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Letter to the Editor

Comparing benefits expected in the design of randomized trials with the results of mature meta-analysis: An analysis on aspiration thrombectomy in acute myocardial infarction

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Thrombectomy has emerged as one of the most promising innovations in the treatment of patients with acute myocardial infarction (AMI) undergoing primary angioplasty [1,2]. More than 20 randomized trials have evaluated this intervention. According to these trials, while mechanical thrombectomy has a questionable effectiveness, aspiration thrombectomy is supported by a quite robust evidence; this latter technique determines a significant reduction of major adverse cardiac events (MACEs).

On the other hand, in the field of evidence-based medicine the concept of statistical significance is increasingly being debated, particularly because demonstrating a significant improvement makes little sense if the magnitude of the improvement has no clinical relevance [3,4]. Randomized trials always incorporate power calculations and power calculations, in turn, require the declaration of a pre-specified expected benefit. The magnitude of the benefit adopted for power calculations (the so-called "margin" or "delta") influences clinical research, e.g. because this magnitude tends to be inversely proportional to sample size. Little research has however been carried out in this area.

Declaring a pre-specified (incremental) benefit for power calculations reflects to a large extent the concept of the minimal important difference and therefore aims at differentiating between clinically relevant incremental benefits and irrelevant ones [5].

In this paper, we have explored this complex issue with regard to the effectiveness of aspiration thrombectomy in AMI. Our analysis was aimed at comparing the (incremental) benefits expected at the stage of trial design with those estimated some years later from a "mature" literature. We selected this specific topic because aspiration thrombectomy has a high level of research interest and, in the near future, has a certain potential of being widely applied in clinical practice. Another reason for this choice is that this topic has been thoroughly investigated by a recent meta-analysis [6].

Methods: The meta-analysis by Kumbhani and co-workers [6] has examined all randomized studies evaluating aspiration thrombectomy in AMI. Since the phases of literature search, data extraction, and data synthesis were not an objective of our work, the clinical material reported by Kumbhani et al. was employed without any change for carrying out our study. We evaluated a single end-point, represented by complete ST-segment resolution (~70%) at 60 to 90 min (STR). The comparison involved thrombectomy (treatment group) vs no thrombectomy (controls).

Among the 18 randomized studies examined by Kumbhani et al., only 15 reported the end-point of STR. Our analysis was therefore based on these 15 trials. This clinical material was assumed to represent a "mature" meta-analytic evidence (see our Supplementary material for a detailed description of these studies).

Our analysis had a simple design. Using these 15 randomized studies, firstly we examined which of these had reported any power calculation focused on the end-point of STR. From each trial, we extracted the information on the margin employed for power calculations and then, from the overall series of trials, we identified which margin was the most frequently used. Finally, we compared this margin with the real benefit observed according to the published meta-analysis. Margins were expressed as incremental benefit [namely, as rate difference (RD)].

In formal statistical terms, the comparison of a point estimate [with its 95% confidence interval (CI)] with this margin can be carried out either a (one-side) non-inferiority analysis or a (two-sided) equivalence analysis [7]. Our primary analysis adopted the (two-sided) equivalence approach, mainly because this approach is simpler to explain (equivalence is demonstrated when, in the graph, the 95% CI of the RD is entirely contained within the area comprised between the two vertical margins). For comparison purposes, we also carried out a secondary analysis based on a (one-side) non-inferiority analysis.
on non-inferiority as well as a standard superiority analysis. By definition, this latter approach evaluates statistical significance without incorporating any assessment of clinical relevance.

Fig. 1. Pooled rate difference between thrombectomy vs no thrombectomy estimated from 15 randomized trials according to STR end-point (i.e. a prognostically favorable outcome). Panel A, equivalence analysis (margins at RD = +30% and +30%); Panel B, non-inferiority analysis (a single margin at RD = +30%); Panel C, traditional superiority analysis with no pre-declaration of margins. The graphs show the point estimate (•) with its 95% CI (horizontal solid bar). Vertical dashed lines indicate the margins that express the expected incremental benefit according to trials' statistical power calculations. According to these margins, Panel A indicates equivalence between the two interventions, while Panel B shows non-inferiority of no thrombectomy vs thrombectomy (the right extreme of the 95% does not cross the margin). In Panel C, clinical relevance is not incorporated in the analysis (the results of which simply indicate that thrombectomy is significantly more effective than no thrombectomy since the lower extreme of the 95% CI does not cross the identify line at RD = 0). Notes: a) In Panels A and B, the term “superiority” refers to the comparison of thrombectomy vs no thrombectomy and has the same meaning as “inferiority” for the comparison of no thrombectomy vs thrombectomy; b) The right margin at RD = +30% was adopted in three trials (namely REMEDIA (2005), DEAR-MI (2006) and PHRAGE (2010)), while the PHRAGE trial adopted RD = +25%; c) Complete references for these trials are given in our Supplementary material.

Results: In the 15 randomized trials, the most frequent definition of margin (3 trials) was an absolute increase of 30% in STR (i.e. a RD of +30% for thrombectomy vs controls).

Fig. 1 summarizes the results of our three analyses. In our primary analysis (Panel A), the benefit expected in the design of the trials (RD = +30%) was much larger than that actually observed according to mature data (RD = +13.6%). More importantly, since the 95% CI for this RD (interval from +7.6% to +19.5% around +13.6%) entirely remained within the two margins, the criterion of equivalence was met. This would imply that the benefit is not clinically relevant.

The non-inferiority analysis (Panel B) confirmed this conclusion. More interestingly, the traditional superiority analysis (Panel C) showed that thrombectomy was significantly more effective than no thrombectomy; however, as previously pointed out, this analysis did not incorporate clinical relevance.

Conclusions: Our results demonstrate, at the same time, equivalence between thrombectomy and no thrombectomy (Panel A) and superiority of thrombectomy vs no thrombectomy (Panel C). This apparent contradiction, which has been thoroughly explained by Ahn et al. [7], can essentially have two interpretations. First, power calculations in these trials adopted an overestimate of the expected benefit. It has been speculated that, in some cases, this may be intentional (though incorrect); in this way, the sample size is reduced and there is an advantage in practical terms. [5] Second, the incremental benefits were actually smaller than the initial (unbiased) expectations.

In the first case, highlighting the contradiction between expected benefits and real benefits observed from mature data can hopefully stimulate investigators to better tailor their sample size to real expectations (and not to opportunistic ones). In the second case, one explanation could be that, as in other areas, early trials of potentially lower quality have yielded larger differences than the more recent ones [8]. In 2009, Sobero and Bruci [9] addressed a very similar issue and offered, in that case, a series of comments that also apply to the interpretation of our results.

In conclusion, inasmuch as this comparison between expected and real benefits has never been systematically made, our preliminary experience can be of some interest. On the one hand, this approach could be extended to other innovative device-based interventions; on the other hand, it could be worthwhile to compare these findings with those obtained from treatments in medical areas other than interventional cardiology.

Finally, in the case of the comparison between thrombectomy and no-thrombectomy, the design of a two-arm trial aimed at demonstrating an absolute difference of at least 13% (from 7% to 20%) would require a size of at least 290 patients (calculated according to Edmiston et al. [10] with power = 90%; alpha = 5%); only 3 of the 15 trials had this sample size.

Conflict of interest statement

The authors have no relationship with industry and no other conflict of interest to be disclosed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jicare.2014.08.015.
References


Supplementary material.