Journal of the American Heart Association

EDITORIAL

Per-Protocol Versus Intention-to-Treat in Clinical Trials: The Example of GLOBAL-LEADERS Trial

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After drug-eluting stent implantation, the classic therapy was dual antiplatelet therapy (DAPT) for 1 year and then stopping P2Y12 inhibitor while maintaining aspirin forever. The main limitation is the increased risk of bleeding with prolonged DAPT strategy might offset the ischemic benefit. Given that ischemic risk is higher in the initial phase whereas bleeding risk is maintained in the long term, deescalation therapies have been proposed, either with shorter DAPT durations or with aspirin-free strategies.[1] In fact, DAPT should follow the Goldilocks principle[2] (not too short, not too long). Recent studies (GLOBAL-LEADERS,[3] TWILIGHT [Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention],[4] TICO [Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome],[5] STOP-DAPT [Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent],[6] SMART-CHOICE [Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Anti- platelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents][7]) suggest that the deescalation strategy with an abbreviated DAPT period after percutaneous coronary intervention (1–3 months) followed by aspirin cessation and P2Y12 inhibitor monotherapy mitigates bleeding risk without losing efficacy for ischemic prevention. Among all these trials, GLOBAL-LEADERS[3] offers the largest sample size and is the only one designed as a superiority trial. Specifically, 15 991 patients undergoing percutaneous coronary intervention with a drug-eluting stent were randomized to deescalation therapy (1-month DAPT plus 23-month ticagrelor monotherapy) or to the control strategy (standard 12-month DAPT followed by 12-month aspirin monotherapy). At intention-to-treat analysis,[3] the deescalation therapeutic strategy failed to show superiority at 2 years for the primary end point of the composite of all-cause mortality or nonfatal Q-wave myocardial infarction (rate ratio, 0.87; 95% CI, 0.75–1.01; P=0.07). In this issue of the *Journal of the American Heart Association (JAHA)*, Gragnano et al.[8] report the results of the per-protocol analysis of GLOBAL-LEADERS trial.

See Article by Gragnano et al.

The looming overarching questions are what is the difference between intention-to-treat and per-protocol analyses and when to use one or the other? The *intention-to-treat* principle measures the effect of *assigning* patients to treatment (not of the treatment itself), and thus it requires that patients assigned to a treatment strategy are kept in that group during the analysis, even if they deviated from their assigned treatment strategy after randomization.[9–11] The *per-protocol* and *as-treated* analyses estimate the effect of *receiving* a

Key Words: Editorials ■ antiplatelet therapy ■ aspirin ■ clinical trial ■ intention-to-treat analysis ■ P2Y12 inhibitors

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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treatment. Per-protocol analyzes data only from participants who follow the protocol, excluding the data after they become protocol deviant/nonadherent.[9–11] As-treated analyses examine the treatment actually received by the participant, without regard to adherence to their randomization assignment. The results of some trials might differ according to the analysis strategy used. For instance, the CABANA (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial[12] investigated atrial fibrillation patients randomized to catheter ablation or medical therapy; no meaningful differences were observed in the primary end point in the intention-to-treat (hazard ratio [HR], 0.86; 95% CI, 0.65–1.15; *P*=0.3) or pre-protocol analyses (HR, 0.74; 95% CI, 0.54–1.01; *P*=0.056), but the as-treated analysis suggested efficacy of the ablation strategy (HR, 0.67; 95% CI, 0.50–0.89; *P*=0.006).[11]

Although it might seem "more logical" to analyze the effect of treatment (ie, per-protocol) instead of the effect of treatment assignment (intention-to-treat), excluding noncompliant poses multiple problems[9–11]:

1. It violates the principle of randomization (random balance for known and unknown confounders). When some participants are excluded, the remaining groups can no longer be considered as balanced.
2. As noncompliance is more frequent in patients with severe disease, exclusion of noncompliant participants would lead to differential exclusion of severe patients in the treated group. This may make the treatment look better than it actually is; thus per-protocol analysis is more prone to type-1 error (false positives).
3. Exclusion of high number of participants causes significant reduction in sample size and statistical power.

