rhages and not the most feared event of intracranial bleeding. Third, and most salient, is the timing of these outcomes. Most of the benefit regarding stroke prevention occurred in the first week of treatment with the combination, whereas most of the bleeding occurred later. In a secondary analysis, the benefit of aspirin plus clopidogrel in preventing ischemic outcomes was significant throughout the first 7 to 30 days of treatment, whereas the risk of major hemorrhage became greater only during the period from 8 to 90 days.

The results are slightly at odds with the only other trial of aspirin plus clopidogrel after minor stroke, which involved Asian patients. The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial showed a similar lower rate of ischemic events with clopidogrel plus aspirin than with aspirin alone, but without a higher rate of bleeding with the combination.[5] The CHANCE trial used a lower loading dose of clopidogrel, but this is an unlikely explanation for the difference, since most bleeding events in the POINT trial occurred long after the loading dose. More likely, the difference was due to a shorter duration of combined treatment (only 21 days in the CHANCE trial vs. 90 days in the POINT trial) and differences in the metabolism of clopidogrel in Asian versus non-Asian persons.

What is the take-home message for the clinician? The evidence from the SAMMPRIS, CHANCE, and POINT trials is that the combination of aspirin plus clopidogrel reduces the chance of recurrent ischemic stroke during the high-risk period in the first few weeks after a TIA or noncardioembolic ischemic stroke. However, to conform to the results of the POINT trial, if dual therapy is used, it should be confined to the first 3 weeks after a TIA or minor stroke and then transitioned to monotherapy. If patient follow-up and adherence to therapy are not reliable, then dual therapy perhaps should not be considered. Dual therapy may also not be advisable in patients with an uncertain diagnosis of TIA, who either would have been excluded from the trial or did not benefit. Finally, patients who are at increased risk for bleeding, such as those with cerebral microbleeding or a history of brain or systemic bleeding, were excluded from this trial and may not be appropriate candidates for such dual therapy. The POINT trial has provided useful data to help us further personalize our efforts in preventing recurrent stroke.

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L-Glutamine and the Dawn of Combination Therapy for Sickle Cell Disease

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In 2017, the U.S. Food and Drug Administration approved L-glutamine (USAN, glutamine) for the prevention of acute vaso-occlusive pain events in persons with sickle cell disease who are older than 5 years of age — only the first drug to be approved for this indication in the 20 years since the approval of hydroxyurea. The much awaited data that supported this landmark approval are available for review in the article by Niihara et al. in this issue of the *Journal*.[1]

In a phase 3, randomized, double-blind, placebo-controlled trial involving 230 patients (5 to 58 years old) with homozygous hemoglobin S or sickle β^0-thalassemia, Niihara et al. compared L-glutamine with placebo, administered orally twice daily for 48 weeks, followed by a tapering period of 3 weeks. The results indicated that the patients in the L-glutamine group had a significantly lower number of acute vaso-occlusive episodes (25% lower), greater time to first and second pain crisis, fewer hospitalization days, and fewer acute chest syndrome episodes than did the patients in the placebo group. The rate of acute events was also lower among the patients who were receiving concomitant hydroxyurea, which indicates a possible additive effect of L-glutamine. The rate of adverse events was similar in the treatment group and the placebo group, and adverse events were mostly related to sickle cell disease. Of note, however, as was the case in the previous phase 2 trial,[2] the dropout rate was high, with only 68%, or 156 patients, completing the trial.

Glutamine is a ubiquitous, conditionally essential amino acid; the production of glutamine becomes insufficient during the neonatal period, periods of stress, or the course of severe diseases, and exogenous supplementation is necessary. Glutamine is a building block for protein synthesis, as well as a precursor of nucleic acids and nucleotides; fuel for rapidly dividing cells, including the cells in the hematopoietic system and in the gut endothelium[3]; and an arginine prodrug.[4] Glutamine is needed for the synthesis of nicotinamide adenine dinucleotide (NAD) and nicotine adenine dinucleotide phosphate (NADP) and is indirectly involved in the recycling of reduced glutathione (glutathione disulfide) to oxidized glutathione, a mechanism that reduces oxidative stress in sickle cell disease. Glutathione is the principal thiol oxidative reduction (redox) buffer in erythrocytes, and its depletion has been linked to hemolysis.

As often happens in medicine, any new breakthrough poses new compelling questions that need to be answered if we want to move toward a rational approach to care. With regard to persons with sickle cell disease, we should remember the lessons learned from years of suboptimal use of hydroxyurea, despite wide scientific evidence of its effectiveness. Among the many reasons that hydroxyurea use is still not as widespread as it should be is its perceived or real adverse-event profile in the target population and the fact that the medical community has been slow to implement its use. The price of L-glutamine is much higher than that of hydroxyurea; 1 year of treatment with Endari (Emmaus Medical) for an average adult is estimated at $40,515, as compared with approximately $1700 for hydroxyurea.[5] Whether the cost will be a hindrance to its use has yet to be determined. This agent certainly has been slow to enter the market because prescribing L-glutamine for patients requires many steps, which may dissuade busy practitioners from actively prescribing it. Because L-glutamine has a putatively different mechanism (or mechanisms) of action and toxicity profile than hydroxyurea, concomitant use is possible and most likely advantageous. In the era of personalized medicine, there is a need to identify subgroups of patients within the population of patients with sickle cell disease who are most likely to benefit from such therapy. Currently, no simple and reproducible biomarker of oxidative stress exists that can guide clinicians in identifying patients who are most likely to have a response and in monitoring adherence and effectiveness. More importantly, data showing how or how often to monitor toxic effects are lacking. Additional studies that focus on different end points, such as prevention of end-organ damage, need to be developed. Studies should include patients who are representative of the entire population with sickle cell disease, particularly those with more severe disease, especially liver and renal disease, who were not included in the initial trial. A multicenter trial of parenteral L-glutamine in critically ill patients without sickle cell disease showed higher mortality in the intervention group than in the control group.[6]

Therefore, caution may be warranted in prescribing L-glutamine to patients with sickle cell disease who have clinically significant renal and hepatic dysfunction. Of note, in the two randomized trials of L-glutamine involving patients with sickle cell disease, three deaths occurred in the L-glutamine groups, as compared with none in the placebo groups[1,2]; the deaths were not considered to be related to the study drug. In the absence of specific guidelines, I believe that L-glutamine may be prescribed to persons older than 5 years of age who have any sickle genotype and continue to have episodes of acute disease exac-

erbations despite appropriate use of hydroxyurea or to those who cannot or do not use hydroxyurea.

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