Clinical Practice Guidelines on the Management of Acute Ischemic Stroke and Intracerebral Hemorrhage in the Philippines

2024

The STROKE SOCIETY of the PHILIPPINES

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DISCLAIMER

This clinical practice guideline (CPG) is intended to be used by physicians and other health care professionals involved in the management of acute stroke. Although adherence to this guideline is encouraged by the Department of Health (DOH), it should not restrict the clinicians in using their clinical judgment and considering patient's values, needs, and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and their responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action.

Developers of this CPG are aware of its limitations. Evidence summaries are based on the best available scientific evidence at the time of its formulation. As such, certain aspects of the interventions or diagnostic tests may not be completely addressed by the included studies.

This CPG is not intended to cover the entirety of the management of acute stroke. It provides recommendations on interventions where variability in clinical practice and some controversies in decision-making exist.

EXECUTIVE SUMMARY

Stroke is the first leading cause of disability worldwide and the second leading cause of death in the Philippines. Though it has been the most common neurological disease in the country, there are considerable variations in the management observed among clinicians in the acute treatment of stroke.

This Clinical Practice Guideline (CPG) on Acute Stroke aims to give recommendations on the aspects of diagnosis and management in the acute phase of the disease, both ischemic and hemorrhagic stroke, where significant variability and controversy in clinical practice is noted. However, it does not aim to cover intermediate hospital management, rehabilitation, recovery, and prevention of stroke. It is intended to be used by general physicians and specialists, other healthcare professionals, policymakers to improve stroke diagnosis and acute stroke management. Its target beneficiaries are the patients in the acute phase of stroke (within 24 to 48 hours of stroke onset) and indirectly the whole of society in the Philippines.

This guideline is based on the current best available evidence, local resources, infrastructure, and the practice context in the country. Guideline recommendations were developed following a standard guideline development methodology outlined in the DOH CPG Manual 2018. The CPG development was organized, directed and spearheaded by the Steering Committee, while current best available evidence was comprehensively searched and reviewed by the Technical Working Group to address seventeen (17) questions. Twenty five (25) experts, comprised of a multi-sectoral panel of representatives, crafted consensus recommendations. All of the members of the Acute Stroke CPG Task Force were evaluated for any COI and any such COI identified were managed accordingly. The GRADE method was used to determine the direction and strength of each recommendation.

Twenty-one (21) recommendations were developed out of 17 clinical questions and their corresponding evidence summaries. Of these, a majority were strong recommendations and were based on moderate certainty of evidence. Further research will most likely have an important impact in our confidence regarding the estimates of the effect of each intervention or accuracy of the diagnostic tests included in this CPG.

Table 1. Summary of Final Recommendations, 2024 Clinical Practice Guidelines on the Management of Acute Ischemic Stroke and Intracerebral Hemorrhage in the Philippines

No.	Recommendations	Certainty of Evidence	Strength of Recommendation
Diagnosis			
1A	Among adult patients suspected with acute stroke within 6 hours, we recommend using non-contrast computed tomography (NCCT) or cranial magnetic resonance imaging (MRI) to rule out acute intracranial hemorrhage.	Moderate ⊕⊕⊕◯	Strong
1B	Among adult patients suspected with acute stroke within 6 hours, we recommend the use of cranial MRI to confirm the diagnosis of acute ischemic stroke.	Moderate ⊕⊕⊕◯	Strong
Acute Stroke Unit			
2	Among adult patients with acute stroke, we recommend admission in a stroke unit compared to the general ward.	Low ⊕⊕◯◯	Strong
Thrombolysis			
3	Among eligible patients with acute ischemic stroke <4.5 hours duration, we recommend the use of intravenous thrombolysis with alteplase.	Moderate ⊕⊕⊕◯	Strong
4	Among patients with acute ischemic stroke with less than 4.5 hours from onset of symptoms, we recommend the use of standard dose alteplase (0.9 mg/kg) over low dose alteplase (less than 0.9 mg/kg).	Low ⊕⊕◯◯	Strong
5	Among patients with acute ischemic stroke of less than 4.5 hours duration, we recommend the use of tenecteplase as an alternative to alteplase for intravenous thrombolysis.	Low ⊕⊕◯◯	Strong
Anti-thrombotic therapy			
6A	Among patients with acute minor non-cardioembolic acute ischemic stroke or high-risk transient ischemic attack within 24 hours from symptom onset, we recommend treatment with dual antiplatelet therapy using aspirin and clopidogrel for 21 days.	Moderate ⊕⊕⊕◯	Strong
6B	Among patients with acute minor non-cardioembolic ischemic stroke or high-risk transient ischemic attack within 24 hours of symptom onset, we suggest against treatment with dual antiplatelet therapy using aspirin and ticagrelor.	Moderate ⊕⊕⊕◯	Weak
Early mobilization			
7	Among acute stroke patients, we recommend against very early mobilization within 24 hours by trained staff (i.e., physical therapists, nurses).	Low ⊕⊕◯◯	Strong
Venous thromboembolism (VTE) prophylaxis			
8	Among immobilized inpatients with acute ischemic stroke, we suggest the use of anticoagulants (low-molecular-weight heparin or unfractionated heparin) versus no anticoagulants for DVT prophylaxis.	Low ⊕⊕◯◯	Weak
9	Among immobilized patients hospitalized with acute ischemic stroke or intracerebral hemorrhage, we recommend against the use of graduated compression stockings.	Low ⊕⊕◯◯	Strong
10	Among immobilized patients hospitalized due to acute ischemic stroke, we suggest the use of intermittent pneumatic compression.	Moderate ⊕⊕⊕◯	Weak

No.	Recommendations	Certainty of Evidence	Strength of Recommendation
11	Among immobilized patients hospitalized with acute ICH, we recommend the use of intermittent pneumatic compression, compared to standard care alone (non-use).	Moderate ⊕⊕⊕◯	Weak
Surgery for intracerebral hemorrhage			
12	Among adult patients with supratentorial spontaneous intracerebral hemorrhage and signs of increased intracranial pressure, surgical evacuation of hematoma on top of best medical management may be considered.	Low ⊕⊕◯◯	Weak
Decompressive hemicraniectomy			
13A	Among adult patients aged 60 years or younger with malignant MCA infarction, surgical decompression on top of medical management may be considered.	Moderate ⊕⊕⊕◯	Weak
13B	Among adult patients aged > 60 years with malignant MCA infarction, surgical decompression on top of medical management may be considered.	Low ⊕⊕◯◯	Weak
Neuroprotective agents			
14A	Among patients with acute ischemic stroke, we do not recommend the routine use of edaravone as add-on therapy.	Low ⊕⊕◯◯	Strong
14B	Among patients with acute intracerebral hemorrhagic stroke, we do not recommend the routine use of edaravone as add-on therapy.	Low ⊕⊕◯◯	Strong
15	Among patients with acute ischemic or hemorrhagic stroke, we do not recommend the routine use of citicoline as an add-on therapy.	Moderate ⊕⊕⊕◯	Strong
16	Among patients with acute ischemic stroke, we do not recommend the routine use of Cerebrolysin® as an add-on therapy.	Low ⊕⊕◯◯	Strong
17	Among patients with acute ischemic stroke, we do not recommend the routine use of NeuroAiD™.	Very Low ⊕◯◯◯	Strong

Chapter 1. INTRODUCTION

Background

According to the most recent WHO data published in 2017, stroke is the second leading cause of death in the Philippines.[1] Deaths totaled 87,402, or 14.12% of all deaths. The Philippines has an age-adjusted death rate of 134.74 per 100,000 population, ranking 29th in the world. Moreover, the stroke burden in the country showed an increasing prevalence of stroke from 0.9% in 2005 [2] to a range of 0.486—6% based on a 2022 systematic review.[3] Higher stroke mortality and morbidity rates are noted particularly in areas outside of major cities where access to quality stroke care is limited. The geographical barrier to access exacerbates the gaps in the foundation of the healthcare system. Addressing these gaps through a systems approach that includes governance, financing, and service delivery, among other things, is an important step toward improving overall stroke outcomes in the country.

Despite the persistent high burden of stroke locally, healthcare costs for stroke treatment remains to be expensive as health care is mostly private and payment is generally borne out-of-pocket. Nonetheless, efforts have been made in recent years to close financial and other gaps in stroke care across the country. The Philippine Health Insurance Corporation (PhilHealth) has increased the reimbursement coverage for acute stroke to PHP 76,000 for ischemic stroke and PHP 80,000 for hemorrhagic stroke cases.[5] The Department of Health (DOH) has also implemented the National Policy Framework on the Prevention, Control, and Management of Acute Stroke in the Philippines (Administrative Order No. 2020-0059) to increase acute stroke management capacity and establish Acute Stroke Ready Hospitals.[6]

Consistent with the goals of the DOH National Policy Framework, the DOH has aimed to develop protocols for acute stroke diagnosis, treatment, and related care in the form of clinical practice guidelines (CPGs) that are up to date, cost-effective, and applicable across the country. Thus, the Stroke Society of the Philippines (SSP), in collaboration with other relevant professional societies, spearheaded the development of this 2024 Clinical Practice Guidelines for the Management of Acute Stroke Infarction and Intracerebral Hemorrhage.

Objectives of the CPG

The objective of this Stroke CPG is to provide evidence-based recommendations to effectively manage individuals with acute stroke. These recommendations will thereby provide prompt, effective and feasible treatment options for both acute ischemic and hemorrhage stroke.

Scope of the CPG

This guideline provides framework, grounded in the latest evidence, to support clinicians in managing adult patients with acute ischemic stroke and intracerebral hemorrhage. They include recommendations for medical and surgical treatments, such as thrombolysis and antithrombotic therapy for ischemic stroke, and surgical intervention for intracerebral hemorrhage. This also evaluates the critical role of stroke units in acute care, current evaluations of neuroprotectants, strategies to prevent venous thromboembolism (VTE), and protocols for rehabilitation. While

designed to inform clinical practice, these guidelines do not replace individualized clinical judgment. They underscore the necessity of tailoring treatment to specific patient circumstances and preferences and reinforce the need for ongoing research to address unresolved challenges in acute ischemic stroke management.

Specific topics prioritized in this CPG include:

- **Diagnostic imaging:** What is the optimal brain imaging modality for acute stroke?
- **Thrombolysis:** Does the administration of thrombolysis improve outcomes after acute ischemic stroke?
- **Anti-thrombotic therapy:** Does the use of dual antiplatelet therapy within the first 48 hours from ictus improve outcomes in acute stroke?
- **Neuroprotective agents:** Does the use of neuroprotective agents (e.g., Citicoline, NeuroAiD™, Cerebrolysin®, Edaravone) improve outcomes for patients with acute stroke?
- **Stroke unit:** Does care in a stroke unit improve outcomes for people with stroke?
- **Decompressive hemicraniectomy:** Does decompressive hemicraniectomy improve the outcomes for patients with acute ischemic stroke? What is the optimal timing to perform decompressive hemicraniectomy in acute ischemic stroke?
- **Early mobilization:** Does early mobilization improve outcomes in acute stroke?
- **Surgery for intracerebral hemorrhage:** Does the use of surgical interventions improve outcomes for patients with acute ICH?
- **Venous thromboembolism prophylaxis:** What interventions prevent DVT/PE among immobile patients hospitalized for stroke?

Aside from these, other priority topics were also identified but were not yet discussed include the following:

- **Non-valvular atrial fibrillation:** What interventions lower the risk of stroke among people with non-valvular atrial fibrillation (e.g., non-vitamin K oral antagonists)?
- **Endovascular thrombectomy:** Does the use of interventional (endovascular) treatments improve outcomes in patients with ischemic stroke?

Target audience

These guidelines apply to all physicians and health care workers who treat and manage acute stroke patients. Although this guideline is intended primarily for clinicians, strong recommendations may be considered by policymakers in what they may mandate as practice standards and payers in what they will pay for.

References

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3. Collantes MEV, Zuñiga YMH, Uezono DR. Incidence and Prevalence of Stroke and its Risk Factors in the Philippines: A Systematic Review. Acta Med Philipp [Internet]. 2022Aug.15 [cited 2024Jan.31];56(14). Available from: **https://actamedicaphilippina.upm.edu.ph/index.php/acta/article/view/1753**

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5. Philippine Health Insurance Corporation. Philhealth Circular No. 2023-0021: Implementing Guidelines on the Case Rates for Acute Stroke. Available online at: https://www.philhealth.gov.ph/circulars/2023/PC2023-0021.pdf

6. Department of Health. Administrative Order No. 2020-0059. Available online at: **https://dmas.doh.gov.ph:8083/Rest/GetFile?id=662603**

Chapter 2. GUIDELINE DEVELOPMENT METHODOLOGY

Guideline preparation

This CPG was created in accordance with the Department of Health's 2018 Manual for Clinical Practice Guideline Development.[1] The Stroke Society of the Philippines was the facilitating agency for this CPG. This was conceptualized soon after the National Stroke Policy became an administrative order in 2020. One of the general guidelines of the National Stroke Policy is to develop protocols for acute stroke diagnosis and treatment and establish referral pathways aligned with the clinical practice guidelines that are updated, cost-effective and widely used nationwide. The CPG task force was composed of the following working groups: Lead CPG Developer/Steering Committee (SC), Oversight Committee (OC), Evidence Review Experts (ERE), and the Consensus Panel (CP). The individual members of these working groups were identified and convened after adequately coordinating with appropriate stakeholders and specialty societies.

The SC along with key stakeholders, namely Stroke Society of the Philippines, Philippine Neurological Association, Academy of Filipino Neurosurgeon, Philippine Heart Association, Philippine College of Physicians, Academy of Family Physicians, Emergency Medicine Physicians, Academy of Rehabilitation Medicine, Neuroradiologist, Interventional Radiologist, Stroke Nurse, a Stroke Survivor, and DOH, identified key areas that need to be addressed by the CPG and ranked outcomes according to its level of importance following the AGREE. This was done through series of consultative meetings both online and through email. These areas included variations in practice, controversies of some drugs, limitations in applicability of current recommendations in program implementation, and underuse or overuse of health technology. Clinical questions with its corresponding outcomes and level of importance were summarized and prioritized by the SC. The SC then finalized the scope and the final list of questions and forwarded them to the ERE for initiation of evidence synthesis.

The SC selected members of a Consensus Panel (CP) based on their knowledge, expertise, and potential conflicts of interest. The CP was composed of 13 multi-sectoral stakeholder groups, ranging from private and public practitioners, primary and specialty care physicians, stroke patient advocates, and program managers. The representatives for each stakeholder group were nominees of various specialty groups. Program managers, patient advocates, and stakeholders were invited by the SC to represent the views of patients and the public.

Evidence synthesis

This CPG employed the de novo mode of CPG development. Following the recommended CPG process in the DOH Manual on Practice Guideline Development, the GRADE approach was used.

Search Methods and Strategies

The Technical Working Group searched for all published local and international studies relevant to the clinical questions on various electronic search engines from database inception up to July 2023 using systematic search strategies. The evidence reviewers conducted literature search from April 2022 to July 2023. A comprehensive and systematic search was done through at least 2 electronic databases (i.e., MEDLINE and CENTRAL) using a combination of keywords and free-text search related to the Population, Intervention, Comparator, and Outcome for each guideline question. The references of included studies were also hand-searched to identify additional studies that may not have appeared in the database search. No language restrictions were applied. The individual search strategies and eligibility criteria for each PICO question is described in the Appendix.

If high-quality and up-to-date systematic reviews were available, they were used as the body of evidence to inform guideline recommendations. Randomized controlled trials (RCTs) were the preferred study design for questions on intervention effectiveness. For diagnosis-related questions, cohort or cross-sectional designs were sought. For other considerations such as cost, reviewers sought for cost-effectiveness studies whenever possible. If no appropriate CEA studies are available, costing estimates were gathered from private and local institutions and reported in the local currency as a range of possible cost. At least two reviewers independently evaluated the titles and abstracts of the search results, as well as their methodological quality. Meta-analyses were performed as needed to obtain overall effect estimates for each critical outcome. Following the GRADE Approach, each outcome and the entire body of evidence were assigned a certainty level (Table 2). For questions with varying levels of certainty across outcomes, the lowest quality outcome rated critical was used to determine the final certainty level. The Consensus Panel rated clinical outcomes for each guideline question on a numerical 1-9 scale based on GRADE categories, with scores of 7-9 being critical, 4-6 important, and 1-3 of limited importance for decision making.

Inclusion and Exclusion Criteria

For each research question, the scope (inclusion and exclusion criteria) of the literature search was dictated by the population, intervention, comparator, outcomes, and methodology. Refer to the Annex document for the inclusion and exclusion criteria of each question.

