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Emerging Therapies in the Management of Acute Ischemic Stroke: Innovative Approaches and Clinical Outcomes- A Comprehensive Literature Review

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ABSTRACT

Worldwide, acute ischemic stroke continues to be the primary cause of death and disability, requiring ongoing improvements in treatment approaches. With an emphasis on current advancements in collateral evaluation, thrombolytic therapy, endovascular thrombectomy, and neuroprotective treatment, this review examines novel treatments for acute ischemic stroke.

To find relevant research published in the past five years, a thorough search of academic databases was carried out. The inclusion criteria for the inclusion of articles on innovative therapeutics and their implications for managing acute stroke were methodological rigor and direct relevance. With an emphasis on the effectiveness and safety of Tenecteplase, the review emphasizes the crucial role that collateral circulation plays in forecasting patient response to reperfusion treatments and the changing landscape of thrombolytic drugs. Furthermore, the treatment of acute strokes has been transformed by developments in endovascular thrombectomy, which provides better functional results for patients with major artery occlusions. Additionally, neuroprotective drugs have potential as complementary treatments, especially when used in combination with reperfusion procedures. Novel treatments for acute ischemic stroke provide fresh chances to improve patient outcomes and lower stroke-related morbidity and death. To provide equal access to improved stroke care, solve outstanding difficulties, and enhance treatment regimens, further research is required.

KEYWORDS: Acute ischemic stroke, management, innovative

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I. INTRODUCTION

In the US, acute ischemic stroke continues to be the primary cause of death and disability (1). A stroke's pathogenesis is diverse. While there may be no discernible difference in the way symptoms appear, ischemia accounts for 87% of acute stroke cases, intracranial hemorrhage (ICH) accounts for 10%, and subarachnoid hemorrhage accounts for 3%. Several risk variables and etiologies may be used to further categorize ischemic stroke into subtypes (2). A mix of clinical characteristics, imaging modalities, and clinical evaluations are used to identify these etiologies. The principal therapeutic choices, such as reperfusion therapy, may be influenced by accurately establishing the etiology of ischemic stroke.

The expression “time is brain” originated from the widespread belief in the early 1900s that severe ischemia caused irreparable damage minutes after symptoms appeared. Researchers discovered that this damage happens in two periods in the late 1970s. At the outset of a stroke, the core, or center portion of the infarct with extremely poor perfusion, is thought to be irrevocably damaged (3). But the penumbra, or region around the core, is made up of neurons that are only dormant and may be saved. While the structural integrity of these neurons is preserved, it is believed that their dysfunction is caused by ischemia-related metabolic and ionic disruptions. Over time, irreparably injured tissue enlarges as a consequence of a loss of perfusion to the penumbra (4).Reperfusion treatment aims to rescue as much neuronal tissue and preserve as much function as possible by restoring blood flow to the ischemic location. According to current practice recommendations, patients who qualify for alteplase should get fibrinolysis 3–4.5 hours after the beginning of symptoms.

II. METHODOLOGY

In order to methodically compile and assess pertinent literature from reliable academic sources, such as PubMed, Scopus, and Google Scholar, we used a comprehensive approach in our narrative review. To achieve a comprehensive examination of the issue, we modified known methodology from prior review studies, taking into account the intricacy of developing therapeutics in acute ischemic stroke.

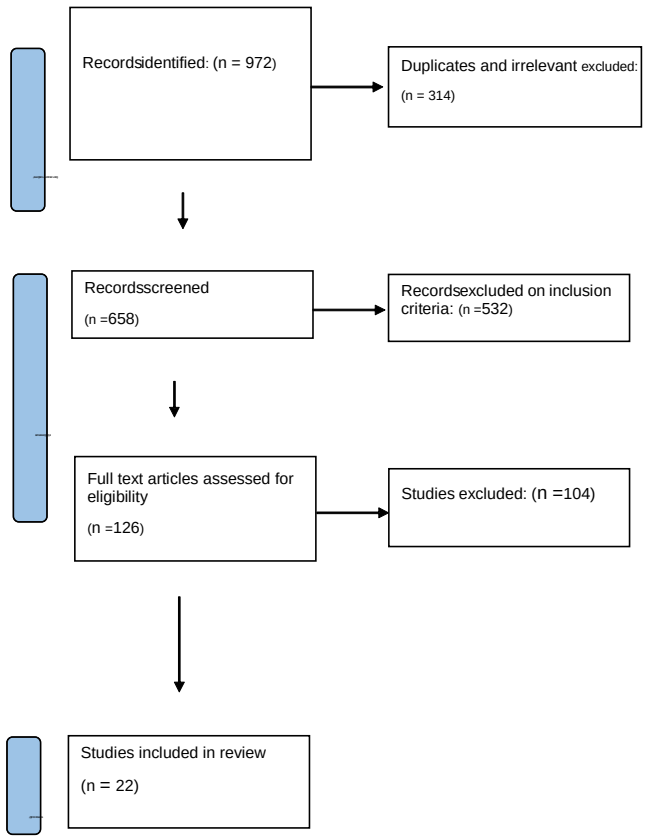
Inclusion and Exclusion Criteria:

