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Opinion Paper

A critical analysis of the noninferiority design of the TALENT trial

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ABSTRACT

In recent years, regulatory approval of stents has been based on studies that have a noninferiority design, which has its own inherent complexities. We critically appraise in this article, the TALENT trial that established the noninferiority of the Indian-manufactured Supraflex stent (a third-generation, sirolimus-eluting stent with an ultrathin strut thickness) compared with the Xience stent (an internationally available, everolimus-eluting stent with a thicker strut) for a device-oriented composite end point at the end of 12 months. Our analysis shows that if the risk ratio rather than absolute risk difference was used to calculate the noninferiority margin, we would obtain a value of 1.48 for the risk ratio. Supraflex would then be noninferior to Xience by 0.92 [95% confidence interval (CI) = 0.59 to 1.47]. The upper bound of the 95% CI of 1.47 is dangerously close to 1.48, indicating that the TALENT trial would just about manage to prove noninferiority.

1. Background and rationale

In the present era, percutaneous coronary intervention using intracoronary stents has become the mainstay in the treatment of coronary artery disease (CAD). Stents have come a long way from the initial bare-metal stent to the current bioresorbable polymer ultrathin strut drug-eluting stents.[1] The newer generation of stents are thinner, have new antiproliferative drugs, a better elution profile, and biocompatible polymers.

In recent years, regulatory approval of stents has been based on studies that have a noninferiority (NI) design. These designs indicate that the new stent is not unacceptably worse than the existing stent [current standard of care (SOC)]. The NI design is inherently complex and includes several components—choice of comparator, NI margin, coupled with the use of absolute risk difference versus relative risk (or hazard ratio) for sample size calculation. Inappropriate use of one or more components may lead to an imprecise conclusion of NI.[2,3] Against this backdrop, we present in this article a critical analysis of the NI design used in the TALENT trial and its consequent implications.

2. Brief summary of the TALENT trial

The TALENT trial[4,5] was a single-blinded, randomized, NI trial of Supraflex (a third-generation, sirolimus-eluting stent with ultrathin strut thickness of 60 μm) compared with Xience (an everolimus-eluting stent with a thicker strut of 81 μm, SOC for CAD lesion) in an "all-comers" European population (n = 1435). This trial concluded that Supraflex was noninferior to Xience for device-oriented composite end point (DoCE) of target lesion failure, which was a composite of cardiac death, target vessel myocardial infarction (MI), and clinically indicated target lesion revascularization at 12 months in both intention-to-treat analysis {35/720 [4.9%] in the Supraflex arm and 37/715 [5.2%] in the Xience arm; absolute risk difference: −0.3% [95% confidence interval (CI), −2.6 to 2], p value <0.0001 [for NI]; *p* value = 0.801 [for superiority]} and per-protocol analysis [23/660 (3.5%) in the Supraflex arm and 30/685 (4.4%) in the Xience arm; absolute difference: −0.9% (95% CI, −3.0 to 1.2); *p* value < 0.0001 (NI); *p* value = 0.41 (superiority)].

3. Critique

We present in the following sections our concerns on the study design:

3.1. Choice of historical control

The CONsolidated Standards Of Reporting Trials (CONSORT) guidelines request specification of whether participants in the

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Table 1
Differences in primary end point and event rates in TALENT, RESOLUTE All-Comers, and SPIRIT IV trials.

Name of the trial	Components of the primary composite end point	Event rates (%)	
TALENT trial	Device-oriented composite end point—cardiac death, target vessel myocardial infarction, or clinically indicated target lesion revascularization at 1 year	SUPRAFLEX 4.9	XIENCE 5.3
RESOLUTE All-Comers trial	Target lesion failure composite end point—cardiac death, any myocardial infarction (not clearly attributable to a nontarget vessel), or clinically indicated target lesion revascularization at 1 year	RESOLUTE 8.2	XIENCE 8.3
SPIRIT IV trial	Ischemia-driven target lesion failure composite end point—cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization at 1 year	XIENCE 4.2	TAXUS 6.8

current trial are similar to those in the trial(s) that established efficacy of the reference treatment.[6] The choice of control in the TALENT trial comes from the RESOLUTE All-Comers trial [which aimed to prove Resolute (zotarolimus-eluting stent) to be non-inferior to Xience].[7] However, the RESOLUTE All-Comers trial did not prove the efficacy of the Xience stent. The largest study with clinical end points that proved the efficacy of the Xience stent was in fact the SPIRIT IV trial (in which the superiority of the Xience stent over TAXUS, a paclitaxel-eluting stent, was established).[8]