Study Quality (risk of bias) Assessment

The methodological quality of each study was appraised using the Cochrane Risk of Bias Tool (i.e., ROB1 tool) or QUADAS-2, whichever was applicable. Studies with similar PICO were pooled and the effect estimates were determined using RevMan 5.0.

Data Synthesis

A systematic synthesis of the evidence was done using RevMan 5.0 wherein appraisal of included studies in the review for each research question and the synthesis of their effect estimates for critical and important outcomes were analyzed. The synthesized data are then compiled into an evidence summary. The balance of benefits and risks became the basis for the draft recommendations. The evidence summaries guided the consensus panel meetings in the decision-making process of the multi-sectoral consensus panel.

Table 2. Certainty in the effect estimates (quality of evidence) in GRADE.

Certainty	Definition and Implications	Randomized trials	Observational studies
HIGH ⊕⊕⊕⊕	The group is very confident that the true effect lies close to that of the estimate of the effect. (Further research is very unlikely to change confidence in the effect estimate)	No serious flaws in study quality	Extremely strong association and no major threats to validity
MODERATE ⊕⊕⊕◯	The group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. (Further research is likely to have an important impact)	Serious flaws in design or execution; quasi-experimental design	Strong consistent association and no plausible confounders
LOW ⊕⊕◯◯	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect. (Further research is very likely to have an important impact)	Very serious flaws in design or execution	No serious flaws in study quality
VERY LOW ⊕◯◯◯	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. (The estimate of effect is very uncertain)	Very serious flaws and at least one other serious threat to validity	Serious flaws in design and execution

Evidence to decision

Face-to-face en banc meetings were held on three dates (February 4, 2023; December 8, 2023; December 15, 2023) which was led by a skilled meeting facilitator / methodologist. To achieve quorum, at least 75% of the panelists was required to be present. Evidence summaries were created and distributed to all Consensus Panelists prior to the meeting. Draft recommendations were formulated by the Technical Working Group based solely on their assessment of the balance between the desirable and undesirable consequences of the intervention/diagnostic test.

Generation of recommendations

Certainty of Evidence and Strength of Recommendations

The certainty of the evidence (CoE) for each outcome of interest was assessed using GRADEPro, which considers the risk of bias and the presence or absence of any indirectness, imprecision, inconsistency, and other considerations (i.e., publication bias). The overall certainty of the evidence was based on the lowest certainty rating of the top seven (7) critical and important

outcomes. The rating of importance of outcomes into critical, important, or relevant was decided on by the multi-sectoral consensus panel.

Rating of Outcomes

The Consensus Panel members reviewed the evidence and the draft recommendation by the Technical Working Group. Through an online survey, they determined the relative importance of all outcomes for each research question in clinical decision-making. Each outcome was scored on a scale of 1 to 9. Outcomes rated 7 to 9 were considered as critical outcomes; 4-6 were considered as important but not critical outcomes; and, those outcomes that were rated 1 to 3 were considered of limited importance. The CP members determined the top seven (7) critical and/or important outcomes for each of the research questions.

Consensus Process

During each en banc meeting, the lead evidence reviewer first presented an overview of the evidence synthesis. The Consensus Panel was then given the opportunity to raise any clarifications or concerns about the evidence presented using a nominal group technique. This technique used a consensus strategy to reach an agreement by systematically reviewing literature, soliciting feedback from stakeholders, and relying on the judgment of experts in the field. Issues considered in determining the direction and/or strength of recommendation included the following: (1) the balance between the benefits and harms of the intervention/test, (2) overall certainty in the evidence for benefits and harms, (3) cost and resource implications, (4) patient or clinician values and preferences, (5) availability and feasibility of the test/intervention, and (6) other factors.

Panelists were then asked to vote "YES," "NO," or "ABSTAIN" for each draft recommendation's direction and strength by raising color-coded flags. Consensus was reached when at least 75% of panelists agreed on the direction and strength of the recommendation. When consensus was not reached, each panelist was asked to explain their vote, and another round of voting began. The procedure was repeated up to three times until agreement was reached. Questions that remained unresolved after three rounds of voting were addressed offline using a modified Delphi approach and the same consensus-building process.

Panelists voted on the direction (i.e., for, against) of recommendations based on their assessment of the desirable and undesirable effects of the intervention/test on outcomes classified as “critical.” A **strong recommendation** was given when the consensus panel was confident that the intervention or test's desirable effects outweighed its negative effects, or vice versa. A **weak recommendation** was issued when the panel was unsure about the trade-offs due to a lack of high-quality evidence, imprecise estimates of benefit or harm, the recommendations' limited applicability to specific populations or settings, or if the anticipated benefits come at a high cost. A standardized language was used to indicate the direction and strength of each recommendation. (e.g., “We suggest” for weak/conditional recommendations, “We recommend” for strong recommendations).

Editorial independence

The Stroke Society of the Philippines (SSP) funded this CPG but had no influence on the final recommendations made at the end of the en banc meetings. Furthermore, any competing interests of each member of the guideline development group (i.e., Steering Committee, Oversight Committee, Consensus Panel, and Technical Working Group) were adequately documented at the start of the CPG development process.

Each member of the Stroke CPG Working Group was asked to complete a Declaration of COI form, which required them to declare any potential financial or intellectual conflicts of interest (COI) that existed in the four years preceding their involvement in the project. A COI Oversight Committee then reviewed each submission, classified each member's COI status, and advised the Steering Committee on the allowed level of participation. The COI classification by the COI Oversight Committee are as follows:

1. **Allowed/Acceptable**– If an individual has no intellectual nor financial conflicts of interest
2. **Manageable B (Broadcast)** – Usually, if an individual only has intellectual conflicts of interest. They can vote but need to declare their intellectual conflicts (e.g., affiliation with institutions, positions in an organization, authorship in paper or related CPG) during the en banc meetings
3. **Manageable C** – For some intellectual and financial conflicts of interest, panelists cannot vote but they can share their expertise to the group. Examples include panelists from government agencies directly involved in the implementation of the program and panelists from the agency funding the guidelines. The specific terms of management shall be set forth by the OC and shall relate to specific clinical questions.
4. **Disqualified** – If an individual has both serious financial and intellectual conflicts of interest can affect the individual's objectivity and independence in decision making

Composition of the Guideline Development Group

Steering Committee

Table 3. Steering Committee Members.

No.	Name	Area of Expertise	Affiliation	Sex	Summary of disclosures or other relevant interest
1	Dr. Maria Epifania Collantes	Vascular neurology, Clinical epidemiology	Stroke Society of the Philippines	F	**Manageable B** speaker for Angel's Initiative
2	Dr. Manuel Mariano	Neurosurgery	Stroke Society of the Philippines	M	**Manageable B** Stocks for Gamma Knife, Capitol Medical, VRP Medical Center
3	Dr. Ma. Cristina Z. San Jose	Vascular neurology	Stroke Society of the Philippines	F	**Manageable B** Speaker's Bureau for pharma companies
4	Dr. Ma. Cristina Valdez	Vascular neurology	Stroke Society of the Philippines	F	**Manageable B** Lecturer for NOACs; speaker for neuro aid and cerebrolysin
5	Dr. Felix Eduardo Punzalan	Cardiology, clinical epidemiology	Philippine Heart Association (PHA)	M	**Manageable A** Lecturer for Merck, Sanofi, BI, Servier ; Member of APSAP, PLAS ; Stocks at MDH (<0.1%)

Evidence Reviewer Experts

Table 4. Evidence Review Experts.

No.	Name	Area of Expertise	Summary of disclosures or other relevant interest
1	Mr. Howell Henrian Bayona	Speech-language pathology, clinical epidemiology	**Acceptable** No financial or non-financial conflicts of interest
2	Dr. Fasi Goldanne Buenaflor	Vascular neurology	**Manageable B** With stocks in Conjug8
3	Dr. Christian Co	Vascular neurology	**Manageable B** Research on thrombolysis
4	Dr. Kristine Anne Co	Vascular neurology	**Acceptable** No financial or non-financial conflicts of interest
5	Dr. Lennie Lynn de Castillo	Vascular neurology	**Manageable B** With stocks in Pasig Doctors
6	Dr. Francesca Rose De Leon	Vascular neurology	**Manageable B** Consultant, PHC
7	Dr. Sharimah Diamla	Vascular neurology	**Acceptable** No financial or non-financial conflicts of interest
8	Dr. Clare Angeli Enriquez	Vascular neurology	**Acceptable** No financial or non-financial conflicts of interest

No.	Name	Area of Expertise	Summary of disclosures or other relevant interest
9	Dr. Marian Irene Escasura	Vascular neurology	**Acceptable** No financial or non-financial conflicts of interest
10	Dr. Anna Angelica Macalalad-Josue	Clinical epidemiology, Guideline methodology, Adult endocrinology	**Acceptable** No financial or non-financial conflicts of interest
11	Dr. Anna Marie Joyce Tenorio Javier	Vascular neurology	**Manageable B** Speaker for Neuroaid
12	Dr. Dan Neftalie Juangco	Vascular neurology	**Manageable B** Interventional neurologist
13	Dr. Muktader Kalbi	Vascular neurology	**Acceptable** No financial or non-financial conflicts of interest
14	Dr. Kathreen Jane Lara	Vascular neurology	**Acceptable** No financial or non-financial conflicts of interest
15	Dr. Jonray Magallanes	Adult pulmonology	**Acceptable** No financial or non-financial conflicts of interest
16	Dr. Jennifer Justice Manzano	Vascular neurology	**Manageable B** With advise to Medrano; speakers bureau (Bayer, Medichem, Otsuka, Ever, Echimes); SC for Angel's Initiative (BI); worked for Novartis
17	Dr. Remy Margarette Berroya Moreno	Vascular neurology	**Acceptable** Visiting Consultant, NKTI
18	Dr. Belinda Mesina-Nepomuceno	Vascular neurology	**Manageable B** Medical Specialist II, Rizal Medical Center; BOT - SSP
19	Dr. Harjoland Obenieta	Spine surgery, Orthopedics	**Acceptable** No financial or non-financial conflicts of interest
20	Dr. Diana Lynn Que	Vascular neurology	**Acceptable** No financial or non-financial conflicts of interest
21	Dr. Julie Ann Kristy Torres	Vascular neurology	**Acceptable** No financial or non-financial conflicts of interest
22	Dr. Patrick Yalung	Vascular neurology	**Manageable B** Treasurer, Philippines Neurocritical Care Society

Consensus Panel

Table 4. Consensus Panel Members.

No.	Stakeholder Group	Members	Expertise	Sex	COI Assessment	COI Disclosure	Sessions attended		
							02/04/23	12/08/23	12/15/23
1	Stroke Society of the Philippines (SSP)	Dr. Artemio Roxas, Jr.	Vascular neurology, clinical epidemiology	M	**Manageable B** (Q6, 8, 11) **Acceptable/ allowed** (all other Qs)	Research on Edoxaban & Dabigatran Advisory Board, Rivaroxaban and Xaretlo; Board of Trustee, Phil Headache Society; Past president, SSP	Y	N	Y
		Dr. Johnny Lokin	Adult neurology	M	**Manageable B** (Q6, 8-11, 14-17) **Acceptable/ allowed** (all other Qs)	Speakers Bureau, for the following: Moleac, Natrapharm, Otsuka, Everpharma, Pfizer, Menarini, Torrent	Y	N	Y
		Dr. Pedro Danilo Lagamayo	Radiology	M	**Disqualified** (Q1) **Acceptable/ allowed** (all other Qs)	Owns stocks in a laboratory	Y	Y	Y
2	Philippine Neurological Association (PNA)	Dr. Guillermo L. Manalo III	Neurology	M	**Manageable B**	Stroke Unit Manager at Mariano Marcos Hospital; Member, SSP – Ilocos chapter; Member - Angels advocacy on Stroke (sponsored by BI)	Y	Y	Y
		Dr. Maria Teresa Cañete	Neurology	F	**C - Manageable with major Constraints**	Research Grant from janssen, Stocks in Cebu Doctors; Research on Neuroaid	Y	Y	Y

No.	Stakeholder Group	Members	Expertise	Sex	COI Assessment	COI Disclosure	Sessions attended		
							02/04/23	12/08/23	12/15/23
		Dr. Loreto Talabucon Jr.	Vascular neurology	M	**Disqualified** (Q3-6, 13-17) **Acceptable/ allowed** (all other Qs)	Research on thrombolysis, neuro aid and other studies; Speaker for various drug companies related to the subject of the CPG	Y	Y	Y
3	Academy of Filipino Neurosurgeons, Inc. (AFN)	Dr. Lynne Lourdes Lucena	Neurosurgery	F	**Acceptable/ allowed**	Works in a regional training and teaching hospital	Y	N	N
		Dr. Jay Villavicencio	Neurosurgery	M	**Manageable B** for questions on surgery	Proctor for Stryker	N	Y	Y
		Dr. Peter Rivera	Neurosurgery	M	**Acceptable/ allowed** (all other Qs)	Lectures on aneurysm, and mechanical thrombectomy	Y	N	N
4	Philippine Academy of Rehabilitation Medicine (PARM)	Dr. Myrna S. Estrada	Rehabilitation medicine	F	**Manageable B**	Researches on Stroke Rehabilitation	N	Y	Y
		Dr. Jose Alvin Mojica	Rehabilitation medicine	M	**Acceptable/ allowed** (all other Qs)	Chair of Rehabilitation Medicine in Manila Doctors Hospital (MDH); Stocks at MDH (<0.1%)	Y	N	N
		Dr. Ephraim Gambito	Rehabilitation medicine	M	**Acceptable/ allowed** (all other Qs)	Adviser, Phil. Academy of Rehab Med.	Y	Y	N
5	Philippine College of Emergency Medicine (PCEM)	Dr. John David Comandante	Emergency medicine	M	**Acceptable/ allowed** (all other Qs)	Medical officer in Ospital ng Maynila; Works at PGH ER Med & at Urgent Care; PCEM Board of Director; Stocks at Medical Center Paranaque (<0.1%)	Y	N	Y

No.	Stakeholder Group	Members	Expertise	Sex	COI Assessment	COI Disclosure	Sessions attended		
							02/04/23	12/08/23	12/15/23
		Dr. Jeremy Cordero	Emergency medicine	M	**Acceptable/ allowed** (all other Qs)	Consultant, Ospital ng Makati; ER Head, Jesus Delgado Memorial Center; EMS Advocacy; Part of the technical group working on EMS Training, TESDA	Y	Y	Y
		Dr. Richard Henry Santos	Emergency medicine	M	**Acceptable/ allowed** (all other Qs)	Training officer, Pasig City Gen; Board member, PCEM	Y	N	Y
6	Philippine Heart Association (PHA)	Dr. Richard Henry P. Tiongco II	Cardiology	M	**Acceptable/ allowed** (all other Qs)	Lecturer for Sanofi, Servier; PHA Board of Director; Stocks at MCM (<0.1%)	Y	N	N
7	Philippine College of Physicians (PCP)	Dr. Rodney Jimenez	Interventional cardiology	M	**Acceptable/ allowed** (all other Qs)	Lecturer for Sanofi; PCP Board of Regents	Y	Y	N
8	Philippine Academy of Family Physicians (PAFP)	Dr. Jane Eflyn Lardizabal-Bunyi	Family medicine, clinical epidemiology	F	**Acceptable/ allowed** (all other Qs)	Treasurer, PAFP	Y	Y	Y
		Dr. Frederick Agustin	Family medicine	M	**Acceptable/ allowed** (all other Qs)	PLM Chair & Training officer; Treasurer of PAFP	Y	Y	Y
		Dr. Cheridine P. Oro-Josef	Family medicine, geriatrics	F	**Acceptable/ allowed** (all other Qs)	Board member, Philippine College of Geriatric Medicine	Y	N	N
9	Department of Health (DOH)	Dr. Ruth Divine D. Agustin	Public health	F	**Manageable B**	DOH Medical Officer	Y	Y	Y
10	Philippine Society of Neuroradiology (PSNHNR)	Dr. Irma David-Kintanar	Neuroradiology	F	**Manageable B** (Q1) **Allowed** (all Qs)	Board of Examiner, CT MRI Society of the Phils.	Y	Y	Y

No.	Stakeholder Group	Members	Expertise	Sex	COI Assessment	COI Disclosure	Sessions attended		
							02/04/23	12/08/23	12/15/23
11	Philippine College of Radiology (PCR)	Dr. Victor Erwin D. Jocson	Interventional neuroradiology	M	**Acceptable/ allowed** (all other Qs)	Lecture on thrombectomy & neuro intervention drugs; Stocks in Makati Med (<0.1%)	Y	N	N
12	Critical Care Nurses Association of the Philippines (CCNAPI)	Diana Jean Serondo	Critical care nursing	F	**Manageable B** (Q3-5, 8, 11)	Lecturer for stroke (thrombolysis & anti-coagulation); Angel's Initiative (receives salary from Boehringer Ingelheim) ; Secretary of Critical Care Nurses Association	Y	Y	N
13	Patient representative	Ms. Lourdes Amarillo	Stroke survivor/ patient advocate	F	**Acceptable/ allowed** (all other Qs)	Associate professor, University of the Philippines Manila	Y	Y	Y

Chapter 3. EVIDENCE AND FINAL RECOMMENDATIONS

Diagnosis

Q1. Should we use non-contrast cranial computed tomography (NCCT) compared to cranial magnetic resonance imaging (MRI) in diagnosing patients suspected of having acute stroke within 6 hours?

