

Duration of Anticoagulant Treatment for Acute Provoked Venous Thromboembolism in Pediatric Patients

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A critical aspect of clinical care is determining when to start and when to stop a treatment. Clinicians and researchers have given more attention to the first decision because starting an intervention too late can be detrimental. For example, starting antibiotic therapy as soon as possible in critically ill patients with sepsis improves survival.¹ Less attention has been paid to the question of when a treatment should be stopped. Prolonged antibiotic therapy increases the risk of antibiotic resistance in critically ill patients.² The variation in time to antibiotic cessation in clinical practice is substantial.³ However, in many trials, shorter courses of antimicrobials were as effective as longer courses and were associated with fewer adverse outcomes.⁴ Decisions about when to start and stop treatment also involve other therapies, including anticoagulant treatment, which requires careful consideration of the risks and benefits.

In this issue of *JAMA*, Goldenberg et al⁵ report findings from a noninferiority randomized clinical trial (RCT) that compared the efficacy and safety of shorter vs longer anticoagulant therapy to prevent recurrent venous thromboembolism without causing more clinically relevant bleeding events in patients younger than 21 years of age who experienced an acute provoked venous thromboembolism. A venous thromboembolism was considered provoked if it could be attributed to a hospitalization-related event, trauma, or a central venous catheter. The patency of the thrombosed blood vessel was ascertained 6 weeks after diagnosis of venous thromboembolism. If the thrombus was not completely occlusive, patients were randomized to a group in which anticoagulant therapy was stopped at 6 weeks or was maintained up to 3 months. Given the trade-off between the risks of recurrent venous thromboembolism and bleeding events, the margin of safety of this noninferiority RCT took into account simultaneously both efficacy (symptomatic recurrent venous thromboembolism) and safety (clinically relevant bleeding events) outcomes, using the bivariate end point analytic approach.⁶ The noninferiority boundary was constructed based on 3 scenarios of risk-benefit trade-off, one of which included an absolute increase of 0% in symptomatic recurrent venous thromboembolism with an absolute risk reduction of 4% in clinically relevant bleeding events.⁶

In both the per-protocol and intent-to-treat analyses (297 and 417 participants, respectively), shorter treatment duration was not inferior to the longer treatment duration with respect to recurrent venous thromboembolism and bleeding events within 1 year after diagnosis of the index venous thromboembolism. The cumulative incidence of the primary effi-

cacy outcome was 0.66% (95% CI, 0%-1.95%) in the 6-week group and 0.70% (95% CI, 0%-2.07%) in the 3-month group. The cumulative incidence for the safety outcome was 0.65% (95% CI, 0%-1.91%) in the 6-week group and 0.70% (95% CI, 0%-2.06%) in the 3-month group. The data suggest that 6 weeks of anticoagulant therapy should be considered for standard treatment in children and adolescents after a provoked venous thromboembolism.

At least 2 lessons can be learned from this trial. First, for patients younger than 21 years of age with acute provoked venous thromboembolism, 6 weeks of treatment is noninferior to 3 months of treatment in terms of efficacy and safety. In other words, a short period of anticoagulant therapy of 6 weeks can effectively and safely prevent recurrent thrombosis. Can these results be applied to all pediatric patients? Few patients with cancer or pulmonary embolism were enrolled in the RCT and patients with active malignancy were excluded. Further studies are needed to confirm the findings in these populations. Should clinicians wait for the results of additional RCTs before changing the current guidelines? Given that the study was conducted at 42 centers in 5 countries over 13 years, it is unlikely to be repeated. Although the data reported by Goldenberg et al⁵ are compelling enough that some practitioners may want to apply them immediately, the results should be applied judiciously and not be extrapolated to patients with unprovoked venous thromboembolism and older patients.

Second, the trial by Goldenberg et al⁵ is innovative not only from a clinical perspective, but also because it used an innovative statistical approach. The benefit-risk assessment of a treatment is a critical step for regulatory review as well as for clinical decision-making. Traditionally, the benefits and risks of a treatment have been evaluated independently although the decision on use of a treatment must consider both benefits and risks. Some authors have proposed different metrics that incorporate both benefits and risks to improve the assessment of an intervention.⁷ In this trial, the authors used the methods proposed by Kittelson et al⁶ that involve a bivariate approach that could be used in noninferiority or superiority RCTs in which there is a trade-off between efficacy and safety (eg, prevention of recurrent venous thromboembolism and bleeding events). The interpretation of the results of a traditional noninferiority RCT is straightforward: the noninferiority of the efficacy (or safety) of a treatment with respect to another treatment is demonstrated if the 97.5% CI of an absolute risk difference (or other statistic) is lower than the prespecified noninferiority margin.

Several methods have been proposed to determine the noninferiority margin^{8,9}; however, there is no agreement on

which method should be used in practice. For the approval of new drugs, the noninferiority margin has to be discussed with regulators. In the bivariate analysis, the CI becomes a confidence region while a noninferiority margin becomes a noninferiority region in which the region is a 2-dimensional space with efficacy on the x-axis and safety on the y-axis (as shown in Figure 2 in the report by Goldenberg et al⁵). Several methods can be used to determine noninferiority regions but they are not agreed upon. A bivariate noninferiority RCT will demonstrate noninferiority if the confidence region does not overlap with the noninferiority region.

The advantage of this analytic approach is that ultimately the final decision on the merits of a treatment is almost always based on efficacy and safety, although there are challenges in its use. First, the efficacy of treatment is often captured by a single end point, whereas the safety of a treatment is often evaluated using multiple safety end points—each end point with different levels of severity. In theory, the bivariate approach can be extended to an analysis with 2 or more end points but this comes at the cost of an increase in statistical complexities as well as in determining the noninferiority region. The trial of Goldenberg et al⁵ has the advantage of having a single efficacy end point and a single safety end point.

Second, the noninferiority region defined by Kittelson et al⁶ is somewhat arbitrary because it is drawn from 3 selected points on the efficacy-safety (risk difference) plane. As such, an infinite number of curves can be drawn that will pass through the points. The tails of these curves beyond the first and third points can be arbitrary. It is difficult to adapt some of the methods used by regulators to define less arbitrary noninferiority regions.

Third, Goldenberg et al⁵ used rectangular confidence regions for the venous thromboembolism and bleeding risk difference. This rectangular region is created by the box formed by extending the CIs for the venous thromboembolism and bleeding risk difference on the plane. There are several methods (eg, ellipsoid region) for constructing multivariate confidence regions (as described by Pallmann and Jaki¹⁰ in the context of bioequivalence studies). Rectangular regions, as defined by Kittelson et al,⁶ are conservative because they tend to be larger compared with other methods. It would be useful to explore less conservative methods to build confidence regions.

When treatment should be stopped is as important as when it should be started. Shorter treatment duration can decrease the risk of adverse events and may be more cost-effective. The findings of the RCT reported by Goldenberg et al⁵ in this issue of *JAMA* demonstrated that among patients younger than 21 years of age with provoked venous thromboembolism, anticoagulant therapy administered for 6 weeks compared with 3 months met noninferiority based on a combination of recurrent venous thromboembolism risk and bleeding risk. The findings suggest that anticoagulant therapy could be stopped sooner than currently recommended and that doing so is likely to be as safe as longer treatment. Quality of life may be improved in many children by decreasing the duration of subcutaneous injections. The trial of Goldenberg et al⁵ suggests that there are instances when an RCT must consider both efficacy and safety. What remains to be determined is when this analytic approach should be used in studies that evaluate when to start and when to stop a treatment for potentially serious conditions.

ARTICLE INFORMATION

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