opinion, well-conducted randomised controlled trials provide the most valid estimates of the relative efficacy of competing healthcare interventions.[10] A meta-analysis of randomized clinical trials (RCTs) that directly (head-to-head) compares two different interventions or drugs is thus considered the highest quality evidence. However, many interventions and drugs have not been directly compared in RCTs. This may relate to a large number of factors, ranging from the need for important resources,[1] fear of negative results for direct comparisons, and the underreporting of non-significant or negative data.[11] For example, placebo-controlled trials are often enough to obtain the regulatory approval of a new drug, once again limiting any ensuing direct comparisons.

On the other hand, especially in interventional cardiology, a high number of non-randomised studies are still performed in order to save

economical resources,[1] to create hypotheses, especially for non-randomisable patients, or to shed light on the generalisability of results from existing randomised experiments.[11]

In an attempt to exploit the broad potential resources of observational databases, various statistical models are currently employed. Several different multivariable approaches are available to control for systematic baseline differences naturally occurring between groups in the non-randomised setting.[10,12] Even more, their striking importance lies on defining the impact of several independent variables on a single dependent variable, thus avoiding confounding effects coming from observed variables in non-randomised studies.

Nevertheless, multivariable analysis should be performed according to precise statistical issues,[13-18] in order to offer understandable results and to offer a more prevalent impact on everyday practice.

TIPS AND TRICKS TO PERFORMING AND INTERPRETING MULTIVARIATE ANALYSIS

In Theory

The first important step for any researcher performing multivariate analysis, and for those reading articles, is to choose the most accurate model.

This choice should be performed according to a simple selection of parameters,[10] that firstly, have differences or similarities in follow-up and secondly, a number of events for covariates.

One of the most historically exploited models is represented by binary logistic regression, which evaluates the independent predictive role of one or more independent variables of interest. Actually, to appraise the logit of the probability of an event (dependent variable) given one or more dependent variables, event probabilities are appraised as a function in order to appraise. This model performs accurately, especially for studies with a similar follow-up, not adjusting for time-variation, and independently from number of events for covariate.

On the contrary, Cox proportional hazard analysis[20] also adjusts for differences in follow-up duration and censored data, by assessing the relationship of explanatory variables to survival time controlling for covariates and known confounders.

Last but not least, propensity score[21] which is defined as the conditional probability of receiving an exposure or treatment given a vector of measured covariates. Propensity could be exploited to perform a matching analysis (by obtaining two sample sizes of patients with a similar risk baseline profile) or may be incorporated into Cox multivariate models, and should be exploited for studies with a low ratio of events per covariate. For both of these models, some similar points should be accurately assessed.

The first choice of variables should be based on prior epidemiological evidence (i.e. an established association from prior well-conducted experimental or clinical studies) and strong associations (e.g. pb0.10 or pb0.05 at bivariate analysis) stemming from the specific dataset of interest.[22,23]

Specifically, for propensity scores both the calibration and possible discrimination of the model should be evaluated. With calibration, the distance between the observed (treatment, yes or no) and the predicted outcome from the model (propensity score) are assessed through the Hosmer–Lemeshow goodness of fit test. On the contrary, with discrimination (through area under-the-curve), authors understand how the predicted probabilities, derived from the model, classify patients into their actual treatment group.

In Practice

In a recent clinical review of our group,[24] we analysed all observational studies comparing bare metal and drug-eluting stents (DES), which demonstrated that independently from any impact factor, a better exploitation and methodological appraisal of multivariable analysis is needed in order to improve the clinical and research impact and reliability of non-randomised studies.

In all studies, a low number of events per variable was a common feature, potentially suggesting overfitted data and misleading associations.[20] Another difficult finding was the lack of reporting and perhaps conducting of internal control, as it was frequently not possible to assess calibration or censoring appraisal.[10] Moreover, any omission of the methodological assessment was not related to the quality rating of the journal in which the paper was published: we found no substantial differences among studies stratified according to the journal of publication's impact factor, thus stressing the need for more careful attention from peer reviewers concerning studies reporting multivariable adjustments.

CLINICAL APPLICATION AND LIMITS OF MULTIVARIATE ANALYSIS

One of the most striking examples of the profound clinical impact of multivariate analysis is represented, among others, by the example of stent thrombosis (ST) and DES, reported by Lagerqvist[25] in 2007 in Nejm. Through an accurate propensity score model, the authors demonstrated the increased risk of ST for DES, data that have never been confirmed in randomised evidence.[26] As a result of the potentially dramatic clinical impact, the work caused a reduction of more than one-third of DES implantation, particularly in North America. This example stresses the crucial point of the limitations of multivariate analysis, even when accurately performed, because they could not account for non-recorded or evaluated features, thus leaving potentially fundamental clinical or interventional properties unanalysed.

In summary, multivariate models, if accurately performed, represent a useful way to analyse observational data, despite the intrinsic limits of their observational nature.