RECOMMENDATION 1A:

Among adult patients suspected with acute stroke within 6 hours, we recommend using either non-contrast computed tomography (NCCT) or cranial magnetic resonance imaging (MRI) to rule out acute intracranial hemorrhage.

Overall Level of Certainty: **Moderate** ⊕⊕⊕◯
Strength of Recommendation: **Strong**

RECOMMENDATION 1B:

Among adult patients suspected with acute stroke within 6 hours, we recommend using cranial MRI to confirm the diagnosis of acute ischemic stroke.

Overall Level of Certainty: **Moderate** ⊕⊕⊕◯
Strength of Recommendation: **Strong**

CONSENSUS ISSUES

The consensus panel recommended either NCCT or MRI for ruling out acute intracranial hemorrhage (ICH) due to their high specificity. As a result, symptomatic ICH can be accurately ruled out with either test, and thrombolysis and/or medical management can be initiated immediately. The panel made a strong recommendation based on the moderate certainty in the reported diagnostic accuracy estimates.

The panel also strongly recommended using cranial MRI to confirm the diagnosis of acute ischemic strokes due to the moderate certainty of evidence indicating that it is more sensitive than NCCT. Because MRI findings allow for better visualization of the location and size of infarcts, subarachnoid hemorrhages, and small bleeds, it is expected that non-specialists / primary care physicians will be able to accurately interpret results. However, the panel identified potential barriers to effective implementation of this recommendation, including limited availability of MRI and trained radiologists, particularly in low-resource settings, higher costs for patients, a longer time required to perform the test, greater familiarity of community practitioners with NCCT, and known contraindications for some patients.

In the following situations, clinicians may consider using cranial MRI and NCCT:

Table Q1.1. Suggested indications for cranial MRI and NCCT.

Cranial MRI	NCCT
1. Patients with symptom onset of less 6 hours. 2. Patients with unknown time of symptom onset. 3. Patients with "wake-up stroke" 4. Patients with minor stroke or NIHSS ≤ 4 5. Patients with posterior circulation stroke 6. Patients with transient ischemic attack	1. Patients with symptoms suggestive of intracranial hemorrhage 2. Patients with head trauma 3. If patient cannot tolerate MRI procedure due to claustrophobia or discomfort during the procedure. 4. If patient has metallic implants, pacemakers and prosthetic valves that are MR incompatible, and morbidly obese or heavy weight patients. 5. If cranial MRI is not accessible.

BACKGROUND

Stroke is the 2nd leading cause of death in the Philippines following ischemic heart disease.[1] It requires immediate response to prevent permanent disability and possible death. Reversal of acute stroke symptoms with the administration intravenous thrombolysis within 3 to 4.5 hours from symptom onset or performing mechanical thrombectomy among eligible patients can drastically improve clinical outcomes.[2,3]

Providing an immediate diagnosis of acute stroke is important to identify patients who may be given intravenous thrombolysis. Cranial magnetic resonance imaging (MRI) or non-contrast computed tomography (NCCT) may be performed to confirm the stroke diagnosis. However, NCCT comes at a lower cost and is more readily available locally compared to MRI.[4-6] This review aimed to synthesize evidence regarding the diagnostic accuracy of both imaging modalities for acute stroke.

SUMMARY OF THE EVIDENCE

Evidence considered

One prospective, single-center, cohort study performed in the USA compared the sensitivity and specificity of NCCT and MRI in the emergency diagnosis of acute stroke within 3 hours, 3-12 hours, and 12-24 hours of symptom onset.[7] This study also compared the accuracy of either imaging modalities for differentiating acute ischemic stroke from hemorrhagic stroke. A total of 356 adult patients suspected to have an acute stroke were recruited. Primary outcomes were sensitivity and specificity in detecting acute stroke. Subgroup analysis was performed to determine accuracy in differentiating between ischemic versus hemorrhagic stroke cases. The study was appraised to have low risk of bias.

Benefits and harms

<u>Diagnostic accuracy</u>

Cranial MRI demonstrated higher accuracy for diagnosing an acute stroke (83% sensitivity, 97% sensitivity) compared to NCCT (26% sensitivity, 98% specificity). Subgroup analysis according to type of stroke showed cranial MRI to have higher sensitivity (83%) than NCCT (16%) for ischemic stroke cases. Both MRI and NCCT exhibited high specificity at 96% and 98%, respectively.[7] For

intracranial hemorrhage, both tests were 100% specific but NCCT had higher sensitivity (89%) than cranial MRI (81%).

Table Q1.1. Summary of findings: cranial MRI and non-contrast CT for acute stroke.

Outcomes	Basis	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Diagnostic accuracy of MRI for acute stroke	1 observational study (N=356)	**Sn 0.83** (0.78, 0.88) **Sp 0.97** (0.92, 0.99)	High sensitivity and specificity	MODERATE ⊕⊕⊕◯
Diagnostic accuracy of NCCT for acute stroke	1 observational study (N=356)	**Sn 0.26** (0.20, 0.32) **Sp 0.98** (0.93, 0.99)	Poor sensitivity, high specificity	MODERATE ⊕⊕⊕◯
Diagnostic accuracy of MRI for acute intracranial hemorrhage	1 observational study (N=356)	**Sn 0.81** (0.61, 0.93) **Sp 1.00** (0.98, 1.00)	High sensitivity and specificity	MODERATE ⊕⊕⊕◯
Diagnostic accuracy of MRI for acute intracranial hemorrhage	1 observational study (N=356)	**Sn 0.89** (0.70, 0.97) **Sp 1.00** (0.98, 1.00)	High sensitivity and specificity	MODERATE ⊕⊕⊕◯
Diagnostic accuracy of MRI for acute ischemic stroke	1 observational study (N=356)	**Sn 0.83** (0.77, 0.88) **Sp 0.96** (0.92, 0.99)	High sensitivity and specificity	MODERATE ⊕⊕⊕◯
Diagnostic accuracy of NCCT for acute ischemic stroke	1 observational study (N=356)	**Sn 0.16** (0.12, 0.23) **Sp 0.98** (0.94, 0.99)	Poor sensitivity, high specificity	MODERATE ⊕⊕⊕◯

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

In terms of diagnostic performance at different time windows from symptom onset (i.e., <3 hrs, 3-12 hrs, > 12 hrs) both NCCT and cranial MRI demonstrated similar accuracies. NCCT showed highest sensitivity between 3-12 hrs (29% sensitivity, 97% specificity) compared to < 3 hrs (27% sensitivity, 100% specificity) or > 12 hrs (22% sensitivity, 98% specificity) from symptom onset. The sensitivity of cranial MRI increased with greater interval from symptom onset: <3 hrs (76% sensitivity, 96% specificity), 3-12 hrs (81% sensitivity, 98% specificity), and > 12 hrs (91% sensitivity, 97% specificity).

NCCT has the following sensitivity and specificity in diagnosing acute ischemic stroke in this time window (>12 hours 16%, 98%; 3-12 hours 20%, 96%; <3 hours 12%, 100%) and cranial MRI has the following sensitivity and specificity in diagnosing acute stroke in this time window (> 12 hours 92%, 96%; 3-12 hours 81%, 99%; < 3 hours 73%, 92%).

Safety outcomes

Adverse events related to the test were not measured in the included study. No other published literature specifically comparing the safety of NCCT and cranial MRI were found. Plain cranial CT scans use relatively low doses of radiation and are considered relatively safe. Cranial MRI was also reported to be safe as it does not require radiation, however, may be contraindicated in patients with metallic implants, claustrophobia, or sensitivity to contrast media.

Certainty of evidence

The certainty of evidence was rated moderate.

Other considerations

Cost and cost-effectiveness

NCCT is cheaper than cranial MRI in the Philippines. The cost of a plain cranial MRI ranges from PHP 5,000 to 12,000. On the other hand, plain cranial CT scan costs between PHP 4,000 to 9,000 depending on the institution where it is performed.[6,8] Although cranial MRI is proven to be more sensitive, other studies have shown that NCCT alone is sufficient for diagnosing acute strokes.[2,6,8] CT may be more cost-effective since clinicians will depend on the clinical presentation of the patient prior to requesting for neuroimaging.

Patient's values and preferences, equity, acceptability, and feasibility

No studies were found investigating patient's values and preferences as well as equity, acceptability, and feasibility considerations related to the cranial MRI or cranial CT scan.

Recommendations from other groups

The 2019 American Heart Association (AHA) strongly recommends NCCT to be effective in identifying intracerebral hemorrhage before intravenous thrombolysis administration among acute ischemic stroke patients who are candidates for thrombolysis (Class 1 – strong; Level of evidence: A – high).[9]

AHA also strongly recommended cranial MRI as an effective test to exclude intracerebral hemorrhage before intravenous thrombolysis administration in acute ischemic stroke patients who are candidates for thrombolysis (Class 1 – strong; Level of evidence B-NR - moderate).[9]

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Acute Stroke Unit

Q2. Should we routinely admit patients with acute stroke in a stroke unit instead of a general ward?

RECOMMENDATION 2:

Among adult patients with acute stroke, we recommend admission in a stroke unit compared to the general ward.

Overall Level of Certainty: **Low** ⊕⊕◯◯
Strength of Recommendation **Strong**

CONSENSUS ISSUES

A strong recommendation was made in favor of stroke units due to their perceived benefits in terms of improving functional outcomes and all-cause mortality, even though effect estimates for these outcomes were of low certainty. To facilitate the implementation of this recommendation, the stroke team composition and facility characteristics must be defined. Neurologists or trained internists, stroke nurses, physiatrists, and allied health rehabilitation specialists were identified as critical members of a stroke team.

BACKGROUND

Guidelines have demonstrated various stroke treatment and management strategies. One of these is admission to an organized inpatient care facility, such as a stroke unit (SU). SU is a specialized, geographically defined hospital unit that manages stroke patients.[1] The multidisciplinary team includes neurologists, cardiologists, radiologists, interventional surgeons, nurses, physiotherapists, occupational therapists, speech and language therapists, dieticians, and social workers.[2] Organized inpatient care for stroke patients can be provided in a ward dedicated for acute stroke patients (stroke ward), a peripatetic team looking after patients with stroke across a range of wards (mobile stroke team), or in a generic setting seeking to improve care for people with stroke within a mixed rehabilitation ward.[3] A general ward on the other hand, is a room where care is provided in an acute medical or neurology ward without routine multi-disciplinary input.[3]

Numerous randomized controlled trials have demonstrated that care in a stroke unit reduces death, disability, and the need for institutionalized care when compared to the general ward.[1,2] To date, however, there are only around 50 established SUs in the country, most of which are located either government or private hospitals in Metro Manila.[4]

SUMMARY OF THE EVIDENCE

Evidence considered

Fifteen RCTs compared outcomes of stroke patients (n=3,523) admitted in a stroke unit versus those in a general ward.[5-20] All the studies included adult patients with acute stroke diagnosed clinically within 24 hours up to 7 days to as long as 9 weeks[16] after symptom onset, excluding subarachnoid hemorrhage and subdural hematoma. Only patients with mild to moderate stroke severity were included while those who were deeply unconscious were excluded. One trial had unpublished data[17], which the reviewers were able access by contacting the trial author.

Six trials[6,10-12,15,16] compared mixed rehabilitation ward with a general ward, while one trial[18] compared a mobile stroke team versus the general ward. Of the 15 trials, only 2 specified the type of stroke[14,18] admitted in the intervention group (i.e., ischemic infarct).

The primary outcome measures include poor outcome defined as a modified Rankin scale (mRS) of 3 to 6, or requiring institutional care at the end of scheduled follow up; length of hospital stay; and all-cause mortality or death. Other outcome measures mentioned include place of residence, NIHSS score, and patient satisfaction. Follow-up duration varied from 6 months to 1 year.

Benefits and harms

Reduction in the odds of poor outcome

Compared with the general ward, admission in a stroke unit showed a reduction in the odds of poor outcome at the end of follow-up (OR 0.78 [95% CI 0.68 to 0.91]; 14 RCTs; n=3,321; low certainty).

Reduction in length of hospital stay

Stroke unit care showed no significant reduction in length of hospital stay (WMD -2.19 [95% CI -5.19 to 0.82]; 10 RCTs, n=2,547; very low certainty) in patients with acute stroke. There was significant heterogeneity with I^2 of 78%. This outcome measure was complicated by variations in definition as well as the methodological calculation of length of stay.

All-cause mortality

All 15 RCTs showed a reduction in the odds of death or all-cause mortality by the end of the follow-up (OR 0.75 [95% CI 0.63 to 0.90]; 15 RCTs; n=3,523; high certainty) in patients admitted in a stroke unit (Table Q2.1).

Safety outcomes

No adverse effects were reported related to admission into a stroke unit.[3, 20-21] Studies have noted that since admission in a stroke unit enables early assessment and management from a multidisciplinary team, secondary complications of stroke can be prevented.

Table Q2.1. Summary of findings: acute stroke unit versus general ward.

Outcomes	Basis	Intervention	Control	Effect estimate (95% CI)	Interpretation	Certainty
Poor outcome (mRS 3-5)	14 RCTs (n=3,321)	873/1845 (47.3%)	810/1476 (54.9%)	**OR 0.78** (0.68, 0.91)	Favors stroke unit	LOW [a,b] ⊕⊕◯◯
Length of hospital stay	10 RCTs (n=1,328)	1328	1219	**WMD -2.19 days** (-5.19, 0.82)	Inconclusive	VERY LOW[a,b,c] ⊕◯◯◯
All-cause mortality	15 RCTs (n=3,523)	348/1947 (17.9%)	381/1576 (24.2%)	**OR 0.75** (0.63, 0.90)	Favors stroke unit	HIGH ⊕⊕⊕⊕

a Downloaded due to potential risk of bias
b Downloaded due to substantial heterogeneity
c Downgraded due to Imprecision
GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Certainty of evidence

The overall certainty of evidence is low due to risk of inconsistency and risk of bias. Serious risk of bias was noted due to the risk of performance bias from difficulty concealing the treating service (stroke unit versus general ward) from the participants and healthcare workers. Certainty of evidence for poor outcome and length of hospital stay was further downgraded due to substantial heterogeneity (I^2 of 59% and 78% respectively). Additionally, length of hospital stay is further downgraded due to imprecision.

Other considerations

Cost and cost-effectiveness

Table Q2.2 shows estimated average costs of stay per 24 hours in a stroke unit versus a general ward among acute stroke-ready hospitals both in urban and rural areas in the Philippines. The cost per day is applicable for private hospitals (e.g., Chinese General Hospital, ACE Medical Center Valenzuela, Mary Mediatrix Medical Center, St. Luke's Medical Center, etc.), as services in a stroke unit and general ward are free for government hospitals in the country.

Table Q2.2. Estimated cost per day of admission in a stroke unit versus general ward in private hospitals.

	Acute Stroke Unit	General Ward
Urban Areas	Php 5,500 - 10,000 / day	Php 1,500 – 4,500/day
Rural Areas	Php 1,500 – 5,000 / day	Php 500 – 3,000/day

Patient's values and preferences, equity, acceptability, and feasibility

No relevant studies were found.

Recommendations from other groups

The 2019 American Heart Association guideline strongly recommends the utilization of a comprehensive and specialized stroke units for management and treatment of patients suffering from stroke of any type.[22] Similarly, the Canadian[24], New Zealand and Australian Guidelines[25] also recommend admission in a stroke unit for better outcomes. The European Stroke Organization in 2013[23], also recommends the establishment of stroke unit in the hospital with a competes, multidisciplinary team in place.

Table Q2.3. Summary of recommendation from other groups.