A per-protocol analysis of a randomized trial is considered by some authors[9] "an observational analysis" that presents potential confounding by unmeasured factors. This has cast doubts on the validity of per-protocol analyses. The prime example is a post hoc analysis of the CDP (Coronary Drug Project)[13] that showed lower mortality among participants who adhered to placebo than among those who did not adhere to placebo. This is frequently used as a warning for investigators who deviate from the intention-to-treat principle.

Intention-to-treat analysis is the most commonly used approach for the primary analysis of randomized clinical trials. Intention-to-treat analysis is agnostic about postrandomization decisions (eg, therapy discontinuation), preserves the original randomization, and maintains sample size; the analysis population is as complete as possible (hence called "full analysis set"); potential bias due to exclusion of patients is avoided; and it is a more conservative approach minimizing type-1 error.[9–11] Intention-to-treat more closely represent clinical practice, thus showing "effectiveness" rather than "efficacy."

However, we should demystify intention-to-treat analysis as it also presents some limitations. The result of an intention-to-treat analysis is affected by the pattern of adherence to treatment strategies. For instance, in a head-to-head trial of 2 active treatments that have differential adherence because of a mild, easily palliated side effect, an intention-to-treat analysis may misleadingly indicate a benefit of the less efficacious treatment. When there is incomplete adherence (as happens in GLOBAL-LEADERS[3]), intention-to-treat analyses may result in an effective intervention appearing to be ineffective (ie, are too conservative) if the poor adherence was because of misplaced concerns about effectiveness or toxicity.[9–11] Therefore, intention-to-treat effects may not provide clinically useful information in some situations.

The validity of per-protocol effect estimates absolutely requires adjusting properly for confounding due to incomplete adherence to the assigned treatments.[9–11] Given that both adherence and loss to follow-up may be influenced by social and clinical factors that occur after randomization, we refer to these biases as postrandomization confounding and selection bias. To adjust for incomplete adherence in per-protocol approach, the analysis strategy ensures that data from participants are censored when the participants deviate from their assigned treatment strategy (ie, a participant's follow-up is terminated at the time at which they cease to follow the protocol). This strategy is actually followed in the current analysis of GLOBAL-LEADERS trial.[8] In order to augment the probability that per-protocol analysis yields a valid estimate of the treatment, 3 general rules need to be followed.[9] First, data from participants should not be censored when they stop treatment for clinical reasons; no protocol would expect to continue statin treatment if rhabdomyolysis is developed. Second, data from participants should be censored when it is no longer certain that they are receiving treatment (ie, if the participant adherence becomes unknown); this rule applies even if the outcome in the participant is later learned through other means. Third, adjustment should be made for confounding due to incomplete adherence (a naïve per-protocol analysis without adjustment for confounding will be valid only if adherence occurred completely at random); as adherent and nonadherent participants generally differ with respect to prognostic factors, a per-protocol analysis must adjust for prerandomization and postrandomization prognostic factors that predict adherence. It is reassuring that the authors of the current article[8] have followed all these rules in their per-protocol analysis of the GLOBAL-LEADERS trial.

Given the high rate of noncompliance with treatment in the GLOBAL-LEADERS study[3] (22% in the experimental arm—perhaps influenced by potential dyspnea induced by ticagrelor—and 7% in the control arm,), the intention-to-treat analysis might have underestimated the true effect of the experimental strategy, as just explained. This the reason for the authors to perform a per-protocol analysis[8] to learn whether the novel deescalation strategy was superior in patients who were *actually* compliant with the strategy and did not deviate from medication decisions.