We took into consideration publications written in English that were published in the recent ten years (2019–2024) and discussed new treatments for acute ischemic stroke. Included were studies with human subjects and those that provide light on new treatment strategies for acute ischemic stroke. On the other hand, research that had no direct bearing on the topic or that lacked rigorous methodology was not included. Every article that was found via preliminary screening using abstracts and titles was carefully evaluated to ascertain its applicability and appropriateness for publication in the review.

Categorization and Analysis:

To arrange and examine the information on novel treatments for acute ischemic stroke, we used a methodical classification methodology. The review's main goals were to clarify the function of novel treatments in the management of acute ischemic stroke and to draw attention to current developments and difficulties in the area. To investigate the effects of novel therapeutic approaches, such as thrombolytics, endovascular thrombectomy, and neuroprotective therapies, on patient outcomes and prognoses in acute ischemic stroke, analytical categories were developed. Examining these new medicines' underlying processes, clinical effectiveness, and possible synergies was the main goal of the review. Our goal in organizing the study around these themes was to provide readers a thorough understanding of how acute ischemic stroke care is developing.

PRSIMA FLOWCHART



III. RESULTS

A. Stratification by collateral status:

Patient outcomes may differ dramatically even with equal degrees of arterial blockage or recanalization with MT or tissue plasminogen activator (tPA). The length of time or gap that ischemic tissue may endure before cell death occurs depends on the degree of collateral perfusion, which is mediated by arteries from nearby vascular areas. While it is still generally true that the better the prognosis, the earlier the intervention is administered following the beginning of the stroke (5). Patients with stronger collaterals could gain more from their care than those with weaker collaterals.

Imaging may be used to assess collateral status. Digital subtraction angiography (DSA) is the gold standard for this kind of imaging, since it shows the temporal characteristics of the arterial, capillary, and venous phases of blood flow across the brain. Nowadays, magnetic resonance perfusion (MRP) or computed tomographic perfusion (CTP) are often used as a quicker and less intrusive substitute (6). The perfusion scans may be used to infer the presence of ischemia penumbra, or hypo-perfused tissue that is reliant on

collaterals, and ischemic core, or permanently infarcted tissue.

The DEFUSE trials, utilizing the RAPID automated software, established and verified thresholds for penumbra, defined as the time to maximum residual function (T max) exceeding 6 seconds, and core, defined as the brain volume where the apparent diffusion coefficient of magnetic resonance imaging (MRI) was less than 600×10^{-6} mm 2/s (7).

The cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) may all be computed using CTP. While increased MMT with reduced CBF and CBV is consistent with core, increasing MTT with maintained or increased CBV implies penumbra (8). A mismatch in volume between the penumbra and the core indicates reasonably strong collateral support and potentially recoverable tissue. Research shows that individuals with superior collaterals have better clinical outcomes after intervention, and that favorable collaterals decrease the transition of penumbra to core (6).