Group	Recommendation	Basis for recommendation	
		Strength	Quality of Evidence
2019 American Heart Association [22]	The use of comprehensive stroke units that incorporates rehabilitation is recommended.	Strong	High
2013 European Stroke Organization (ESO) [23]	According to the ESO recommendations, we propose a stroke unit which is not a stand-alone unit but tightly woven into the hospital infrastructure. A stroke unit should be staffed with a multi-professional team, including stroke physician, stroke nurses, physiotherapists, speech therapists, occupational therapists, social workers, and neuropsychologists.	Not specified	Not specified
2019 Heart and Stroke Foundation of Canada. Canadian Stroke Best Practice Recommendation [24]	Patients admitted to hospital with an acute stroke or transient ischemic attack should be treated on an inpatient stroke unit.	Strong	High
2022 Australian and New Zealand Clinical Guidelines for Stroke Management [25]	All stroke patients should be admitted to hospital and be treated in a stroke unit with an interdisciplinary team.	Strong	High

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Thrombolysis

Q3. Should we use intravenous thrombolysis with alteplase among patients with acute ischemic stroke < 4.5 hours duration?

RECOMMENDATION 3:

Among eligible patients with acute ischemic stroke <4.5 hours duration, we recommend the use of intravenous thrombolysis with alteplase.

Overall Level of Certainty: **Moderate** ⊕⊕⊕◯
Strength of Recommendation: **Strong**

CONSENSUS ISSUES

A strong recommendation in favor of giving intravenous thrombolysis with alteplase was made since its anticipated desirable effects were assessed to outweigh its undesirable effects. High certainty of evidence showed that alteplase increases the likelihood of survival and level of function at 3 months in patients with acute ischemic stroke, but also increases the risk of symptomatic intracerebral bleeding which is characterized by a clinically significant deterioration in the neurologic status of the patient. Despite this known risk, the evidence suggested that the risk of death resulting from such bleeding events as well as other potential causes were not significantly higher in those who are given alteplase. In addition, such risks may also be mitigated by other existing treatments in case they do occur.

This recommendation is intended to apply only to patients with acute ischemic stroke of less than 4.5 hours duration regardless of the patient's eligibility for other interventions (e.g., mechanical thrombectomy). Administering alteplase much earlier than 4.5 hours is also expected to result in better clinical outcomes. The comparative effectiveness of different alteplase doses is also beyond the scope of this guideline question—evidence from included trials in this review were between 0.8 to 1.1 mg/kg.

The panel also recognized that there may be significant variability between patients and physicians in terms of how they value the risk of bleeding associated with alteplase vis-à-vis the probability of maintaining higher levels of functioning. Thus, physicians should still carefully discuss the balance of benefits and risks with individual patients prior to administering the intervention.

Another key consideration that may affect the implementation of this recommendation include the local availability of alteplase. Although still not widely available in several areas in the country, access to alteplase has considerably improved over the past few decades and efforts the Department of Health to further increase accessibility are ongoing (e.g., inclusion in the Philippine National Drug Formulary and PhilHealth coverage). In case a newer drug like alteplase becomes available in the future, the evidence base will be re-examined, and the current guideline recommendation will be consequently updated.

BACKGROUND

Since 1996, intravenous recombinant tissue plasminogen activator with alteplase has been used as the primary treatment for recanalization in adult patients with acute ischemic stroke, reversing or reducing the extent of neurologic injury if given within 4.5 hours of onset of stroke symptoms.[1]

SUMMARY OF THE EVIDENCE

Evidence considered

Eight RCTs were included in this review: Haley 1993[3]; ECASS 1995[4]; NINDS 1995[5]; ECASS II 1998[6]; ATLANTIS B 1999[7]; ATLANTIS A 2000[8]; ECASS 3 2008[9]; and IST3 2012[10]. Two systematic reviews were found that included the same 8 RCTs, with one being a meta-analysis of individual participant data. [1,2] The overall risk of bias in the included studies is rated low.

A total of 2,672 participants were included. Since the time to treatment delay of interest is within 4.5 hours, only participants who were randomized within 4.5 hours of symptom onset were included for those studies that randomized participants to up to 6 hours of symptom onset. All studies included participants aged 18 to 80 years old, except for the IST3 trial that did not specify an upper age limit.

Six of the studies used alteplase dose of 0.90mg/kg (maximum of 90mg) while two trials[3,4] used 0.85mg/kg and 1.10 mg/kg respectively. All trials used placebo as their control for the entirety of the study, except for IST3 which used placebo only for the first 276 patients and was open label thereafter. Haley 1993, and the NINDS 1995 study randomized all participants within 3 hours of symptom onset. The ECASS 3 2008 randomized participants from 3 to 4.5 hours of symptoms. The rest of the studies had participant randomized within 6 hours of symptoms.

Efficacy outcomes of 6 studies[4-9 were measured based on modified Rankin scale (mRS) scores at 3 months or the Oxford Handicap Scale (OHS) scores at 6 months (IST 3). Haley 1993 used the NIHSS scale to measure functional outcomes. Safety outcomes were also measured, which included any hemorrhage, any intracerebral hemorrhage (ICH), symptomatic ICH and fatal ICH.

Benefits and harms

Intravenous thrombolysis with alteplase within 4.5 hours conferred benefit towards good functional outcomes – alive and favorable outcome, defined as a modified Rankin score of 0 to 1; or alive and independent, defined as a modified Rankin score of 0 to 2, and all-cause mortality on follow-up at 3 months. As for safety, treatment led to more symptomatic intracerebral hemorrhage.

<u>Functional outcomes at 3 months</u>

Meta-analysis of 6 trials[4-9] showed that patients who received intravenous thrombolysis exhibited greater odds of survival and having a favorable functional outcome (i.e., being alive and having an mRS 0 to 1; OR 1.54 [95%CI 1.27 to 1.87]; P < 0.0001). Intravenous thrombolysis was associated with higher odds for having an mRS score of 0 to 2 (OR 1.41 [95%CI 1.22 to 1.69]; P = 0.0005). [4-9]

All-cause mortality at 3 months

No significant difference in all-cause mortality was seen between patients receiving intravenous thrombolysis versus control (RR 0.93 [95%CI 0.80 to 1.08]; P = 0.35; 8 RCTs).

Safety outcomes

Risk of bleeding / intracerebral hemorrhage

The safety outcome of interest is the likelihood of symptomatic ICH, defined in the studies as a decrease in the NIHSS score of ≥4 points. Meta-analysis of the 7 included trials showed increased risk of symptomatic ICH with intravenous thrombolysis with alteplase compared to the control (RR 5.68 [95%CI 3.25 to 9.95]; P < 0.001).

Table Q3.1. Summary of outcomes: alteplase versus placebo/control for acute ischemic stroke < 4.5 hrs.

Outcomes	Basis	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Alive and favorable outcome (mRS 0-1 on follow-up)	6 RCTs (n=1,751)	**OR 1.54** (1.27, 1.87)	Favors intervention	HIGH ⊕⊕⊕⊕
Alive and independent (mRS 0-2 on follow-up)	6 RCTs (n=1,751)	**OR 1.41** (1.16, 1.71)	Favors intervention	HIGH ⊕⊕⊕⊕
All-cause mortality	8 RCTs (n=2,627)	**RR 0.93** (0.80, 1.08)	No significant difference between the two groups	MODERATE ⊕⊕⊕◯
Symptomatic ICH (worsening of ≥4 pts on the NIHSS)	7 RCTs (n=2,600)	**RR 5.68** (3.25, 9.95)	Favors control	HIGH ⊕⊕⊕⊕
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio				
GRADE Working Group Certainty of Evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.				

Certainty of evidence

The overall certainty of evidence is moderate. Most of these studies were found to be at low risk for bias. The over-all certainty of evidence is moderate due to the certainty of evidence for all-cause mortality following the serious risk of imprecision.

Other considerations

Cost and cost-effectiveness

Published price for alteplase 50mg powder for infusion is PHP 38,186.81 per vial. At the current recommended dose of 0.90 mg/kg, a patient uses 1 – 2 vials, depending on his weight. In government institutions, alteplase is given for free, and the cost of other direct expenses associated with the procedure, such as neuroimaging, may be partially or fully subsidized by PhilHealth and/or the Malasakit Center Fund. In private institutions, the cost for neuroimaging varies.

Patient's values and preferences, equity, acceptability, and feasibility

There are currently no local studies evaluating the patient's and clinician's values and preference, equity, acceptability, and feasibility of intravenous thrombolysis with alteplase versus no thrombolysis in patients with acute ischemic stroke < 4.5 hours duration.

A study by Brown et al in 2005 surveyed emergency physicians to determine the proportion of emergency physicians resistant to using alteplase in the ideal and the factors that influence this resistance.[14] The results showed 40% of respondents were either "unlikely" or "uncertain" to use tPA even in the ideal setting, defined as availability of a CT scanner, neuroradiology and neurology support, administrative support, and having the appropriate candidate. Of these respondents, 65% (95%CI 61% to 69%) cited the risk of symptomatic intracerebral hemorrhage, 23% (95%CI 19% to 27%) cited the perceived lack of benefit as the reasons for their choice, and 12% (95%CI 9% to 15%) gave both as their primary reasons for resistance.

In 2010, a study by Scott et al[15] determined the baseline proportion of emergency physicians with favorable attitudes and beliefs toward alteplase use, prior to behavioral intervention. Of the 278 emergency physicians from 24 hospitals, 199 surveys were completed. The results showed that 99% of respondents (95%CI 98% to 100%) indicated use of alteplase in eligible patients as either acceptable or ideal patient care; 27% (95%CI 22% to 32%) indicated use of tPA represented a legal standard of care; 83% (95%CI 79% to 88%) were "likely" or "very likely" to use alteplase given an ideal setting; 65% (95%CI 59% to 71%) were uncomfortable using tPA without a consultation; 49% (95%CI 43% to 55%) indicated the science regarding use of tPA in stroke is convincing; 30% remained neutral. The characteristics associated with favorable attitudes included non-emergency medicine board certification older age, and a smaller hospital practice environment.

Recommendations from other groups

Both the European Stroke Organization and the American Heart Association/American Stroke Association recommend the use of intravenous alteplase for patients with acute ischemic stroke of <4.5 hours duration.[12,13]

Table Q3.1. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation and certainty of evidence
2021 ESO[12]	Recommends the use of intravenous thrombolysis with alteplase for patients with acute ischemic stroke of <4.5 hours duration.	Strong recommendation, high quality of evidence
2019 AHA/ASA [13]	Recommends IV alteplase (0.90 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is for selected patients who may be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in this table to determine patient eligibility.	Class I (strong recommendation), level of evidence A (high)
	Recommends IV alteplase (0.90 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is also for selected patients who can be treated within 3 and 4.5 h of ischemic stroke symptom	Class I (strong recommendation), level

	onset or patient last. known well. Physicians should review the criteria outlined in this table to determine patient eligibility.	of evidence B-R (moderate)

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Thrombolysis

Q4. Should we use low-dose compared to standard-dose intravenous alteplase thrombolysis among patients with acute ischemic stroke of less than 4.5 hours duration from the onset of symptoms?

RECOMMENDATION 4:

Among patients with acute ischemic stroke with less than 4.5 hours from onset of symptoms, we recommend the use of standard dose alteplase (0.9 mg/kg) over low dose alteplase (less than 0.9 mg/kg).

Overall Level of Certainty: **Low** ⊕⊕◯◯
Strength of Recommendation: **Strong**

CONSENSUS ISSUES

The panel concluded that the current available evidence does not definitively demonstrate that low-dose alteplase is as effective as standard dose regimen in reducing the risk of death or disability. Greater value was placed on establishing comparable efficacy over a reduction in risk of intracerebral bleeding. Practitioners should prefer standard doses, despite the associated cost, until data from future trials show clear non-inferiority of low-dose regimens.

BACKGROUND

Thrombolytic therapy with alteplase at a standard dose of 0.9 mg/kg has been shown to be effective in treating acute ischemic stroke.[1] However, the Japanese drug safety authority has approved the use of alteplase at a lower dose of 0.6 mg/kg following an uncontrolled, open-label study that demonstrated equivalent clinical outcomes and a lower risk of intracerebral hemorrhage.[2]

SUMMARY OF THE EVIDENCE

Evidence considered

Evidence for this guideline question included one multi-center RCT (ENCHANTED) conducted in 13 countries that recruited a total of 3,310 acute stroke patients who were eligible for thrombolytic therapy.[3] Patients were eligible if they had acute ischemic stroke and met guideline-recommended criteria for treatment with intravenous alteplase, including symptom onset within 4.5 hours. Standard of care for acute ischemic stroke was given to all patients, following existing practice guidelines in the respective countries. Patients were randomly assigned to receive either a standard dose of intravenous alteplase (0.9 mg per kilogram; 10% as a bolus and 90% as an infusion over a period of 60 minutes; maximum dose, 90 mg) or low dose of intravenous alteplase (0.6 mg per kilogram, 15% as a bolus and 85% as an infusion over a period of 60 minutes; maximum dose, 60 mg).

At 90 days, the primary outcome measured was the combined endpoint of disability or death (modified Rankin scale of 2-6). To test for non-inferiority, the upper boundary of the 95% confidence interval for the odds ratio of the outcome with low-dose alteplase as compared with standard-dose alteplase had to fall below a margin of 1.14; this non-inferiority margin was derived from a meta-analyses of alteplase trials with effects on poor outcomes reported.[4] Secondary outcomes include symptomatic intracerebral hemorrhage (safety outcome) as defined by the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST).[5] Other secondary outcomes include distribution of modified Rankin scale scores, death at 7 day and 90 days, and neurologic deterioration during the first 72 hours.

Benefits and harms

Death or disability

Poorer functional outcome (i.e., mRs 2-6) occurred in 855 of 1,607 patients (53.2%) in the low-dose group compared to 817 out of 1,599 patients (51.1%) in the standard dose group. The effect estimate showed an odds ratio of 1.09 (95%CI 0.95 to 1.25), with the upper boundary of the 95% confidence interval exceeding the pre-specified boundary for non-inferiority of 1.14; (one-sided P = 0.51 for non-inferiority). This implies that the non-inferiority of low-dose alteplase to standard dose was not strongly established. The certainty of evidence regarding the reported effect estimate was rated low due to risk of bias and imprecision.

Mortality at 90-days

For the outcome mortality at 90-days, lower rates were reported in the low-dose group (8.5%) compared to those in the standard-dose group (10.3%), but this effect was affected by imprecision (OR 0.80 [95% CI 0.63 to 1.01]; moderate certainty).

Safety outcomes

Incidence of symptomatic intracerebral hemorrhage

Major symptomatic intracerebral hemorrhage according to SITS-MOST criteria occurred in 17 of 1654 patients (1.0%) in the low-dose group and in 35 of 1643 patients (2.1%) in the standard dose group (OR 0.48, 95% CI 0.27 to 0.86; moderate certainty).

Serious adverse events

There was no significant difference between the low-dose group and the standard-dose group in the overall reported rate of serious adverse events, which occurred in 25.1% and 27.3% of the patients, respectively (OR 0.89, 95% CI 0.76 to 1.04; low certainty).

Certainty of evidence

Overall certainty of evidence was rated from low to moderate due to issues on risk of bias and imprecision (i.e., for the primary outcome death or disability, serious adverse events).

Table Q4.1. Summary of findings: standard dose vs. low-dose alteplase for acute ischemic stroke.

Outcome	Basis	Effect Size (95% CI)	Interpretation	Certainty of Evidence
Primary outcome: death or disability* (mRS 2-6)	1 RCT (n=3,310)	**OR 1.09** (0.95, 1.25)	Inconclusive^	LOW[a,b] ⊕⊕◯◯
Mortality at 90 days	1 RCT (n=3,310)	**OR 0.80** (0.63, 1.01)	Inconclusive	MODERATE[a] ⊕⊕⊕◯
Symptomatic ICH by SITS-MOST Criteria#	1 RCT (n=3,310)	**OR 0.48** (0.27, 0.86)	Favors low-dose alteplase	MODERATE[a] ⊕⊕⊕◯
Serious adverse event++	1 RCT (n=3,310)	**OR 0.89** (0.76, 1.04)	Inconclusive	LOW[a,b] ⊕⊕◯◯

* Disability was defined by a score of 2 to 5 on the mRS, with higher scores indicating a greater degree of disability (mRS 6=death)
a. Downgraded due to risk of bias
b. Downgraded due to imprecision
^ exceeded the boundary for non-inferiority of 1.14 (i.e., an upper boundary of the 95% confidence interval for the odds ratio with low-dose alteplase as compared with standard-dose alteplase of less than 1.14)
# The main definition of symptomatic intracerebral hemorrhage used in the study was the definition from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): a large local or remote parenchymal intracerebral hemorrhage (>30% of the infarcted area affected by hemorrhage with mass effect or extension outside the infarct) in combination with neurologic deterioration from baseline (increase of ≥4 in in the NIHSS score) or death within 36 hours.
++ Serious adverse events were defined by standard criteria and included those that resulted in death, were life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in persistent or substantive disability or incapacity, or resulted in a medical or surgical intervention to prevent permanent impairment to body structure or function.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Other considerations

Cost and cost-effectiveness

Based on a survey conducted by the Stroke Society of the Philippines, the cost of thrombolysis can reach as much as PHP 136,688 to PHP 228,678 in private hospitals while the range of expenditures in government hospitals cost between PHP 3,239–PHP 35,903.[6] Alteplase is given based on a patient's weight. For a 60 kg patient, the total dose that should be given for the low dose regimen is 36 mg while that for the standard dose is 54 mg. Each vial of alteplase contains 50 mg. Therefore, cost would be doubled in most cases (use of two vials) in the standard dose regimen.