Rates of protocol deviation were higher in the experimental group than in the control group both at 1 year (10% versus 6.5%) and 2 years (13.8% versus and 9.8%, respectively); of note, this difference emerged early and was maintained over time. As previously explained, changes of medications for medical reasons (ie, adverse effects, new diagnosis) were anticipated in the study and did not qualify as protocol deviation; this explains the difference between treatment noncompliance per se (22% in the experimental arm) and actual protocol deviation (13.8% in the experimental arm). As expected, protocol deviators presented a more severe clinical situation (older; more extensive atherosclerosis; more often with history of chronic obstructive pulmonary disease, chronic kidney disease, and prior coronary revascularization). Therefore, the authors performed proper adjustment for pre- and postrandomization confounding instead of a naïve (ie, without adjustment) per-protocol analysis (ie, to avoid the situation that arose in the CDP trial) to account for the observational nature of per-protocol analysis.

The most important result is that per-protocol analysis confirms the results of the intention-to-treat. After censoring data from protocol deviators, the rate of the primary end point in the per-protocol analysis did not differ significantly between both arms (rate ratio, 0.88; 95% CI, 0.75–1.03; P=0.10). The same effect was observed in the key safety end point of major bleeding. Both per-protocol results parallel the intention-to-treat data. Yet, of high clinical relevance, the experimental deescalation strategy significantly improved the rate of net adverse clinical events (a composite of death, myocardial infarction, stroke, revascularization, bleeding) with a rate ratio of 0.90 (95% CI, 0.83–0.97; P=0.008). The point estimates were similar in all end points between per-protocol and intention-to-treat strategies, although the CIs were slightly wider for the per-protocol analysis because the number of end points was lower due to the artificial censoring of protocol deviators. Importantly, the per-protocol analysis was confirmatory of the intention-to-treat findings also in the TICO,[5] SMART-CHOICE,[6] and STOP-DAPT[7] trials, as also observed in GLOBAL-LEADERS. This fact adds reliability to the robustness of the deescalation strategy.

We want to highlight the fact that, unlike the intention-to-treat estimates, the results of the per-protocol analysis of GLOBAL-LEADERS significantly improved the rate of net adverse clinical events in the deescalation strategy. Although GLOBAL-LEADERS is an open-label trial, other double-blind trials such as TWILIGHT and TICO confirm the superiority of this DAPT deescalation. Both trials investigated either 12-month ticagrelor or 12-month DAPT after an initial 3-month DAPT period. In the TWILIGHT trial,[5] the deescalation strategy showed a 44% reduction in the primary end point of major bleeding while maintaining efficacy (no difference in ischemic end points). The TICO trial[6] showed improved net adverse clinical events by 34% in the ticagrelor monotherapy, at the expense of a 44% reduction in major bleeding in the ticagrelor-monotherapy arm with ischemic events not different in both arms. The open-label STOP-DAPT[6] and SMART-CHOICE[7] trials confirmed the benefits of DAPT deescalation both in bleeding events and in ischemic events.

The mechanism of the benefit of this deescalation strategy remains unknown. One potential explanation is that dropping aspirin reduces bleeding risk, whereas the maintenance of the more potent antiplatelet agent ticagrelor preserves the antithrombotic effect. This hypothesis is supported by a mechanistic substudy of the TWILIGHT trial. Using Badimon chamber (the gold-standard method to evaluate blood thrombogenicity),[14] thrombus formation under dynamic flow conditions was similar in both ticagrelor monotherapy and ticagrelor+aspirin.[15] This suggests that aspirin does not enhance the global antithrombotic effect of ticagrelor, hinting that aspirin does not add benefits, just bleeding. In fact, the role of aspirin is decreasing with current evidence, especially in primary prevention.[1] Another potential pathophysiological explanation is the adenosine-mediated vasodilatory effect of ticagrelor, which might enhance myocardial perfusion.

Strong points of this article[8] include the large sample size, the similar results obtained in intention-to-treat and per-protocol analysis, and the fact that the positive net adverse clinical events results with the deescalation strategy are confirmed in independent trials (TWILIGHT, TICO, STOP-DAPT and SMART-CHOICE).[4–7] As with all studies, this also has limitations. Apart from the limitations of a per-protocol analysis, some additional limitations specific of the design of the GLOBAL-Leaders trial[3] apply here. This was an open-label trial so neither patients nor investigators were blinded to treatment strategy. Moreover, secondary end points were not centrally adjudicated by an independent committee but were reported by investigators; the fact that the trial was monitored for consistency of event definitions and event underreporting can mitigate (but not completely eliminate) this limitation.

