

## Absence of proof or proof of absence? The risk of underpowered studies in cardiovascular medicine



Mario Gaudino<sup>1\*</sup>, MD; Umberto Benedetto<sup>2</sup>, PhD; David P. Taggart<sup>3</sup>, PhD

1. Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, NY, USA; 2. Bristol Heart Institute, University of Bristol, School of Clinical Sciences, Bristol, United Kingdom; 3. University of Oxford, Oxford, United Kingdom

In this issue of EuroIntervention Kjølner-Hansen and colleagues report the results of a *post hoc* analysis of the SORT OUT II trial comparing the 10-year rate of a composite outcome of death, myocardial infarction and repeat revascularisation between patients receiving a single drug-eluting stent in the proximal left anterior descending (LAD) vs. non-proximal LAD<sup>1</sup>. The authors report no difference between the two groups (HR 0.82, 95% CI: 0.65-1.03).

Article, see page 764

The analysis has some limitations. The definition used by the authors is somewhat arbitrary and difficult to understand: why not compare LAD vs. non-LAD lesions? Why group the distal LAD with the circumflex or right coronary artery? Lesions of the proximal LAD are traditionally considered to have significantly higher prognostic significance than any other coronary lesions<sup>2</sup>, so the biological rationale for the comparison is also questionable.

Most importantly however, with only 365 patients and 90 events in the proximal LAD group, the study is largely underpowered to detect even moderate differences between groups.

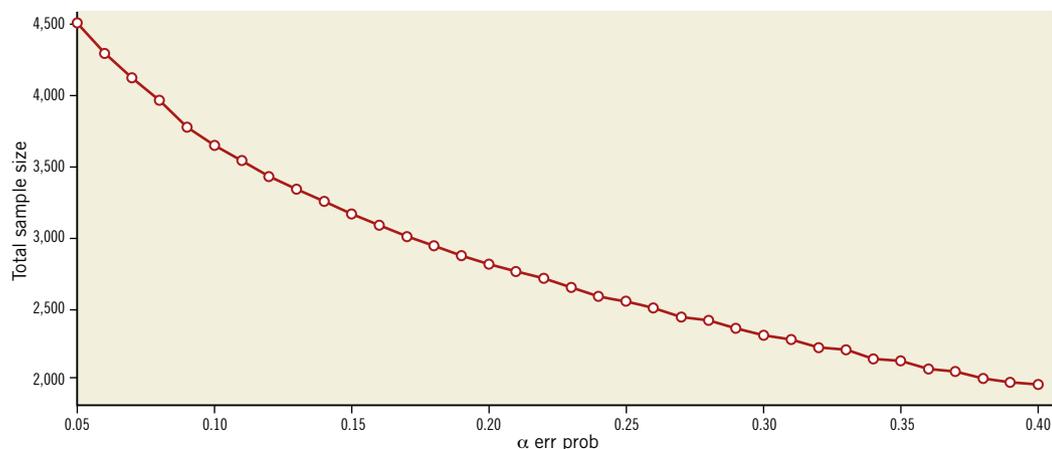
It is interesting to note how the authors quote in the text two surgical series comparing percutaneous intervention with minimally

invasive surgical revascularisation for treatment of proximal LAD disease<sup>3,4</sup> that, with 189 and 130 patients respectively, share both the sample size limitations and the negative conclusions of their paper.

Power is a crucial factor of every analysis. Studies with a small sample size have a high risk of type I and type II errors (**Figure 1**). When negative (as in this case), underpowered studies have substantial chances of missing true treatment effects. When positive, they are very likely to provide wrong estimates of the treatment effect. The limitations of underpowered studies and the risk associated with their interpretation in different fields of medical research have been described repeatedly<sup>5</sup>.

It is worth noting that recently two very important clinical questions in the cardiovascular field have been answered using a meta-analytic approach. Head et al, combining the patient-level data of 11 randomised trials comparing coronary surgery with percutaneous interventions in the treatment of patients with multivessel disease, were able to show for the first time a significant difference in mortality in favour of the surgical arm<sup>6</sup>. Our group, by combining individual data from six trials comparing the use of the radial artery with the saphenous vein as the second conduit in coronary

\*Corresponding author: Department of Cardiothoracic Surgery, Weill Cornell Medicine, 525 E 68th St, New York, NY 10065, USA. E-mail: mfg9004@med.cornell.edu



**Figure 1.** Correlation between sample size and *p*-value for a 20% assumed relative risk reduction between proximal LAD and non-proximal LAD groups.

surgery provided the first demonstration of a clinical benefit associated with the arterial conduit based on randomised data<sup>7</sup>.

Unfortunately, the merging of individual data sets requires a substantial amount of resources, time and persistence. Despite the recommendations of scientific and professional societies and scientific journals, sharing of data is still a complex and often painful process. However, the uncertainty and risk inherent in small studies should not be underestimated, and every effort should be made to provide the scientific community and our patients with data from adequately powered studies.

### Conflict of interest statement

The authors have no conflicts of interest to declare.

### References

1. Kjølner-Hansen L, Bligaard N, Kelbæk H, Christiansen EH, Thuesen L, Hansen PR, Engstrom T, Junkers A, Abildgaard U, Lassen JF, Jensen JS, Jeppesen JL, Galloe AM. Ten-year clinical outcome of patients treated with a drug-eluting stent in the proximal left anterior descending artery segment compared with patients stented in other non-left main coronary segments. *EuroIntervention*. 2018;14:764-71.
2. Klein LW, Weintraub WS, Agarwal JB, Schneider RM, Seelaus PA, Katz RI, Helfant RH. Prognostic significance of severe narrowing of the proximal portion of the left anterior descending coronary artery. *Am J Cardiol*. 1986;58:42-6.
3. Thiele H, Neumann-Schriedewind P, Jacobs S, Boudriot E, Walther T, Mohr FW, Schuler G, Falk V. Randomized comparison of minimally invasive direct coronary artery bypass surgery versus sirolimus-eluting stenting in isolated proximal left anterior descending coronary artery stenosis. *J Am Coll Cardiol*. 2009;53:2324-31.
4. Hong SJ, Lim DS, Seo HS, Kim YH, Shim WJ, Park CG, Oh DJ, Ro YM. Percutaneous coronary intervention with drug-eluting stent implantation vs. minimally invasive direct coronary artery bypass (MIDCAB) in patients with left anterior descending coronary artery stenosis. *Catheter Cardiovasc Interv*. 2005;64:75-81.
5. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, Munafò MR. Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci*. 2013;14:365-76.
6. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, Hlatky MA, Holm NR, Hueb WA, Kamalesh M, Kim YH, Mäkilallio T, Mohr FW, Papageorgiou G, Park SJ, Rodriguez AE, Sabik JF 3rd, Stables RH, Stone GW, Serruys PW, Kappetein AP. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet*. 2018;391:939-48.
7. Gaudino M, Benedetto U, Fremes S, Biondi-Zoccai G, Sedrakyan A, Puskas JD, Angelini GD, Buxton B, Frati G, Hare DL, Hayward P, Nasso G, Moat N, Peric M, Yoo KJ, Speziale G, Girardi LN, Taggart DP; RADIAL Investigators. Radial Artery or Saphenous Vein Grafts in Coronary Artery Bypass Surgery. *N Engl J Med*. 2018;378:2069-77.