REFERENCES

1. Obama B. Modern health care for all Americans. N Engl J Med. 2008 Oct 9;359(15):1537-41.

2. Banerjee A, Lane DA, Torp-Pedersen C, et al. Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: A modelling analysis based on a nationwide cohort study. Thromb Haemost. 2011 Dec 21;107(3).

3. Biondi-Zoccai G, Lotrionte M, Agostoni P, et al. Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. Int J Cardiol. 2011 Aug 4;150(3):325-31.

4. Landoni G, Mizzi A, Biondi-Zoccai G, et al. Reducing mortality in cardiac surgery with levosimendan: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2009 Aug;23(4):474-8.

5. Galiè N, Manes A, Negro L, Palazzini M, et al. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J. 2009 Feb;30(4):394-403.

6. Biondi-Zoccai G, Sheiban I, Romagnoli E, et al. Is intravascular ultrasound beneficial for percutaneous coronary intervention of bifurcation lesions? Evidence from a 4,314-patient registry. Clin Res Cardiol. 2011 Nov;100(11):1021-8.

7. Sangiorgi GM, Morice MC, Bramucci E, et al. Evaluating the safety of very short-term (10 days) dual antiplatelet therapy after Genous™ bio-engineered R stent™ implantation: the multicentre pilot GENOUS trial. EuroIntervention. 2011 Nov;7(7):813-9.

8. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in Transcatheter Aortic Valve Implantation Outcomes in Lower Surgical Risk Patients A Glimpse Into the Future. J Am Coll Cardiol. 2012;59(3):280-7.

9. Wazni O, Wilkoff B, Saliba W. Catheter ablation for atrial fibrillation. N Engl J Med. 2011 Dec 15;365(24):2296-304. Review.

10. Biondi-Zoccai G, Romagnoli E, Agostoni P, et al. Are propensity scores really superior to standard multivariable analysis? Contemp Clin Trials. 2011 Sep;32(5):731-40.

11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008-12.

12. Katz MH. Multivariable analysis: a practical guide for clinicians. Cambridge University Press, New York, 2006.

13. Concato J, Feinstein A.R., Holford T.R. The Risk of Determining Risk with Multivariable Models. Annals of Internal Medicine. 1993;118:201-10.

14. Weitzen S, Lapane KL, Toledano AY, Hume AL, Mor V. Principles for modeling propensity scores in medical research: a systematic literature review. Pharmacoepidemiol Drug Saf. 2004;13:841-853.

15. Weitzen S, Lapane KL, Toledano AY, Hume AL, Mor V. Weaknesses of goodness-of-fit tests for evaluating propensity score models: the case of the omitted confounder. Pharmacoepidemiol Drug Saf. 2005;14:227-38.

16. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biom J. 2009;51:171-84.

17. Austin PC. The performance of different propensity-score methods for estimating relative risks. J Clin Epidemiol. 2008;61:537-45.

18. Rubin DB. Estimating causal effects from large data-sets using propensity scores. Ann Intern Med. 1997;127:757-63.

19. Biondi-Zoccai GG, Agostoni P, Sangiorgi GM, Airoldi F, Cograve J, Chieffo A, et al. Real-world eluting-stent comparative Italian retrospective evaluation study investigators. Incidence, predictors, and outcomes of coronary dissections left untreated after drug-eluting stent implantation. Eur Heart J. 2006;27:540–6.

20. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II.Accuracy and precision of regression estimates. J Clin Epidemiol. 1995;48:1503–10.

21. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Stat Med 2007;26:734–53

22. Katz MH. Multivariable analysis: a practical guide for clinicians. New York: Cambridge University Press; 2006.

23. Steyerberg EW, Eijkemans MJ, Habbema JD. Stepwise selection in small data sets: a simulation study of bias in logistic regression analysis. J Clin Epidemiol. 1999;52:935–42.

24. D'Ascenzo F, Cavallero E, Biondi-Zoccai G, Moretti C, Omedè P, Bollati M, Castagno D, Modena MG, Gaita F, Sheiban I. Use and misuse of multivariable approaches in interventional cardiology studies on drug-eluting stents: a systematic review. J Interv Cardiol. 2012 Dec;25(6):611-21.

25. Lagerqvist B, James SK, Stenestrand U, Lindbäck J, Nilsson T, Wallentin L; SCAAR Study Group. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med. 2007 Mar 8;356(10):1009-19

26. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabatè M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet. 2012 Apr 14;379(9824):1393-402.

27. D'Ascenzo F, Bollati M, Clementi F, Castagno D, Lagerqvist B, de la Torre Hernandez JM, Ten Berg JM, Brodie BR, Urban P, Jensen LO, Sardi G, Waksman R, Lasala JM, Schulz S, Stone GW, Airoldi F, Colombo A, Lemesle G, Applegate RJ, Buonamici P, Kirtane AJ, Undas A, Sheiban I, Gaita F, Sangiorgi G, Modena MG, Frati G, Biondi-Zoccai G. Incidence and predictors of coronary stent thrombosis: Evidence from an international collaborative meta-analysis including 30 studies, 221,066 patients, and 4276 thromboses. Int J Cardiol. 2013;167(2):575-84.