B. Advancements with fibrinolytics:

Despite the fact that alteplase has been the industry standard for more than 25 years, current research on the use of tenecteplase as a substitute thrombolytic has shown positive results. Third-generation thrombolytic drug tenecteplase is bioengineered to preserve our native tissue plasminogen activator's complete fibrinolytic function (4). It is 80 times more resistant to plasminogen activator inhibitor type 1 (PAI-1) than alteplase is. PAI-1 prevents tissue plasminogen activator from converting plasminogen to plasmin. An intravenous bolus administered over a 5-second period is possible due to the resistance to PAI-1, which causes a clearance that lasts four times longer than alteplase. Bolus administration has benefits, such as the ability to decrease drug mistakes and save nursing resources. Furthermore, tenecteplase has a 15-fold greater specificity for clot-bound fibrin than alteplase, which may lead to a decreased risk of bleeding and systemic fibrinogen depletion (4). These factors may contribute to tenecteplase's potential for a good safety profile.

Endogenous tissue-type plasminogen activator (tPA) is released by brain parenchyma cells that have been subjected to ischemia. Plasminogen coupled to fibrin is converted into plasmin by endogenous and recombinant tPA. After that, plasmin is released from plasminogen that is attached to fibrin, breaking apart fibrin molecules into fibrin degradation products. Types 1 and 2 of plasminogen activator inhibitors stop tPA from turning plasminogen into plasmin.

The effectiveness and safety of tenecteplase and alteplase have been directly compared in many studies. The goal of the 2022 NOR-TEST 2 Part A experiment was to determine whether tenecteplase 0.4 mg/kg was non-inferior to alteplase 0.9 mg/kg in patients with moderate to severe ischemic stroke, which was characterized as an NIHSS $\geq$6 (9). This was due to the initial NOR-TEST trial having a high proportion of patients with small stroke. The tenecteplase group had an imbalance in the rates of ICH with symptoms, which led to the early termination of this experiment. Additionally, compared to alteplase, tenecteplase was linked to a higher 3-month death rate and less good functional results. The NOR-TEST Part B study is now under progress to assess tenecteplase 0.25 mg/kg at a lower dosage (9).

Tenecteplase has recently been assessed for usage in the prehospital context due to the convenience of bolus delivery without the need for infusion pumps. Phase 2, randomized, open-label TASTE-A study was published in 2022 (10). It assessed the efficacy of tenecteplase 0.25 mg/kg vs alteplase in mobile stroke units (MSUs) for patients whose symptoms started within 4.5 hours. Researchers discovered that when tenecteplase was administered early in comparison to alteplase, there was a higher incidence of early reperfusion, a quicker rate of clinical recovery, and a shorter time to medication commencement. There were no reported safety issues. The AcT trial, a multicenter, open-label, phase 3 randomized controlled trial, provided additional support for these findings by showing that intravenous tenecteplase dosed at 0.25 mg/kg is as safe and effective as alteplase in patients who present within 4.5 hours of the onset of stroke symptoms (11).

While the majority of the existing research comprises of modest, phase-2 randomized-controlled trials, meta-analyses have provided supportive data about the safety and effectiveness of tenecteplase. Within six hours of the beginning of symptoms, Burgos and colleagues assessed five randomized-controlled studies comparing alteplase and tenecteplase. All all, they discovered no variation in sICH or in the functional result at 90 days (12). Prior to thrombectomy, Katsanos and colleagues examined data from four randomized controlled trials including patients with LVO (13). In comparison to patients receiving alteplase, they discovered that those getting tenecteplase had two times better chances of having good clinical outcomes at three months and three times higher odds of attaining effective recanalization.

An appealing fibrinolytic drug for those suffering from acute ischemic stroke is tenecteplase. According to recent research, tenecteplase seems to be similarly effective in terms of effectiveness and safety in addition to having advantageous pharmacological properties and an easy-to-administer dosage form. Tenecteplase given as a 0.25 mg/kg push (maximum, 25 mg) seems most suitable for acute ischemic stroke, based on the majority of data. Tenecteplase seems to be more effective than alteplase in individuals receiving thrombectomy if they have significant vascular occlusions.

C. Thrombolysis:

The effectiveness of using tPA was shown by a seminal research published in 1995 by the National Institute of

Neurological Disorders and Stroke. Subsequent research has broadened the inclusion criteria for tPA usage to include 4.5 hours following the beginning of symptoms since then (14). Benefits have been shown for a range of age groups, types of ischemic strokes, and stroke severity.