Patient's values and preferences, equity, acceptability, and feasibility

No relevant studies were found.

Recommendations from other groups

The 2019 AHA/ASA recommends IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) for selected patients who can be treated within 3 to 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline

state. Additionally, a lower dose of IV alteplase (0.6 mg/kg) was not shown to be non-inferior to standard-dose IV alteplase for reducing death and disability at 90 days.[7] The European Stroke Organization also strongly recommends standard-dose alteplase (0.9 mg/kg) over low-dose alteplase for patients with acute ischemic stroke of < 4.5 h duration who are eligible for intravenous thrombolysis.[8]

Table Q4.1. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation and certainty of evidence
2019 American Heart Association/American Stroke Association[7]	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who can be treated within 3-4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state. In a recent trial, a lower dose of IV alteplase (0.6 mg/kg) was not shown to be noninferior to standard-dose IV alteplase for the reduction of death and disability at 90 days.	Class 1 (strong recommendation), level of evidence A (high)
2021 European Stroke Organization [8]	For patients with acute ischemic stroke of < 4.5 h duration who are eligible for intravenous thrombolysis, we recommend standard-dose alteplase (0.9 mg/kg) over low-dose alteplase.	Strong recommendation, high certainty of evidence

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Thrombolysis

Q5. Should we do thrombolysis with tenecteplase as an alternative to standard-dose alteplase for intravenous thrombolysis among patients with acute ischemic stroke of less than 4.5 hours duration?

RECOMMENDATION 5:

Among patients with acute ischemic stroke of less than 4.5 hours duration, we recommend the use of tenecteplase as an alternative to alteplase for intravenous thrombolysis.

Overall Level of Certainty: **Low** ⊕⊕◯◯
Strength of Recommendation: **Strong**

CONSENSUS ISSUES

The panel agreed that tenecteplase could be used as an alternative to alteplase because current evidence suggests it is non-inferior to alteplase in terms of improving functional outcomes, lowering mortality, and safety profile. Tenecteplase is more easily available and less expensive than alteplase because it is already an FDA-approved medication for myocardial infarction patients. Nonetheless, its use for thrombolysis in acute ischemic stroke remains off-label, requiring separate FDA approval for this indication.

BACKGROUND

Alteplase, a recombinant tissue plasminogen activator, is currently the only FDA-approved systemic reperfusion treatment for AIS.[1,2] For nearly three decades, intravenous alteplase has been the standard of care for most AIS patients with an onset of less than 4.5 hours, providing the opportunity for achieving better clinical outcomes.[3] However, alteplase is associated with serious complications, including an increased risk of major bleeding. Because of its short half-life (4-5 minutes), it is administered as a bolus or via infusion. Furthermore, it can be rapidly inactivated by plasminogen activator inhibitor-1 (PAI-1).

Concerns about the limited time window for administering alteplase, as well as the risk of bleeding, prompted the development of alternative thrombolytic therapies that are safe and easy to administer. One of these thrombolytic agents is tenecteplase, a genetically modified form of alteplase. It has emerged as a potential alternative to alteplase due to its higher affinity to fibrin (fewer bleeding complications), longer half-life (slower clearance), and increased resistance to inactivation by PAI-1 (greater thrombolytic potency).[4]

SUMMARY OF THE EVIDENCE

Evidence considered

We included 10 RCTs and 4 observational studies that enrolled a total of 7,770 patients with AIS treated with IVT with tenecteplase (TNK) or alteplase.[5-18] Of these studies, 3,750 patients were allocated to TNK and 4,020 were allocated to alteplase (control). Eight out of ten RCTs were multi-center trials. The time window was 4.5 hours in seven trials, 3 hours in two trials, and < 6 hours in one trial.

Benefits and harms

Good functional outcome at 3 months

Using mRS 0-2 as a definition of a good functional outcome, no significant difference was observed between tenecteplase and alteplase based on 6 RCTs (RR 1.07 [95%CI 0.99 to 1.17] I^2=39%; N=3,585; very low certainty).

Mortality at 3 months

There was no difference in terms of mortality at 3 months among those who received tenecteplase versus alteplase with (RR 0.94 [95%CI 0.76 to 1.17] I^2=0%; 13 RCTs; N=7,272; low certainty).

Safety outcomes

Symptomatic intracerebral hemorrhage

There was no difference in terms of symptomatic ICH among those who received tenecteplase versus alteplase (RR 1.00 [95%CI 0.75 to 1.32] I^2=40%; 13 RCTs; N=7,272; very low certainty).

Table Q5.1. Summary of findings: tenecteplase versus alteplase for acute ischemic stroke.

Outcomes	Basis	Effect estimate (95% CI)	Interpretation	Certainty of evidence
Good functional outcome mRS 0-1 at 3 months	10 RCTs (n=5,090)	**RR 1.04** (0.97, 1.12)	Tenecteplase is non-inferior to alteplase	LOW[a,b] ⊕○○○
Good functional outcome mRS 0-2 at 3 months	6 RCTs (n=3,585)	**RR 1.07** (0.99, 1.17)	Tenecteplase is non-inferior to alteplase	LOW[a,b] ⊕○○○
Mortality at 3 months	13 RCTs (n=7,272)	**RR 0.94** (0.76, 1.1)	Tenecteplase is non-inferior to alteplase	MODERATE[b] ⊕⊕⊕○
Symptomatic intracerebral hemorrhage	13 RCTs (n=7,272)	**RR 1.00** (0.75, 1.32)	Tenecteplase is non-inferior to alteplase	LOW[b,c] ⊕⊕○○

a. downgraded due to risk of bias
b. downgraded due to indirectness
c. downgraded due to imprecision
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Certainty of evidence

The overall certainty of the evidence was rated very low due to indirectness, imprecision, and/or risk of bias. There was a disparity in the population in the included studies (i.e., one study included wake-up strokes, another study included subjects given tenecteplase between 4.5 to 6 hours post symptom onset) as well as differences in the definition of symptomatic intracranial hemorrhage. Bias was related to lack of treatment blinding to participants and personnel due to the open-label nature of the included RCTs (except Haley 2010[5]). Moreover, there were also variations in the doses given for the tenecteplase group.

Other considerations

Cost and cost-effectiveness

Tenecteplase use has additional practical applications that may offer advantages to its use for AIS including potential cost savings and ease of administration. Both tenecteplase and alteplase are administered as a single dose. The average wholesale price of one 50 mg vial of TNK is about USD 450 (PHP 22,500), whereas one 50 mg vial of tPA is about USD 1,000 (PHP 50,000).[19]

Patient's values and preferences, equity, acceptability, and feasibility

TNK is not yet approved by the US Food and Drug Authority (FDA) for use in AIS.[20] The use of tenecteplase for stroke is off-label; hence, the product insert and drug packaging would describe dosing instructions for myocardial infarction. This may be a potential issue in terms of patient acceptance. The simpler manner of administration of tenecteplase may offer some advantages, including faster transport for patients requiring mechanical thrombectomy, less risk for infection, and less risk for dosing errors.

Recommendations from other groups

Four reputable clinical practice guidelines were issued following the publication of most of the randomized controlled trials listed in this evidence summary. The TRACE[8] trial, however, was only published in August 2021. There are no two guidelines that agree on the use of tenecteplase. The most recent recommendations from Australian[21] and American[3] groups are both conditional. However, only the European Stroke Organization Guidelines recommends against using tenecteplase instead of alteplase.[22] Tenecteplase was not mentioned in the most recent stroke guidelines published by the Canadian Heart and Stroke Foundation.

Table Q5.2. Recommendations from other clinical practice guidelines.

Group	Recommendation	Basis for recommendation	
		Strength	Quality of evidence
2019 Australian Stroke Foundation [21]	For patients with potentially disabling ischemic stroke who meet thrombolysis eligibility criteria ≤ 4.5 hr from time last known well, intravenous tenecteplase (0.25 mg/kg, maximum of 25 mg) or alteplase (0.9 mg/kg, maximum of 90 mg) should be administered to patients with stroke due to LVO.	Strong[a]	Moderate to high
	Tenecteplase may be used as an alternative to alteplase for those without LVO.	Weak	Moderate
2019 American Heart Association/ American Stroke Association [3]	It may be reasonable to choose tenecteplase (single IV bolus of 0.25 mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.	IIB recommendation	B-R
	Tenecteplase administered as a 0.4 mg/kg single IV might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	IIb	B-R
2017 European Stroke Organization [22]	For patients with acute ischaemic stroke of <4.5h duration and not eligible for thrombectomy, we suggest intravenous thrombolysis with alteplase over intravenous thrombolysis with tenecteplase.	Weak	Low
2018 Canadian Heart and Stroke Foundation [23]	Tenecteplase not discussed. Only alteplase is recommended	N/A	N/A
French Neurovascular Society[24]	It is reasonable to use tenecteplase 0.25 mg/kg in patients with cerebral infarction within 4.5 hrs of symptoms and for whom mechanical thrombectomy (MT) is planned.	Moderate	Low
	Tenecteplase 0.25 mg/kg can be used as an alternative to alteplase 0.9 mg/kg in patients with acute cerebral infarction < 4.5 hrs related to medium or small vessel occlusion not retrievable with MT.	Weak	Low
	For patients with acute ischemic stroke of < 4.5 hrs duration and not eligible for thrombectomy, tenecteplase 0.25 mg/kg can be used as a safe and effective alternative to alteplase 0.9 mg/kg.	Weak	Low
	Tenecteplase 0.25 mg/kg could be considered as an alternative to alteplase 0.9 mg/kg in the treatment of acute cerebral infarction < 4.5 hrs without vessel occlusion.	Weak	Limited

a. recommendation is based on only 395 participants.

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Anti-thrombotic therapy

Q6. Should we use dual antiplatelet therapy as first line treatment over antiplatelet monotherapy among patients with acute minor non-cardioembolic ischemic stroke or transient ischemic attack within 24 hours of symptom onset?

RECOMMENDATION 6A:

Among patients with acute minor non-cardioembolic acute ischemic stroke or high-risk transient ischemic attack within 24 hours from symptom onset, we recommend treatment with dual antiplatelet therapy using aspirin and clopidogrel for 21 days.

Overall Level of Certainty: **Moderate** ⊕⊕⊕◯
Strength of Recommendation: **Strong**

RECOMMENDATION 6B:

Among patients with acute minor non-cardioembolic ischemic stroke or high-risk transient ischemic attack within 24 hours of symptom onset, we suggest against treatment with dual antiplatelet therapy using aspirin and ticagrelor.

Overall Level of Certainty: **Moderate** ⊕⊕⊕◯
Strength of Recommendation: **Weak**

CONSENSUS ISSUES

A strong recommendation in favor of giving dual antiplatelet therapy with aspirin and clopidogrel for was made due to the high certainty of evidence that it reduces risk of 3-month stroke recurrence by about 30% if given for 21 to 30 days without no significant increase in harms (i.e., bleeding requiring transfusion, intracranial bleeding). Despite this net benefit, the panel highlighted that adherence to this recommendation would depend on the cost of clopidogrel as well as the ability local government units to ensure access to these drugs. Although clopidogrel is not part of the Philippine National Drug Formulary, its cost is still mostly shouldered by patients. Clopidogrel resistance and differences in the pharmacokinetics between Filipinos/Asians and other ethnicities were also mentioned as potential factors that may be influence its efficacy. However, clopidogrel resistance has only been observed in in vitro studies for some populations and remains to be proven in clinical trials.

On the other hand, the weak recommendation against using DAPT with ticagrelor plus aspiration reflects the panel's assessment that although the benefits and harms of the intervention are closely balanced, it comes at a high cost, which may reduce eventual patient compliance. Currently, the cost of ticagrelor is mostly paid for by patients; however, a health technology assessment for the drug is being undertaken to determine if it is cost-effective for the government to fund. The THALES trial suggested that ticagrelor plus aspiration resulted in approximately 20% reduction in stroke recurrence within the first 30 months post-stroke, but also a 3-fold increase in the risk of serious adverse events. The panel felt that additional high-quality trials are needed to ascertain the balance of benefits and harms of the treatment.

These recommendations apply only to a specific subset of patients with mild non-cardioembolic stroke (i.e., NIHSS ≤3, ABCD ≥4) within the acute phase who are not eligible for thrombolytic treatment. Moreover, the interventions were limited to only DAPT that were given to patients within the first 24 hours since this CPG focuses on the role of DAPT for acute stroke management and not its long-term outcomes. Evidence for the outcomes of the included DAPT if given beyond 24 hours as well as the effects of other drug combinations (e.g., cilostazol with aspiration) will be covered in a separate guideline question. The range of acceptable daily doses in the included studies were 50-325 mg for aspirin, 75 mg for clopidogrel (with 300-600 mg loading dose), 180 mg for ticagrelor (with 180 mg loading dose).

BACKGROUND

Patients who had an acute ischemic stroke or transient ischemic attack (TIA) are at an increased risk of recurrent thrombotic events, with a 3-month risk of 10.5%.[1] Those who are not eligible for reperfusion therapy, including thrombolysis (tPA) or endovascular thrombectomy (EVT), receive aspirin monotherapy within the first 48 hours to prevent secondary strokes and improve long-term outcomes according to the results of the International Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST). [2]

Dual antiplatelet therapy (DAPT) using aspirin and clopidogrel given within the first 24 hours after symptom onset was initially studied in the FASTER trial, where it was found to decrease the risk of stroke recurrence without a concomitant increased risk of hemorrhage. [3] This beneficial effect of dual antiplatelet therapy was supported by the results of the CHANCE[6] and POINT[7] trials. In addition, no associated increase in bleeding risk was found if DAPT given for 21 days. Results of these trials led to the updating of the AHA/ASA and ESO guidelines for acute treatment of ischemic stroke.[3,4]

The combination of ticagrelor and aspirin was compared to aspirin alone in the THALES study. Although associated with decreased stroke recurrence, there is a concomitant increase in severe hemorrhage.[8] On the other hand, triple antiplatelet therapy with aspirin, clopidogrel, and dipyridamole does not decrease stroke recurrence and is associated with significantly increased risk of severe bleeding. A meta-analysis and updated systematic review was conducted by Li in 2021[2] which included randomized, placebo-controlled trials that enrolled patients with mild ischemic stroke or high-risk TIA within 3 days of presentation and elucidated the effectiveness and safety of DAPT therapy with clopidogrel or ticagrelor and aspirin versus aspirin alone. This evidence review aimed to assess if dual antiplatelet therapy should be used as first line treatment over antiplatelet monotherapy among patients with acute minor non-cardioembolic stroke.

SUMMARY OF THE EVIDENCE

Evidence considered

Four randomized controlled trials evaluated the efficacy and safety of dual antiplatelet therapy (DAPT) versus monotherapy among a total of 21,463 patients with acute minor non-cardioembolic ischemic stroke or transient ischemic attack within 24 hours. These trials were: (1) FASTER (Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence)[5], (2) CHANCE (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events)[6], (3) POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) [7], and (4) THALES (The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death)[8]. Two systematic reviews published in 2021 included these 4 RCTs. The meta-analysis by Li et al.[2] included more outcomes in their analysis—thus, this study was used as the basis to inform this guideline recommendation.

All 4 RCTs recruited patients with acute minor ischemic stroke and high-risk TIA within 24 hours (less than 24 hours for 3 trials and less than 12 hours in 1 trial). Patients with NIHSS ≤ 3 were considered as having minor ischemic stroke in the POINT and CHANCE trials, while an ABCD2 ≥ 4 or more defined high-risk TIA. In the FASTER trial, patients with TIA were included if they have either weakness or speech disturbance as part of the symptom complex with a duration of 5 minutes or more.