3.2. Choice of end points

In the TALENT trial, the primary end point was composite of cardiac death, target vessel MI, or clinically indicated target lesion revascularization at one year. This primary end point is different from the RESOLUTE All-Comers trial [cardiac death, any MI (not clearly attributable to a nontarget vessel), or clinically indicated target lesion revascularization at 1 year] that has been used as the control trial for calculating the NI margin.[7] This is also different from the SPIRIT IV trial in which the primary end point was cardiac death, target-vessel MI, or ischemia-driven target lesion revascularization at 1 year.[8] The primary end point in the TALENT trial thus appears to be a mixture of SPIRIT IV and RESOLUTE All-Comers trials.

3.3. Choice of event rate and power of the study

The event rate chosen for the TALENT trial was 8.3% in both arms based on the results of the RESOLUTE trial. This gave the TALENT trial a total sample size of 1435. If the investigators of the TALENT trial had chosen event rates from the SPIRIT IV trial (an event rate of 4.2%), the total sample size to prove NI would come to 2474, a much larger number. The final event rate of 5.3% in the Xience arm of the TALENT trial proves that the choice of 8.3% from the RESOLUTE trial was in fact an underestimate. We did a post hoc sample size calculation based on the event rate of 5.3%, and the total sample size worked out to be 3086 patients. We also did a post hoc power calculation for the TALENT trial using the final obtained event rate of 4.9% for Xience and 5.3% for Supraflex. We found that the study was powered at only 55% (with a two-sided α of 10%) and 45% (with a two-sided α of 5%). The trial could have included an interim analysis or an adaptive design that would have shown lower event rates than expected in both the arms, and consequently, the sample size could have been revised.

Table 1 highlights the differences in the primary composite end point used along with the event rates in the TALENT, RESOLUTE All-Comers, and SPIRIT IV trials.

3.4. Choice of the NI margin

In the TALENT trial, the NI margin was considered as 4% between the Supraflex arm and the Xience arm, i.e., fifty percent of the expected event rate of the control arm (8.3%) based on the RESOLUTE All-Comers trial.[7] If the SPIRIT IV trial had been used as the control, the NI margin would have been 2.1% (i.e., fifty percent of the 4.2% event rate), which would have been nearly half of the selected margin and hence would have resulted in a larger sample size of

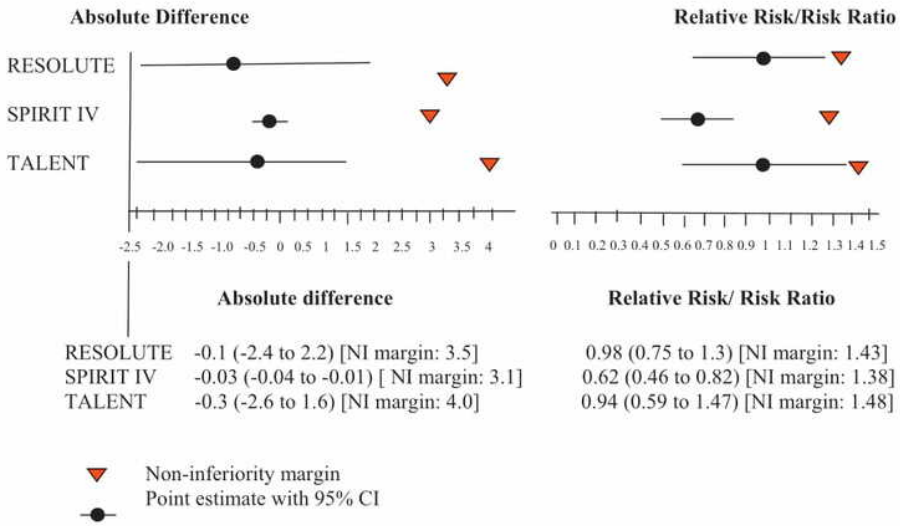

Fig. 1. Comparison of the primary outcome of the RESOLUTE trial, SPIRIT IV trial, and TALENT trial with respect to absolute difference and relative risk. NI = noninferiority; CI = confidence interval.