The use of tPA in patients with a moderate National Institutes of Health Stroke Scale (NIHSS) score is still unclear, nevertheless, since it does include a risk of bleeding. When compared to aspirin therapy alone, a recent research did not demonstrate any advantage in treating stroke patients with an NIHSS score of less than 5, although this trial was ended early due to poor trial enrollment (15). With varying degrees of success, several studies have attempted to extend the tPA time frame based on the presence of strong collateral markers. The WAKE-UP research included stroke patients who were sleeping at the time of the stroke, which is known as "wake-up" strokes. These patients had MRI acute diffusion restriction without any further chronic abnormalities on fluid-attenuated inversion recovery (FLAIR) sequences. In this cohort, tPA therapy increased symptomatic hemorrhagic transformation (HT) but also improved the 90-day functional outcome (16). In a different trial, patients with perfusion mismatch received tPA within a longer time frame of up to nine hours after the beginning of symptoms. Collateral perfusion was measured by either MRP or CTP (17). Although a larger proportion of patients in the therapy group had little to no impairments, their HT was more symptomatic.

D. Progress in Thrombectomy Technology:

Approximately 80% of patients with cerebral artery occlusions do not demonstrate recanalization with fibrinolysis alone, despite the fact that intravenous thrombolytics have transformed the management of acute ischemic stroke (18). In addition, many patients cannot utilize thrombolytics due to their many contraindications and limited therapy window. Treatment options for individuals with anterior big artery occlusions have been greatly enhanced by developments in nonpharmacologic endovascular thrombectomy, which mechanically removes clots. When patients with anterior major artery occlusions undergo endovascular thrombectomy instead of thrombolytics alone, significant studies have shown better functional results.

A multicenter, randomized clinical study as part of the historic MR CLEAN experiment to assess the functional results of intra-artery therapy for emergency revascularization in patients with proximal cerebral arterial blockage. If a patient could get treatment within six hours of the beginning of symptoms, they qualified. 81.5% of patients allocated to the treatment arm had retrievable stents in place, and 89% of the 500 recruited patients had received intravenous alteplase prior to randomization. With no significant differences in mortality or sICH, they discovered an absolute difference of 13.5% in the rate of functional independence favoring the endovascular intervention group (19). Subsequent to MR CLEAN, a number of additional seminal investigations, including as EXTEND-IA, ESCAPE, SWIFT PRIME, and REVASCAT, shown comparable results and reaffirmed the advantages of endovascular thrombectomy in conjunction with thrombolytics for qualifying patients (20)(6).

The effectiveness of reperfusion was shown to rely on the period from symptom onset as a proxy for salvageable tissue, much as in intravenous thrombolytic studies. The period from the last known well was used to calculate the patient's eligibility for endovascular thrombectomy. This included the patient's waking up with symptoms. After 7.3 hours, there was no discernible effect for endovascular thrombectomy, according to a meta-analysis of the previously stated studies (21). But rather of depending only on time, new developments in neuroimaging have developed a tissue-based method.

The effects of endovascular thrombectomy versus standard of care in patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery with a last known well within 6 to 24 hours were investigated in a multicenter, randomized controlled trial carried out by DAWN investigators. Furthermore, they only included individuals whose infarct volume, as determined by DWI or CTP, did not match the severity of their clinical deficiency. There were no appreciable variations in the incidence of ICH or death, however 49% of patients in the endovascular thrombectomy group and 13% in the standard of care group, respectively, attained functional independence at 90 days (22). Comparable outcomes were seen in the DEFUSE-3 study, which assigned patients to endovascular thrombectomy or standard of care based on the last known well, which occurred between 6 and 16 hours ago, and viable tissue found by perfusion imaging. They discovered that functional independence after endovascular treatment was 45%, whereas it was only 17% in the group receiving conventional care. Both mortality and ICH with symptoms were statistically insignificant (23).

According to current recommendations, patients with LVO in the anterior circulation who also fulfill other eligibility requirements for DAWN or DEFUSE 3 should have mechanical thrombectomy within 24 hours of the last known normal. Because posterior LVOs are linked with a high mortality rate and poor functional results, there is minimal evidence about thrombectomy for these types of lesions. According to a recent meta-analysis, individuals undergoing thrombectomy who had posterior LVOs were more likely to die but were less likely to get sICH than anterior LVOs undergoing thrombectomy (24). Additionally, functional results were poorer for individuals with posterior LVO. The authors discovered no variation in the successful recanalization rate. Because of these drawbacks, thrombectomy in patients with posterior LVO is assessed case-by-case, taking into account the pre-morbid mRS score, the site of the blockage, the last known well, and NIHSS.