The FASTER, CHANCE and POINT trials compared the combination of clopidogrel and aspirin to aspirin monotherapy alone. The duration of treatment was 90 days for FASTER and POINT trials, and 21 days for the CHANCE trial. Only the THALES trial compared combined aspirin and ticagrelor therapy versus aspirin monotherapy for a total duration of 30 days.[8]

Benefits and harms

Functional outcome

Functional outcome at 30 days was only reported in the THALES trial.[8] Overall disability (i.e., modified Rankin scale score > 1) was seen in 23.8% of the patients in the ticagrelor–aspirin group and in 24.1% of the patients in the aspirin group (OR 0.98 [95%CI 0.89 to 1.07]). This difference was not statistically significant (P = 0.61). The outcome of disabling stroke (i.e., modified Rankin scale score >2) was documented in 2.7% of the patients in the ticagrelor–aspirin group and in 3.5% of the patients in the aspirin group.[8]

Stroke recurrence at 2 weeks

No study reported recurrent stroke at 2 weeks as an outcome.

Stroke recurrence at 90 days

All 4 studies included stroke recurrence (both ischemic and hemorrhagic) as an outcome. All studies measured stroke recurrence within 90 days after randomization, except for the THALES trial that only followed up patients until 30 days. The meta-analysis indicated that DAPT, when started within 24 hours of symptom onset, reduced the risk of stroke recurrence by 24% (RR 0.76 [95%CI 0.68 to 0.83]; I^2=0%) or an absolute risk reduction of 2% (95%CI -0.032 to -0.008; I^2=57%). The number needed to treat for a stroke outcome is 46 (95%CI 35 to 48).

All-cause mortality

Meta-analysis of CHANCE, POINT and THALES revealed that DAPT was not associated with an increased risk of all-cause mortality (RR 1.30 [95%CI 0.90 to 1.89]; I^2=0%). This estimate translates to a risk difference (RD) of 0.001 (95%CI -0.001 to 0.003) and a number needed to treat of 1663 (95%CI 258 to 1283).

Safety outcomes

Major bleeding

Meta-analysis of the 4 RCTs showed that DAPT increased the risk of severe or moderate bleeding (RR 2.17 [95%CI 1.16 to 4.08]; I^2=41%; RD 0.003 [95%CI <0.001 to 0.007]). Further analysis was made stratified by treatment regimen or duration and results. It showed that the association was mainly seen with ticagrelor (RR 3.25 [95%CI 1.66 to 6.39]) or treatment duration over 21 days (RR 2.86 [95%CI 1.75 to 4.67]; RD 0.005 [95%CI 0.003 to 0.007]).

Intracranial hemorrhage

DAPT was not associated with an increased risk for ICH (RR 2.02 [95%CI 0.91 to 4.50]).

Effect of treatment regimen type on efficacy and safety

Aspirin + clopidogrel

DAPT using aspirin and clopidogrel within 24 hours of symptom onset showed a significant reduction in stroke recurrence within 90 days (RR 0.71 [95%CI 0.61 to 0.81]; N=10,447; 3 RCTs). In terms of safety, DAPT was not associated with an increased risk for major bleeding (RR 1.71 [95%CI 0.71 to 4.01]; N=10,447; 3 RCTs) or intracranial hemorrhage (RR 1.33 [95%CI 0.70 to 2.52]; N=5,566). Data from the CHANCE and POINT revealed that DAPT had no clear benefit on reducing all-cause mortality (RR 1.28 [95%CI 0.73 to 2.23]; N=10,051) and risk. No study reported on functional outcome and stroke recurrence at 2 weeks.

Aspirin + ticagrelor

Data from the THALES trial showed significant benefit with DAPT using aspirin plus ticagrelor in terms of stroke recurrence within 90 days (RR 0.81 [95%CI 0.69 to 0.95]). However, it did not significantly improve functional outcome (OR 0.98 [95%CI 0.89 to 1.07]) or lower all-cause mortality (RR 1.33 [95%CI 0.81 to 2.19]). Ticagrelor was associated with a 3-fold increase in the risk of intracranial hemorrhage (RR 3.32 [95%CI 1.33 to 8.25]; N=11,016).

Effect of treatment duration on safety

Based on the CHANCE trial, no increase in major bleeding was seen when the DAPT is given for 21 days or less (RR 0.88 [95%CI 0.32 to 2.41]; 1 RCT; N=5,170). However, there was high certainty evidence from 3 RCTs showing increased risk for major bleeding when DAPT is given for more than 21 days (RR 2.86 [95%CI 1.75 to 4.67]; 3 RCTs; N=16,293).

Table Q6.1. Summary of findings: dual anti-platelet therapy for acute stroke.

Outcomes	Basis	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Aspirin plus clopidogrel vs. aspirin only				
Stroke recurrence within 90 days (ischemic and hemorrhagic)	3 RCTs (10,447)	**RR 0.71** (0.62, 0.81)	Favors dual antiplatelet	HIGH ⊕⊕⊕⊕
All-cause mortality	2 RCTs (10,051)	**RR 1.28** (0.73, 2.23)	No significant difference	MODERATE ⊕⊕⊕○
Adverse events: major bleeding	3 RCTs (10,447)	**RR 1.71** (0.73, 4.01)	No significant difference	MODERATE ⊕⊕⊕○
Adverse events: intracranial hemorrhage	2 RCTs (5,566)	**RR 1.33** (0.70, 2.52)	No significant difference	MODERATE ⊕⊕⊕○
Aspirin plus ticagrelor vs. aspirin only				
Functional outcome (mRS>1)	1 RCT (11,016)	**OR 0.98** (0.89, 1.07)	No significant difference	MODERATE ⊕⊕⊕○
Stroke recurrence within 90 days (ischemic and hemorrhagic)	1 RCT (11,016)	**RR 0.81** (0.69, 0.95)	Favors dual antiplatelet	HIGH ⊕⊕⊕⊕
All-cause mortality	1 RCT (11,016)	**RR 1.33** (0.81, 2.19)	No significant difference	HIGH ⊕⊕⊕⊕
Adverse events: major bleeding	1 RCT (11,016)	**RR 3.27** (1.67, 6.43)	Favors monotherapy	HIGH ⊕⊕⊕⊕
Adverse events: intracranial hemorrhage	1 RCT (11,016)	**RR 3.33** (1.34, 8.28)	Favors monotherapy	MODERATE ⊕⊕⊕○

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Certainty of evidence

The certainty of evidence is rated low due to serious risk of inconsistency, indirectness, and imprecision. For the safety outcome of major bleeding, there is a major difference in the results depending on the treatment regimen (aspirin plus clopidogrel versus aspirin plus ticagrelor) and treatment duration (21 days versus more than 21 days). The methodological quality of the included studies was high.

Since our treatment onset of concern is within 48 hours and the studies included patients within 12 and 24 hours of stroke onset, the evidence is downgraded for indirectness. Three studies used clopidogrel plus aspirin while one study used ticagrelor plus aspirin, all compared to aspirin monotherapy. Treatment duration for one study is 21 days, 30 days for once study while the other two is 90 days.

Other considerations

Cost and cost-effectiveness

Aspirin at a dose of 80mg ranges from PHP 2.45 to 3.90 pesos depending on the brand. Clopidogrel 75mg tablet costs PHP 9.00 to 67.50. Ticagrelor 90mg tablet costs PHP 80.00 pesos each. For aspirin monotherapy, it will cost PHP 73.50 117.00 pesos per month, and this is continued lifelong.

For dual antiplatelet therapy, it will cost additional PHP 189.00 to 1417.50 pesos for 21 days of clopidogrel (CHANCE trial), PHP 810.00 to 6,075.00 pesos for 90 days of clopidogrel (FASTER trial, POINT trial) and PHP 2,400.00 for 30 days of ticagrelor.

Patient's values and preferences, equity, acceptability, and feasibility

There are currently no local studies evaluating the patient's values and preference, equity, acceptability, and feasibility of using dual antiplatelet therapy versus monotherapy in acute ischemic stroke and transient ischemic attack.

Recommendations from other groups

The American Heart Association/American Stroke Association recommends treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days. It is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset in patients presenting with minor non-cardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase.[3]

The European Stroke Organization also strongly recommends the use of 21-days of dual antiplatelet therapy with aspirin and clopidogrel in people with a non-cardioembolic minor ischemic stroke or high-risk TIA in the past 24 hours.[4] They weakly recommend 30-days of dual antiplatelet therapy with aspirin and ticagrelor in people with non-cardioembolic mild to moderate ischemic stroke or high-risk TIA in the past 24 hours.[4]

Table Q6.2. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation and certainty of evidence
2019 AHA/ASA [3]	Dual antiplatelet with aspirin and clopidogrel within 24 hours after symptom onset and continued for 21 days	Class 1 (strong recommendation), level of evidence A (high)
2021 ESO[4]	Dual antiplatelet with aspirin and clopidogrel within 24 hours of symptom onset for 21 days	Strong recommendation, high quality of evidence
	Dual antiplatelet with aspirin and ticagrelor within 24 hours of symptom onset for 30 days	Weak recommendation, moderate quality of evidence

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Early mobilization

Q7. Should we do very early mobilization (24 hours) by trained staff (i.e., physical therapists, nurses) versus usual treatment among patients with acute stroke?

RECOMMENDATION 7:

Among acute stroke patients, we recommend against very early mobilization within 24 hours by trained staff (i.e., physical therapists, nurses)

Overall Level of Certainty: **Low** ⊕⊕◯◯
Strength of Recommendation: **Strong**

CONSENSUS ISSUES

The recommendation against very early mobilization stems from a lack of clear evidence supporting its superiority or harm compared to standard treatment. While current evidence indicates no significant difference between the two approaches, some practitioners note a perceived increased risk of adverse outcomes or complications, particularly when patients engage in out-of-bed activities within the first 24 hours of admission. It is essential to distinguish between "very early mobilization" and "early rehabilitation," highlighting the nuanced differences between the two approaches.

BACKGROUND

There has been a growing focus on understanding the elements of care that contribute to the beneficial effects of stroke units. Early mobilization is one such element proposed to enhance survival and recovery outcomes in stroke patients. However, there is limited clarity on the specifics of early mobilization and its providers. Moreover, it remains uncertain whether very early mobilization independently improves stroke outcomes. The term "early mobilization" lacks a standardized definition, as there is no consensus on what constitutes "early" (e.g., hours, days, weeks, or months) or "mobilization" (e.g., movement of cells, joints, limbs, or individuals). Preclinical research suggests a critical window of heightened neuroplasticity shortly after a stroke.[1] Nevertheless, some clinicians express concerns that early upright activity may impede reperfusion of salvageable penumbral tissue.

SUMMARY OF THE EVIDENCE

Evidence considered

Six randomized controlled trials assessed the efficacy and safety of very early mobilization compared to usual care by trained staff among a total of 2419 patients with acute stroke within 24 hours.[2-7] The participants included were broadly representative of the stroke population, with one multicenter trial (AVERT III 2015)[2] dominating the numbers with 2104 participants. Trials such

as AVERT Phase II[3], Very Early Rehabilitation or Intensive Telemetry After Stroke (VERITAS)[4], Akershus Early Mobilization in Stroke Study (AKEMIS)[5], Lausanne trial[6], AVERT Phase III[7], and Ischemic Stroke and Early Vertical Positioning (SEVEL) initiated early mobilization interventions within 24 to 72 hours of stroke onset, compared to usual care (later mobilization plus monitoring) in a stroke unit environment. Inclusion criteria were generally broad, with variations in age, stroke severity (specified only in the Lausanne and SEVEL trials), and stroke type (intracerebral hemorrhage patients excluded only in the Lausanne trial). The interventions tested varied, with some focusing on frequent and ongoing mobility training supported by therapists or nurses (AVERT, VERITAS), while others tested a graduated head-raising protocol in bed followed by out-of-bed mobility after 52 hours (Lausanne trial).

Benefits and harms

Functional outcome at 3 months

Very early rehabilitation did not show significant improvement in functional outcome (mRS 0-2) (575 out of 1205, 48%) compared to usual care (623 out of 1215, 51%) at the end of the scheduled follow-up (OR 0.88 [95% CI 0.75 to 1.03]; 6 RCTs; N=2,419; P= 0.11; moderate certainty).

Death

There was no statistically significant difference in the number of deaths among those who received early mobilization (99/1160, 8.5%) compared to those who received usual care (80/1145, 7.0%) (OR 1.24 [95%CI 0.91 to 1.68]; 5 RCTs; N=2,305; P= 0.17; moderate certainty).

Safety outcomes

Serious complications

There was no statistically significant difference in the incidence of serious complications between those who received early mobilization (153 out of 1223, 12.5%) compared to those who received usual care (138 out of 1220, 11.3%) (OR 1.13 [95%CI 0.87 to 1.46]; 6 RCTs; N=2,442; P= 0.36). The certainty of evidence was rated low due to serious risk of bias and imprecision.

Minor complications

There was no statistically significant difference in the incidence of minor complications between those who received early mobilization (248 out of 1196, 20.7%) compared to those who received usual care (252 out of 1191, 21.2%) (OR 0.95 [95%CI 0.77 to 1.17]; 5 RCTs; N=2,387; P= 0.63). The certainty of evidence was rated low due to serious risk of bias and imprecision.

Certainty of evidence

The overall certainty of evidence is rated low due to imprecision and inconsistency. For most outcomes, the certainty of evidence was moderate and downgraded only due to imprecise confidence intervals.

Table Q7.1. Summary of findings: very early mobilization versus usual treatment.

Outcome	Basis	Effect Estimate (95%CI)	Interpretation	Certainty of Evidence
Functional outcome (mRS 0-2 at 3 months	6 RCTs (N=2,419)	**OR 0.88** (0.75, 1.03)	Inconclusive	MODERATE[a] ⊕⊕⊕◯
Death	5 RCTs (N=2,305)	**OR 1.24** (0.91, 1.68)	Inconclusive	MODERATE[a] ⊕⊕⊕◯
Serious complications	6 RCTs (N=2,442)	**OR 1.13** (0.87, 1.46)	Inconclusive	LOW[a,b] ⊕⊕◯◯
Minor complications	5 RCTs (N=2,387)	**OR 0.95** (0.77, 1.17)	Inconclusive	MODERATE[a] ⊕⊕⊕◯
a Downgraded due to imprecision b Downgraded due to inconsistency (I^2=55%)				
***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio				
GRADE Working Group Certainty of Evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.				

Other considerations

Cost and cost-effectiveness

The cost of physical therapy per session in the Philippines typically falls within the range of PHP 600 to PHP 1,500. The actual price may vary depending on the specific program prescribed by the doctor and the number of sessions required. For stroke patients, therapy costs generally range from PHP 700 to PHP 1,200 per session. This fee typically covers the necessary physical therapy following an initial medical procedure. Typically, therapy begins with six sessions and may be adjusted based on the patient's progress and needs.

Patient's values and preferences, equity, acceptability, and feasibility

No relevant evidence were found.

Recommendations from other groups

Table Q7.2. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation, Certainty of evidence
AHA/ASA 2019[8]	It is recommended that early rehabilitation for hospitalized stroke patients be provided in environments with organized, interprofessional stroke care.	Class 1 (strong recommendation), level of evidence A (high)
AHA/ASA 2019[8]	High-dose, very early mobilization within 24 hours of stroke onset should not be performed because it can reduce the odds of a favorable outcome at 3 months.	Class 3 (weak recommendation – no benefit), level of evidence B-R (moderate)

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Venous thromboembolism (VTE) prophylaxis

Q8. Should we use anticoagulants among immobile patients hospitalized with acute ischemic stroke for deep vein thrombosis (DVT) prophylaxis?

RECOMMENDATION 8:

Among immobilized in-patients with acute ischemic stroke, we suggest the use of anticoagulants (low-molecular-weight heparin or unfractionated heparin) versus no anticoagulants for DVT prophylaxis.

Overall Level of Certainty: **Low** ⊕⊕◯◯
Strength of Recommendation: **Weak**

CONSENSUS ISSUES

The panel gave a recommendation in favor of using anticoagulants due to their assessment that the desirable effects of anticoagulants outweigh its undesirable effects and because of its wide availability. Although the included evidence showed that giving LMWH or unfractionated heparin may significantly reduce the incidence of DVT compared to placebo, there is also a potential for increased risk of intracerebral hemorrhage and minor bleeding. The low level of certainty in these effect estimates primarily contributed to the weak recommendation. Another source of uncertainty was identified from the difference in the dosing of anticoagulants for DVT prophylaxis used in the included studies (once every 8-12 hours) compared to that used in current practice by neurologists (once daily at lower doses) as well as the absence of more recent studies that used placebo as comparator. Future guidelines should assess the impact of using higher doses of heparin and the comparative effectiveness of different types of anticoagulants for this acute ischemic stroke patients.