2474 patients instead of the 1435 that actually formed the sample size.

3.5. Choice of absolute risk difference (quantitative metric) rather than relative risk (ratio) for calculation of the NI margin

Macaya *et al*[9] analyzed nine NI stent trials that compared new stents to second-generation stents. They found that all of these trials demonstrated NI to the control group when absolute difference (expressed as the difference between the event rates in the two groups when expressed as proportions) was considered as the outcome measure. However, when these absolute differences were converted to risk ratios/relative risk (ratio of the event rates of the SOC *vs.* control), four of these trials failed to show NI.[11] For the TALENT trial, similarly, we converted the absolute difference into a risk ratio and plotted both the absolute difference and the risk ratio (Fig. 1) for the trial along with the same for the SPIRIT IV and RESOLUTE trials. We obtained a value of 1.48 for the risk ratio for the TALENT trial. This indicates a maximum relative increase of 48% events with Supraflex *vis-a-vis* Xience, which would be the NI margin. Thus, with the use of the risk ratio of 1.48, we calculated that Supraflex would be noninferior to Xience by 0.92 (95% CI = 0.59 to 1.47). The upper bound of the 95% CI of 1.47 is dangerously close to 1.48. The TALENT trial thus "just managed" to prove NI.

3.6. Critique of the post hoc sensitivity analysis

According to the *post hoc* sensitivity analysis carried out by the authors of the TALENT trial, they have stated that the NI margin of 2.1% found in the study (corresponding to a hazard ratio of 1.48) was estimated based on the observed DoCE (composite end point). The event rate seen in the Xience group was far lower at 5.3% than the originally envisaged 8.3% event rate taken from the RESOLUTE All-Comers trial. As discussed earlier, these low event rates and the relatively narrow NI margin would require a much larger sample size (n = 2474) to conclude true NI.

4. Our perspective of the trial

The TALENT study that used an Indian-manufactured stent was carried out in centers entirely outside the country and showed the Supraflex stent to be noninferior to the Xience stent for a DoCE at 12 months in an all-comer population. Studies such as these will ensure that patients will now have cost-effective stent options available to them. In the discussion section, the authors of the TALENT trial have alluded to at least three limitations—(1) the proportion of the observed DoCE in the control group being much lower than the initial estimates, (2) a wide NI margin as determined in retrospect, and (3) single blinding and a lower all-cause mortality than previously anticipated. Our critique apart from addressing the end points and NI margin has also discussed the choice of the historical control and the use of the absolute risk difference, a quantitative metric rather than the relative risk, a ratio. The authors of the TALENT trial have alluded only to the absolute risk difference and not the relative risk.

There has been considerable amount of debate in the literature about the use of absolute measures in comparison with that of relative measures. Reporting of relative measures is more popular as it is able to depict the strength of an intervention compared with a control or standard-of-care intervention. However, the use of relative measures is limited by the ability to portray the exact magnitude of effect between the interventions. Moreover, when the occurrence of the event in the control group is low, the relative measures can illustrate a much wider difference between the two groups than the actual difference. On the other hand, reporting of absolute measures delineates the actual effect size of the intervention. However, absolute measures may be very small for very effective treatments, thus apparently minimising the efficacy of the intervention.[10,11] This issue has been addressed by the 2010 CONSORT guidelines [6] in which use of both is recommended to give an integrated insight into the efficacy of the intervention. Readers of the TALENT trial would need to understand both the absolute and relative risk measures (along with their 95% confidence intervals) of the TALENT trial and the consequent implications for a balanced perspective of the study and informed clinical decision-making.

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None.

Conflict of interest

None of the authors have any conflicts of interest.

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