The first conclusion is the per-protocol analysis of the GLOBAL-LEADERS trial[8] support the deescalation of DAPT therapy after percutaneous coronary

intervention, although the exact strategy (duration and drug) remain uncertain. The second conclusion is that the per-protocol and the intention-to-treat treatment effect estimates provided consistent results for primary and secondary analysis so these findings support the validity of the initial interpretation of trial results. It is important to learn the limitations of both intention-to-treat and per-protocol analysis in order to be cognizant of when to apply each analysis.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Santos-Gallego CG, Badimon J. Overview of aspirin and platelet biology. *Am J Cardiol*. 2021;144(suppl 1):S2–S9. doi: 10.1016/j.amjcard.2020.12.018
2. Santos-Gallego CG, Badimon J. Duration of antiplatelet therapy after complex PCI in the TWILIGHT-COMPLEX trial: the Goldilocks dilemma. *Cardiovasc Res*. 2020;116:e93–395. doi: 10.1093/cvr/cvaa135
3. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018;392:940–949. doi: 10.1016/S0140-6736(18)31858-0
4. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. *N Engl J Med*. 2019;381:2032–2042. doi: 10.1056/NEJMoa1908419
5. Kim B-K, Hong S-J, Cho Y-H, Yun KH, Kim YH, Suh Y, Cho JY, Her A-Y, Cho S, Jeon DW, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA*. 2020;323:2407–2416. doi: 10.1001/jama.2020.7580
6. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI. *JAMA*. 2019;321:2414–2427. doi: 10.1001/jama.2019.8145
7. Hahn J-Y, Song YB, Oh J-H, Chun WJ, Park YH, Jang WJ, Im E-S, Jeong J-O, Cho BR, Oh SK, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention. *JAMA*. 2019;321:2428–2437. doi: 10.1001/jama.2019.8146
8. Gragnano F, Zwahlen M, Vranckx P, Heg D, Schmidlin K, Hamm C, Steg PG, Gargiulo G, McFadden EP, Onuma Y, et al. Ticagrelor monotherapy or dual antiplatelet therapy after drug-eluting stent implantation: per-protocol analysis of the GLOBAL LEADERS trial. *J Am Heart Assoc*. 2022;11:e024291. doi: 10.1161/JAHA.121.024291
9. Hernan MA, Robbins JM. Per-protocol analyses of pragmatic trials. *N Engl J Med*. 2017;377:1391–1398. doi: 10.1056/NEJMsm1605385
10. Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: intention-to-treat versus per-protocol analysis. *Perspect Clin Res*. 2016;7:144–146. doi: 10.4103/2229-3485.184823
11. Smith VA, Coffman CJ, Hudgens MG. Interpreting the results of intention-to-treat, per-protocol, and as-treated analyses of clinical trials. *JAMA*. 2021;326:433–434. doi: 10.1001/jama.2021.2825
12. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding and cardiac arrest among patients with atrial fibrillation: the CABANA clinical trial. *JAMA*. 2019;321:1261–1274. doi: 10.1001/jama.2019.0693
13. The Coronary Drug Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. *N Engl J Med*. 1980;303:1038–1041. doi: 10.1056/NEJM198010303031804
14. Zafar MU, Santos-Gallego CG, Badimon L, Badimon J. Badimon perfusion chamber: an ex vivo model of thrombosis. *Methods Mol Biol*. 2018;1816:161–171. doi: 10.1007/978-1-4939-8597-5_12
15. Baber U, Zafar MU, Dangas G, Escolar G, Angiolillo DJ, Sharma SK, Kini AS, Sartori S, Joyce L, Vogel B, et al. Ticagrelor with or without aspirin after PCI: the TWILIGHT platelet substudy. *J Am Coll Cardiol*. 2020;75:578–586. doi: 10.1016/j.jacc.2019.11.056