BACKGROUND

Immobility among patients with acute ischemic stroke (AIS) predisposes them to a higher risk of thromboembolic complications including deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT and PE are more likely to occur in the first 3 months after stroke.[4] The incidence rate of DVT in patients with stroke varies from 10% to 75%.[2] Another study published in 2021 estimated the incidence rate of DVT among patients with acute ischemic stroke after thrombolysis to be at 15.8% (75/474 patients).[3]

In earlier guidelines, the AHA strongly suggested the use of anticoagulation to prevent venous thromboembolism in immobilized stroke patients.[5] However, current guidelines show conflicting recommendations regarding the use of anticoagulation in preventing venous thromboembolism in these patients. The American Heart Association (AHA) states that the benefit of prophylactic-dose subcutaneous heparin (i.e, unfractionated heparin [UFH] or LMWH) in patients with AIS is not well established (Class IIb, level B-R evidence).[6] On the other hand, the European Stroke Organization recommends that prophylactic anticoagulation with UFH (5000U 2, or 3 daily) or LMWH or heparinoid be considered in immobile patients with AIS in whom the benefits of reducing

the risk of VTE is high enough to offset the increased risks of intracranial and extracranial bleeding associated with their use.[7]

The use of anticoagulants is offset by the higher risk of bleeding in some patients. Moreover, Asians have been shown to have 70.0% lower VTE rates compared to Caucasians, hence, the use of prophylactic anticoagulation to prevent VTE among stroke patients given the bleeding risks has shown practice variations. This review aimed to synthesize current evidence on the effects of anticoagulants in reducing the risk of thromboembolism and in improving functional outcomes.

SUMMARY OF THE EVIDENCE

Evidence considered

Six RCTs published between 1977 to 1995 comparing any heparin versus no heparin for venous thromboembolism in admitted patients with acute infarct were considered for this review.[8-13] McCarthy 1977 and McCarthy 1988 randomized respectively 32 and 305 subjects admitted for acute stroke within 48 hours of onset to receive either 5000 units of calcium heparin subcutaneously every 8 hours for 14 hours, within 48 hours of onset of acute stroke or no heparin. Treatment duration was 14 days and 12 weeks, respectively.[8,9] Pambianco et al 1995 randomized 360 patients to receive either no heparin or 5000 units of heparin subcutaneously every 8 hours, with a follow-up period of 3 years.[10] Turpie et al 1987 included 75 subjects with acute stroke, randomized to receive either Org 10172 LMW heparinoid (n=50) with loading dose of 1000 anti-factor-Xa units (1-25 ml) intravenously, followed by subcutaneous injections every 12 hours of 750 anti-factor-Xa unit (090 ml) or saline placebo intravenously and subcutaneously every 12 hours.[11] Prins et al 1989 randomized a total of 60 subjects to either 2500 U of anti-Xa Kabi 2165 or saline 0.9% subcutaneously twice daily for 14 days.[12] Finally, Elias et al 1990 randomized 30 patients to either treatment with Dalteparin 15,000 IU subcutaneously once a day or no treatment. Treatment duration was also 14 days.[13]

Benefits and harms

<u>Incidence of DVT</u>

A total of 372 of 862 patients (43.2%) received either low molecular weight heparin or unfractionated heparin in the randomized controlled trials using placebo as control, while 490 of 862 patients (56.84%) received placebo. Anticoagulation with any heparin showed significant reduction in incidence of DVT among hospitalized patients with acute ischemic stroke (RR 0.32 [95%CI 0.25 to 0.42]; $P < 0.001$).

<u>Safety outcomes</u>

Bleeding was significantly higher in the heparin group compared with placebo (RR 3.35 [95%CI 1.43 to 7.85]; $P = 0.006$). Mortality was not significantly different between the two groups.

Table Q8.1. Summary of findings: anticoagulants for reducing thromboembolism.

Outcomes	Basis	Effect Estimate (95% CI)	Certainty of Evidence	Interpretation
Incidence of DVT	6 RCTs (N=734)	**RR 0.32** (0.25, 0.42)	Favors intervention	LOW ⊕⊕◯◯
Mortality	6 RCTs (N=499)	**RR 0.74** (0.53, 1.02)	No significant difference	MODERATE ⊕⊕⊕◯
Adverse events: intracerebral hemorrhage	5 RCTs (N=696)	**RR 1.57** (0.57, 4.30)	Inconclusive	MODERATE ⊕⊕⊕◯
Adverse events: minor bleeding	3 RCTs (N=370)	**RR 3.28** (0.42, 25.73	Inconclusive	LOW ⊕⊕◯◯
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio				
GRADE Working Group Certainty of Evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.				

Certainty of evidence

Certainty of evidence is low for incidence of DVT due to serious risk of bias and inconsistency. Sources of bias were related to absence of blinding, allocation concealment, and intention-to-treat analysis in majority of the studies. Certainty of evidence for mortality was low because of serious imprecision. Certainty of evidence for hemorrhage was also moderate due to serious risk of bias.

Other considerations

Cost and cost-effectiveness

No study was found on the cost-effectiveness of heparin as thromboprophylaxis in the Philippine setting or in other Asian countries. The estimated cost of the intervention in private and government institutions are shown in Table 2.

Table Q8.2. Cost of heparin prophylaxis.

Unit cost	Treatment Cost	Total Cost
Private	PHP 1,422.00 per dose (LMWH 40 mg / 0.4 mL) (given 2x daily for 14 days)	PHP 39,816.00
Government	PHP 301.80 (LMWH 0.4 mL) (given 1x for 14 days) PHP 84.90 (unfractionated heparin)	PHP 4,225.20

A 2006 study from Germany estimated the cost effectiveness of the low-molecular-weight heparin (LMWH) subcutaneous enoxaparin sodium 40mg once daily (ENOX) relative to no pharmacological prophylaxis (NPP) and subcutaneous unfractionated heparin (UFH) 5000IU three times daily (low-dose UFH [LDUFH]).[14] They found an incremental cost of €1106 for enoxaparin per clinical VTE avoided versus NPP (€1 ≈ $US1.07; average of the first quarter of 2003). LMWH was considered a very cost-effective option for thromboprophylaxis compared with NPP and a cost-saving alternative compared with unfractionated heparin.

Another 2021 study showed that enoxaparin prophylaxis had significantly lower adjusted mean total hospitalization costs compared to unfractionated heparin prophylaxis.[15] The mean adjusted total index hospital cost for the enoxaparin prophylaxis group was $1427 lower than that for the UFH group, which suggested that enoxaparin might reduce the economic burden in medically ill patients at risk of VTE. No comparison with no thrombophylaxis was done.

Patient's values and preferences, equity, acceptability, and feasibility

No evidence was found specifically investigating the perception of hospitalized stroke patients on thrombophylaxis using anticoagulants. Cross-sectional surveys on perceptions on thrombophylaxis among patients with a wide range of conditions including stroke showed that 67% to 90% of participants believed in the safety and efficacy of thrombophylaxis.[16-18] Most (60 to 70%) of the participants never minded receiving injections, while 31% to 68% reported tolerable adverse effects. Furthermore, most participants were satisfied with the dose scheduling of heparin or enoxaparin, expressing that it did not interfere with their daily activities or sleep pattern.[16,17]

Recommendations from other groups

The 2016 ESO Guidelines recommends prophylactic anticoagulation with unfractionated heparin (UFH), low molecular weight heparin (LMWH), or heparinoid in patients with whom the benefits of reducing the risk of venous thromboembolism are high enough to offset the increased risks of intracranial and extracranial bleeding. Moreoever, LMWH or heparinoid was recommended over UFH because of its greater reduction in risk of DVT, greater convenience from single instead of multiple daily injections, reduced staff costs, and higher patient comfort, However, these advantages should be weighed against the higher risk of extracranial bleeding, higher drug costs, and risks in elderly patients with poor renal function.[7]

In contrast, the 2019 American Heart Association guidelines stated that the benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in patients with AIS is not well established.

Table Q8.3. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation and certainty of evidence
ESO 2016[7]	Consideration of prophylactic anticoagulation with unfractionated heparin (UFH) (5000 U 2 or 3 daily), low molecular weight heparin (LMWH), or heparinoid in immobile patients with ischaemic stroke in whom the benefits of reducing the risk of venous thromboembolism is high enough to offset the increased risks of intracranial and extracranial bleeding associated with their use	Weak recommendation, moderate quality of evidence
AHA 2019[6]	The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin or LMWH) in patients with AIS is not well established	Class 2b (moderate strength of recommendation), level of evidence A (high)

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Venous thromboembolism (VTE) prophylaxis

Q9. Should we use graduated compression stockings (GCS) as add-on therapy to standard of care among adult immobilized patients hospitalized due to acute stroke?

RECOMMENDATION 9:

Among immobilized patients hospitalized with acute ischemic stroke or intracerebral hemorrhage, we recommend against the use of graduated compression stockings.

Overall Level of Certainty: **Low** ⊕⊕◯◯
Strength of Recommendation: **Strong**

CONSENSUS ISSUES

A strong recommendation was made by the panel members against using GCS due to their assessment that its undesirable effects outweigh its potential benefits. Although the evidence suggesting that it confers no additional benefit for reducing DVT is of low certainty, there is high certainty of evidence showing it is associated with greater risk for adverse events. This recommendation also reflects the need for clinicians to explain to patients the risk and benefits associated with GCS, as some patients may still place more value on avoiding serious health outcomes such as DVT over adverse effects. This guideline recommendation applies to stroke patients who are unable to get out of bed without assistance, including those who undergo physical therapy but remain non-ambulatory and others who are immobilized due to agitation or restlessness.

BACKGROUND

Compression therapy is a frequently used physical therapy in conditions involving venous insufficiency in the lower limbs that may lead to deep venous thrombosis (DVT).[1] Forms of compression therapy include elastic and non-elastic bandages, boots, hosiery or stockings, and pneumatic devices. Graduated compression stockings (GCS) or anti-embolism stockings exert the greatest degree of compression at the ankle, and the level of compression gradually decreases up the garment. These are manufactured under strict medical and technical specifications, including consistency and durability, to provide a specific level of ankle pressure and graduation of compression.

GCS are often prescribed and have the advantage of being more acceptable to patients, relatively easier to put on, and less cumbersome than pneumatic devices. However, not all patients tolerate GCS, and problems with compliance are common. Although their use is usually safe, several adverse effects and complications such as including allergic reaction and skin necrosis have been reported.[1] Evidence regarding the safety and effectiveness of GCS as an add-on to standard care (i.e., early mobilization, hydration, and appropriate antithrombotic medication) for immobile ischemic stroke patients in reducing the risk of venous thromboembolism and mortality were synthesized.[2,3]

SUMMARY OF THE EVIDENCE

Evidence considered

Two RCTs comparing the use of graduated compression stockings as add-on therapy versus standard of care only among adult immobilized patients hospitalized due to acute stroke.[2,3] The first study by Muir et al in 2000 is a single-center RCT which included 97 acute stroke patients.[2] The type of stroke, whether ischemic or hemorrhagic, was not specified. Patients were randomized to receive either thigh-length graded compression stockings or standard of care and were followed-up 5-9 days post ictus.[2] The second study (CLOTS Trial I) by Dennis et al in 2009 is a multi-center RCT which included 2,518 acute ischemic and hemorrhagic stroke patients, with the latter comprising only 10% of cases.[3] Patients were also randomized to receive either thigh-length graded compression stockings or standard of care and were followed-up at 7-10 days and 25-30 days from ictus.[3] For both studies, there was risk of performance bias because patients were not blinded of the intervention used.

Benefits and harms

Incidence of DVT

The use of graded compression stockings compared to standard of care did not confer any statistically significant effect in terms of reducing the risk of venous thromboembolism or mortality among acute stroke patients. In terms of development of DVT, there was no significant difference between use of GCS compared to standard of care alone (RR 0.90 [95% CI 0.76 to 1.07]; P = 0.23).

Mortality

Likewise, no significant benefit was seen with GCS in terms of mortality reduction (RR 1.11 [95%CI 0.88 to 1.42]; P = 0.38). The certainty of evidence is low due to inconsistency and imprecision of both studies.

Safety outcomes

GCS significantly increased the risk of skin breaks. A statistically significant increase in the risk of adverse events (skin breaks, ulcer, blisters, necrosis) was noted among the patients allocated with GCS (RR 4.02 [95%CI 2.34 to 6.91]; P < 0.001). Complications associated with compression therapy in real-world scenarios include skin irritation, pruritus, superficial venous thrombophlebitis at the upper stocking border, decompensation of heart failure or the spread of bacterial and/or fungal infection, nerve damage, venous thromboembolism, arterial thrombosis, and skin or limb necrosis.[4] The certainty of evidence concerning these harms is rated high.

Table Q9.1. Summary of findings: graduated compression stockings for venous thromboembolism prophylaxis.

Outcomes	Intervention	Control	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Incidence of DVT (2 RCTs, n=2615)	206/1321 (15.59%)	228/1294 (17.62%)	**RR 0.90** (0.76, 1.07)	No significant difference	LOW ⊕⊕◯◯
Mortality (2 RCTs, n=2615)	131/1321 (9.92%)	114/1294 (8.81%)	**RR 1.11** (0.88, 1.42)	No significant difference	MODERATE ⊕⊕⊕◯
Adverse events (1 RCT, n= 2518)	64/1256 (5.10%)	16/1262 (1.27%)	**RR 4.02** (2.34, 6.91)	Favors control	HIGH ⊕⊕⊕◯

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Other considerations

Cost and cost-effectiveness

GCS unit prices range from PHP 1,000 to 7,000 depending on brand, size, and compression level. Other considerations would include number of stocking replacement, and duration of use.

Patient's values and preferences, equity, acceptability, and feasibility

A systematic review of 16 studies found lower patient adherence with thigh-high GCS compared to knee length stockings.[5] Data on outpatient setting is lacking, however it was likely that adherence reduces further once patients have been discharged from hospital.[5]

Recommendations from other groups

The American Heart Association (AHA) 2022 guideline for the management of patients with spontaneous intracerebral hemorrhage (ICH) stated that GCS of knee-high or thigh-high length alone are not beneficial for DVT prophylaxis in non-ambulatory patients with spontaneous ICH.[6] Similarly, the 2019 AHA guidelines strongly recommended against the use of GCS among ischemic stroke patients.[7] This recommendation was adapted from the AHA guidelines for adult ischemic and hemorrhagic stroke rehabilitation and recovery guidelines in 2016.[8] A similar recommendation against GCS was made by the 2016 European Stroke Organization (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischemic stroke.[9] The level of evidence for all these guidelines was level B (moderate quality) from limited populations evaluated in 1 or more RCTs and meta-analyses.

Table Q9.2. Recommendations from other clinical practice guideliens.

Group	Recommendation	Class of Recommendation	Certainty of Evidence
AHA 2022[6]	In non-ambulatory patients with spontaneous ICH, GCS of knee-high or thigh-high length alone are not beneficial for DVT prophylaxis	III (weak recommendation)	B-R (moderate)
AHA 2019[7]	In ischemic stroke, elastic compression stockings should not be used.	III (weak recommendation)	B-R (moderate)
AHA 2016[8]	In ischemic stroke, it is not useful to use elastic compression stockings.	III (weak recommendation)	B (moderate)
	In ICH, it is not useful to use elastic compression stockings.	III (weak recommendation)	C (limited data)
ESO 2016[9]	We recommend that GCS should not be used in patients with ischemic stroke.	Strong recommendation	Moderate

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Venous thromboembolism (VTE) prophylaxis

Q10. Should we use intermittent pneumatic compression (IPC) among immobilized patients hospitalized due to acute ischemic stroke?

RECOMMENDATION 10:

Among immobilized patients hospitalized with acute ischemic stroke, we suggest the use of intermittent pneumatic compression.

Overall Level of Certainty: **Moderate** ⊕⊕⊕◯
Strength of Recommendation: **Weak**

CONSENSUS ISSUES

A recommendation in favor of using IPC among acute ischemic stroke patients as moderate-certainty evidence showed that it significantly reduces the incidence of any venous thromboembolism (VTE) and deaths. Minor adverse events were significantly more common with IPC use, but the panel assessed the desirable effects to clearly outweigh these undesirable effects. The weak strength of recommendation reflects the panel's concerns regarding the ability of practitioners and healthcare institutions to provide this intervention. At present, the cost of IPC remains high, and most hospitals still do not have sufficient supply of IPC machines to cater to all acute ischemic stroke patients, which raises and issue on how equity may be ensured whenever recommending this intervention.