E. Endovascular thrombectomy:

The use of intravenous thrombolytics as a stopgap measure before endovascular thrombectomy may theoretically result in quicker ischemia clearance, a smaller clot, and the breakdown of embolic debris downstream of the blockage. Delaying a final endovascular operation, raising the chance of ICH with symptoms, and embolizing a big vessel thrombus into a possibly inaccessible vessel are possible drawbacks (25). Recent studies have assessed the effectiveness and safety of endovascular thrombectomy alone in eligible patients with major artery occlusions who come to thrombectomy-capable facilities, taking into account the associated benefits and hazards.

Regarding the functional result in Chinese patients having a large-vessel blockage, two randomized controlled studies, DIRECT-MT and DEVT, indicated that endovascular thrombectomy alone was not inferior to endovascular thrombectomy followed with intravenous alteplase (26) (27). However, when it came to the functional result for Japanese patients, the SKIP randomized clinical study was unable to show that endovascular thrombectomy by itself was non-inferior (28). Notably, there are a few restrictions on these studies. The DIRECT-MT trial included broad confidence intervals around the main outcome and was powered for a large noninferiority margin. Using the fixed-margin technique, both DEVT and SKIP were powered for substantial noninferior margins instead of the smallest clinically meaningful difference. To more conclusively determine whether intravenous thrombolytics should be used in conjunction with endovascular thrombectomy in patients with anterior large-vessel occlusions, larger trials including a wider range of patients are required. Future research is also required to determine if alteplase should be taken into account prior to transfer to a facility equipped to perform an endovascular thrombectomy.

F. Neuroprotective treatment:

The goal of the current, successful treatment for acute stroke is to clear the artery blockage. Since the 1990s, research has been conducted to determine if pharmacologic and non-pharmacologic neuroprotective medicines may directly treat ischemic brain tissue; however, no significant progress has been made in this area. Excitotoxicity inhibitors, apoptosis inhibitors, free radical scavengers, and anti-inflammatory medicines are examples of candidate agent mechanisms (29). Interestingly, nevertheless, most neuroprotective clinical studies were conducted before the thrombectomy period. Adjunct administration of neuroprotective drugs during or after reperfusion represents an appealing but unproven therapeutic option. As shown in a study uric acid study, post hoc analysis have indicated that some neuroprotective medications are more advantageous in the sub-population of patients who received MT (6). A favorable safety profile that had been previously shown in Phase II/III clinical studies (ENACT, ESCAPE-NA1) was recently expanded upon by two randomized controlled trials (FRONTIER and ESCAPE-NEXT). Pre-hospital randomization and in-the-field delivery of intravenous nerinetide vs placebo by qualified paramedics in a population of suspected stroke patients constituted a significant departure from the FRONTIER design (30). This allowed for earlier administration than the in-hospital administration stipulated by ESCAPE-NEXT (inclusion within 12 h) or before hospital admission within 3 h following symptom start or last-seen normal (median of 60 min for nerinetide vs. 68 min for placebo). The findings of FRONTIER and ESCAPE-NEXT were presented at the 15th World Stroke Congress in Toronto, Canada, in October 2023. Publications of both studies are still forthcoming. Their findings already appear to be quite significant: It is evident from FRONTIER that the idea of pre-hospital, ultra-early neuroprotection may be used to "buy time" and improve the benefits of recanalization by postponing definitive brain infarction by "freezing the penumbra." ESCAPE-NEXT, a key Phase III study that used an exclusively in-hospital treatment regimen, was unable to show effectiveness, which is significant data whose interpretation is still up for debate (30). Subsequent attempts to substantiate this intriguing idea of neuroprotection either fail miserably or become considerably more challenging.

Tighter control over blood pressure and glucose in the early aftermath of an acute stroke has been studied in a few trials, but overall the results have not been encouraging (23)(24). The idea of stem cell treatment for regenerative medicine is appealing and well accepted in the medical community. There are now active trials looking at the transfer of stem cells both chronically, months to years after an ischemic stroke, and acutely, hours after the stroke. Although treatment has not yet shown functional effectiveness, initial data indicate that it is safe (25).

IV. DISCUSSION

A thorough analysis of new treatments for acute ischemic stroke is given in the narrative review, together with information on current developments, their clinical consequences, and potential future paths.

The significance of collateral circulation in influencing patient outcomes is a basic feature of the pathophysiology of acute ischemic stroke. The network of substitute blood vessels known as collateral circulation is what allows ischemic brain tissue to remain perfused in the case of arterial blockage. According to Liebkind and Liaw (2020), the review emphasizes how crucial collateral status is in predicting a patient's reaction to reperfusion therapy like thrombolysis and thrombectomy (6). Clinicians may now identify patients who would benefit most from prompt intervention thanks to the advancement of advanced imaging tools like digital subtraction angiography (DSA) and magnetic resonance

perfusion (MRP), which have completely changed the evaluation of collateral status.

The review places a lot of attention on the changing field of thrombolytic treatment for acute ischemic stroke, especially with regard to tenecteplase's potential as a fibrinolytic agent of the third generation. Higher fibrin specificity and a longer half-life are only two of the pharmacological benefits that tenecteplase has over alteplase, and these benefits might lead to better clinical results (4). Meta-analyses have shown the safety and effectiveness of tenecteplase, particularly in patients undergoing thrombectomy, and have highlighted the drug's potential to be a useful adjunct to acute stroke therapy protocols (12) (13).

The revolutionary effect of endovascular thrombectomy on acute stroke therapy is another important topic included in the study. For patients with large vessel occlusions (LVOs), endovascular thrombectomy has become a crucial strategy that improves functional outcomes and facilitates effective recanalization (19) . Endovascular thrombectomy has been widely used in clinical practice due to clinical studies like MR CLEAN and ESCAPE, which have shown its superiority over conventional therapy alone. Treatment options for patients who are not eligible for or resistant to thrombolytic therapy have been further extended by the incorporation of sophisticated thrombectomy devices and procedures (6).

The paper also discusses the prospects and difficulties in treating acute ischemic stroke with neuroprotective measures. Recent studies like FRONTIER and ESCAPE-NEXT have offered positive evidence on the effectiveness and safety of neuroprotective medications, especially when used in combination with reperfusion treatments, despite the mixed findings of earlier clinical trials (Stoll et al., 2024). The notion of providing neuroprotective medications as an adjuvant during or after reperfusion is a promising therapeutic approach that may augment the advantages of recanalization by maintaining ischemic penumbra.

V. CONCLUSIONS

The study concludes by offering a thorough summary of recently developed treatments for acute ischemic stroke, emphasizing developments in endovascular thrombectomy, collateral evaluation, thrombolytic therapy, and neuroprotective care. These advancements highlight how acute stroke treatment is changing and provide fresh chances to enhance patient outcomes and lessen the burden of stroke-related morbidity and death. Clinicians may improve the quality of life for stroke patients by using advances in pharmacology, imaging technology, and interventional procedures to provide prompt and customized therapies.

Notwithstanding the encouraging developments mentioned, a few drawbacks should be taken into account. First off, the review mostly uses data from meta-analyses and clinical trials, which might introduce biases related to patient selection and study design. Additionally, differences in patient demographics, the cause of stroke, and the healthcare settings across studies may restrict how broadly the results may be applied. Moreover, while the study encompasses a wide array of novel treatments, it could not include the whole of current investigations and advancements in the treatment of acute ischemic stroke.

Future studies on acute ischemic stroke should concentrate on resolving outstanding issues and investigating uncharted therapeutic territory. This entails improving the patient selection standards for novel treatments, such as neuroprotective therapies and collateral evaluation for thrombectomy eligibility. Furthermore, in order to guarantee that everyone has fair access to cutting-edge stroke care, efforts must be made to simplify delivery routes and enhance treatment processes. In addition, recent technical developments like telestroke networks and artificial intelligence show promise for improving stroke diagnosis, triage, and therapy selection. In order to fully use new therapeutics and eventually enhance outcomes for stroke patients throughout the globe, collaborative interdisciplinary research projects are crucial.

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