BACKGROUND

Venous thromboembolism is a common and serious medical complication following acute stroke. The incidence of stroke-related VTE in immobilized stroke patients ranges from 10% to 75%. The onset of DVT following acute stroke can be as early as the second day, peaking between days 2 and 7; if left untreated, proximal DVT carries a 15% risk of death.[1,2] Current clinical practice guidelines (CPG) recommend the use of intermittent pneumatic compression to reduce the risk of DVT in acute stroke patients.[3,4]

Intermittent pneumatic compression is an effective treatment for a variety of circulatory disorders. Its common physiologic effects include decreasing venous stasis by increasing endothelial shear stress and decreasing A-V pressure gradient by increasing arterial inflow. IPC use for venous thromboembolism prophylaxis and lymphedema treatment has been well established.[5] We reviewed evidence to determine whether IPC may be recommended as an add-on therapy to the standard of care (hydration and aspirin) to prevent the incidence of venous thromboembolism among immobile patients with acute ischemic stroke.

SUMMARY OF THE EVIDENCE

Evidence considered

One large RCT met the inclusion criteria for this review.[6] It was a multicenter, parallel group trial study conducted in 2013 that included 2,876 immobile patients hospitalized due to acute ischemic stroke within 3 days from stroke onset. These patients were randomized to receive either standard care (i.e., aspirin and hydration) or standard care plus IPC. The IPC was delivered using sequential compression, first around the distal calf, then to the proximal calf, and then to the thigh. The inflation of the sleeve was gradual, and the compression was circumferential. A maximum pressure of 45 mmHg was delivered to one leg at a time with a frequency of 2 cycles per minute.

Benefits and harms

Incidence of VTE

In terms of preventing the incidence of venous thromboembolism, effect favors the use of intermittent pneumatic compression compared to the standard of care (RR 0.67 [95%CI 0.53 to 0.86]). Similarly, effect favors intervention compared to control when it comes to reducing mortality (RR 0.80 [95% CI 0.64 to 1.01]).

Safety outcomes

Reported any adverse events including skin breaks, falls and fractures favors non-use of intermittent pneumatic compression (RR 2.24 [95% CI 1.31 to 3.82]). However, majority of these adverse events occurred either when the IPC sleeves had been removed or when skin breaks affected the heels (which are not covered by IPC). Therefore, they were unlikely to be caused by the use of IPC.[6]

A 2022 systematic review found that reported adverse events were limited to bleeding and skin injury, with no difference in the incidence of adverse events between groups.[7] Rabe et al. 2020[8] also showed fewer incidence of adverse events ranging from 1 to 10%, which non-severe events such as skin irritation, discomfort, pain and forefoot edema. Most of these adverse events were caused by inadequate fit, improper application of compression devices, or incorrect indication.[8]

Certainty of evidence

There is moderate certainty of evidence on the use of intermittent pneumatic compression (IPC) for immobile patients hospitalized for acute ischemic stroke due to common issues regarding risk of bias (blinding). Likewise, the certainty of evidence is moderate for mortality due to imprecision. In terms of adverse events, there is moderate certainty for risk of bias.

Table Q10.1. Summary of findings: intermittent pneumatic compression for acute ischemic stroke.

Outcomes	IPC	Standard care	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Any VTE (1 RCT, n=1438)	122/1438 (8.5%)	174/1438 (12.1%)	**RR 0.67** (0.53, 0.86)	Favors IPC	MODERATE ⊕⊕⊕◯
All-cause mortality (1 RCT, n=1438)	156/1438 (10.8%)	189/1438 (13.1%)	**RR 0.80** (0.64, 1.01)	Favors IPC	MODERATE ⊕⊕⊕◯
Any adverse events (1 RCT, n=1438)	44/1438 (3.05%)	20/1438 (1.39%)	**RR 2.24** (1.31, 3.82)	Favors control	MODERATE ⊕⊕⊕◯

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Other considerations

Cost and cost-effectiveness

In the Philippines, IPC cost varies between private and government-owned hospitals. A cost estimate, which included the cost of sleeves and one day use of machine, ranges between P2,250.00 to P3,250.00 for government hospitals and between P5,515.00 to P7,600.00 for private hospitals. With an average hospital stay of 7 days for acute ischemic stroke patients, [9] mean cost of IPC use was estimated between P3,750.00 to P5,000.00 (government) and P8,791.00 to P11,200.00 (private).

Table Q10.2. Cost estimates for intermittent pneumatic compression.

Parameter	Intervention	
	Private	Government
Cost of sleeves	4,969 to 7,000.00	2,000.00 to 3,200.00
Use of machine per day	546 to 600.00	250.00
Average length of hospital days	7 days*	7 days*
Cost of pneumatic compression per patient	**PHP 8, 791 to 11,200.00**	**PHP 3,750.00 to 5,000.00**

In the CLOTS3 study, a within-trial cost utility analysis was performed to estimate the cost-effectiveness of IPC with an intention-to-treat analysis. From the results of this analyses, the estimated average cost of the use of intermittent pneumatic compression was estimated at £64.10 (~PHP 4,300) per patient, including the cost of sleeves, fitting, and monitoring. With the mean hospital stay of 19.5 days and a median of 9 days, the mean cost of using IPC during hospitalization was estimated to be at £12,567 (~PHP 840,000).[6]

Patient's values and preferences, equity, acceptability, and feasibility

Grenall et al in 2020 did a systematic review regarding factors affecting adherence to intermittent pneumatic compression.[10] Results of the review, which included 20 studies, identified eight factors which affected adherence to intermittent pneumatic compression: patient discomfort (restlessness, insomnia during the night due to noise), healthcare professionals' knowledge and behaviors (nurses never initiated IPC therapy and errors in application of the IPC therapy), mobilization (most of the respondents said that they had just mobilized), equipment supply and demand (non-availability of sleeves or machine in the patient), the use of guidelines (hospitals using protocols resulted to higher provision of prophylaxis), intensive care context (adherence of VTE prophylaxis was higher in the ICU than elsewhere in the hospitals) , computer-assisted prescribing (increased prescribing of IPC but not over-all adherence) and patients' knowledge of IPC (patients' lack of knowledge regarding DVT and importance of IPC). Results of this study, however, were largely based on direct observation rather than self-report and included studies that had low sample sizes.

Recommendations from other groups

The 2016 ESO Guidelines[3] and the 2019 AHA/ASA guidelines[4] for the management of acute ischemic stroke strongly recommends the use of intermittent pneumatic compression for the prevention of venous thromboembolism.

Table Q12.3. Summary of recommendations from other CPGs.

Group	Recommendation	Strength of recommendation and certainty of evidence
ESO 2016[3]	We recommend that intermittent pneumatic compression (IPC) (thigh-length, sequential) should be used for immobile patients with ischemic stroke. It should not be used in patients with open wounds on the legs and should be used with caution in those with existing DVT, heart failure, severe peripheral vascular disease or confusion where attempts to mobilize when unsupervised could lead to falls and injury.	Strong recommendation, moderate quality of evidence
AHA/ASA 2019[4]	In immobile stroke patients without contraindications, intermittent pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended over routine care to reduce the risk of deep vein thrombosis (DVT).	Class 1 (strong recommendation), level of evidence B-R (moderate)

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Venous thromboembolism (VTE) prophylaxis

Q11. Should we use intermittent pneumatic compression (IPC) as add-on therapy to standard of care compared to non-use among immobilized patients hospitalized with acute intracerebral hemorrhage (ICH)?

RECOMMENDATION 11:

Among immobilized patients hospitalized with acute ICH, we suggest the use of intermittent pneumatic compression, compared to standard care alone (non-use).

Overall Level of Certainty: **Moderate** ⊕⊕⊕◯
Strength of Recommendation: **Weak**

CONSENSUS ISSUES

The recommendation in favor of intermittent pneumatic compression (IPC) was based on moderate certainty evidence indicating its effectiveness in reducing the incidence of symptomatic and asymptomatic deep vein thrombosis (DVT). Despite a notable increase in skin breaks and a trend towards more falls with injury, the absolute risk of these adverse events was low, and many of them were not definitively linked to IPC use.

Acknowledging the limited availability of IPC and its associated cost, the panel opted for a weak recommendation. This acknowledges that while IPC can be beneficial, other factors such as accessibility and affordability should be considered when implementing this intervention.

BACKGROUND

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), poses a potentially life-threatening risk and is associated with significantly adverse outcomes. Autopsy findings indicate that 50% of patients who succumb to acute stroke exhibit evidence of PE. VTE is a crucial and preventable occurrence, especially in hospitalized patients. Local data showed that 2.8% of patients in the medical and neurological ICUs develop VTE.[1] Effective and efficient strategies to prevent VTE exist, but literature showed that despite chemoprophylaxis, VTE still occurred in 2.9% of neurocritical care patients.[2] Patients who are hospitalized due to intracerebral hemorrhage (ICH) present with unique challenges due to competing risk of bleeding and re-bleeding.

The latest AHA/ASA guideline for acute ICH management asserts that graduated knee- or thigh-high compression stockings alone lack effectiveness as prophylactic therapy for VTE prevention, carrying a class 3 (harm) strength of recommendation.[3] The current endorsed recommendation advocates for the use of intermittent pneumatic compression (IPC) initiated on the day of ICH diagnosis. IPC involves inflatable sleeves wrapped around the legs, connected to a bedside electric pump via tubing. Theoretically, IPC mitigates VTE risk by enhancing venous blood flow in the deep veins of the leg and stimulating the release of intrinsic fibrinolytic substances.

SUMMARY OF THE EVIDENCE

Evidence considered

The CLOTS 3 RCT with a total enrollment of 2,876 stroke patients, including both ischemic and hemorrhagic cases (322 ICH patients) across 94 UK centers, was used as the basis for this guideline recommendation.[4] Inclusion criteria involved stroke patients admitted to the hospital within 3 days, immobilized and unable to move without assistance (i.e., not able to get up from a chair/out of bed and walk to the toilet without the help of another person). Standard stroke care, encompassing early mobilization, hydration, and antiplatelet or anticoagulant drugs as per local protocols, was provided to all patients. Random assignment placed participants into either the 'routine care plus thigh-length IPC (Kendall SCD™ Express system)' or the 'routine care and no IPC' group.

The primary outcome at 30 days focused on the occurrence of symptomatic or asymptomatic DVT in the popliteal or femoral veins, confirmed through imaging. Secondary outcomes included death, any DVT or PE, skin breaks, falls with injuries or fractures, duration of IPC use within 30 days, any DVT or PE, survival, and functional status at 6 months. Notably, there was no subgroup analysis for ICH concerning the secondary outcomes.

Benefits and harms

Incidence of DVT

Proximal DVT within 30 days occurred in 11 of 163 patients (6.7%) in the IPC group and in 27 of 159 patients (17%) in the routine care and no IPC group (RR 0.40 [95%CI 0.20, 0.77]; moderate certainty).

Safety outcomes

Safety outcomes were sought but there were no critical outcomes reported in the eligible study found.

Certainty of evidence

The overall certainty of evidence is rated moderate due to indirectness. The methodological quality of the included study was high.

Other considerations

Cost and cost-effectiveness

Patients are responsible for purchasing IPC sleeves, with private hospitals like St. Luke's Medical Center, Makati Medical Center, and The Medical City charging between PHP 4,969 to 7,000 for the sleeves. The daily rental cost for the bedside electric pump in these private hospitals is approximately PHP 546 to 600. In government hospitals such as the Philippine General Hospital and Quirino Memorial Medical Center, IPC sleeves cost around PHP 2,000, while the machine rental is about PHP 250 per day. For 7-30 day usage, IPC expenses can range from PHP 8,791 to PHP 25,000 in private hospitals and PHP 3,750 to PHP 9,500 in government hospitals.

Table Q11.1. Summary of findings: intermittent pneumatic compression for acute intracerebral hemorrhage.

Outcomes	Basis	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Proximal DVT	1 RCT (N=322)	RR 0.40 (0.20, 0.77)	Favors intervention	MODERATE[a]
a Downgraded due to indirectness *__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).__CI:__ confidence interval; __OR:__ odds ratio; __RR:__ risk ratio				
GRADE Working Group Certainty of Evidence __High certainty:__ We are very confident that the true effect lies close to that of the estimate of the effect. __Moderate certainty:__ We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. __Low certainty:__ Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. __Very low certainty:__ We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.				

Patient's values and preferences, equity, acceptability, and feasibility

Unfortunately, the IPC sleeves and electric pump are not available in most government hospitals. In cases where they are available, the supply is often limited.

Recommendations from other groups

The European Stroke Organization in 2014[5] strongly recommends intermittent pneumatic compression (IPC) to improve outcome and reduce the risk of DVT in immobile patients with ICH. The American Heart Association/American Stroke Association in 2022[3] also strongly recommends intermittent pneumatic compression starting on the day of diagnosis of non-ambulatory patients with spontaneous ICH for DVT and pulmonary embolism prophylaxis.

Table Q11.2. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation and certainty of evidence
ESO 2014[5]	We recommend intermittent pneumatic compression to improve outcome and reduce the risk of DVT in immobile patients with ICH[5].	Strong recommendation, moderate certainty
AHA/ASA 2022[3]	In non-ambulatory patients with spontaneous ICH, intermittent pneumatic compression (IPC) starting on the day of diagnosis is recommended for VTE (DVT and pulmonary embolism [PE]) prophylaxis.	Class I recommendation (strong), level of evidence B-R (moderate)

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Surgery for intracerebral hemorrhage

Q12. Should we do surgery on top of best medical management versus best medical management alone among patients with supratentorial intracerebral hemorrhage (ICH)?

RECOMMENDATION 12:

Among adult patients with supratentorial spontaneous intracerebral hemorrhage and signs of increased intracranial pressure, surgical evacuation of hematoma on top of best medical management may be considered.

Overall Level of Certainty: **Low** ⊕⊕◯◯
Strength of Recommendation: **Weak**

CONSENSUS ISSUES

The panel acknowledges that surgery may enhance functional outcomes and reduce the risk of secondary surgeries, especially in patients with intracerebral hemorrhage (ICH) showing signs of increased intracranial pressure, clinical deterioration, and progressive bleed volume. However, the certainty of these effects is low and may vary based on individual patient characteristics. The recommendation is particularly relevant to patients meeting specific criteria associated with ICH.

Given resource limitations and feasibility concerns, the panel issues a weak recommendation. Implementation may face challenges, especially in areas lacking access to neurosurgeons. Institutions without neurosurgeons could consider transferring eligible patients to facilities with neurosurgical capabilities. Manpower issues also impact timely surgical interventions, and while general surgeons may perform decompressive hemicraniectomy, its relative effectiveness and safety compared to clot evacuation surgery are not addressed in this guideline.

The panel does not provide a specific recommendation on the optimal timing of surgery or whether minimally invasive surgery should be preferred. However, existing evidence suggests potential benefits with both ultra-early surgery (<8 hrs) and minimally invasive surgery in improving functional outcomes.

BACKGROUND

Approximately 30% of strokes are hemorrhagic. Hemorrhagic strokes are more deadly than infarctions due to the sudden rise in intracranial pressure. However, if a patient survives, functional and neurologic outcomes are expected to be better than infarcts. It is also thought that the time window of recovery in ICH is shorter (within 10 weeks then plateaus) than in infarcts (26 weeks then plateaus).[1-5]

The outcome of ICH is determined by the severity of the primary and secondary injuries. The hematoma and perihematomal edema cause mechanical disruption of brain tissue, resulting in primary injury. Secondary injury results from inflammation, cellular dysfunction, and gliosis. Evacuation of the hematoma may reduce its volume, lowering the risk of herniation and death, but it may not result in less disability than the best medical management.[1-5]

SUMMARY OF THE EVIDENCE

Evidence considered

We found one systematic review and meta-analysis published in 2020 including 21 studies done between 1989 to 2019 involving 4,145 patients, comparing any surgery aimed at clot removal with the best medical treatment for spontaneous ICH.[5] The evidence base included any type of surgery for hematoma evacuation, including craniotomy, craniopuncture, stereotactic aspiration, and endoscopy-guided aspiration, with or without local clot mobilization with thrombolytics or similar agents. The outcomes assessed were good functional outcome defined as mRS 0 to 3, GOS 4 to 5, eGOS 5 to 8 or BI ≥ 60 at 3, 6, or 12 months post-op. Mortality and adverse events were also reported.[5]

One of the studies (Pantazis 2006)[6] looked at ultra-early surgery (i.e., surgery < 8 hours from the onset of stroke) versus best medical management. The study included 108 (54 for each arm) patients who had hematomas 30 ml or above. No significant difference between groups were observed in terms of age (61 ± 15 yrs), hematoma volume (55.3 ± 23.8 mL vs 56.7 ± 25.4 mL), location of hematoma, or Glasgow Coma Scores on admission. Patients were randomly assigned to either surgery or the best medical treatment, regardless of their clinical status. The ICH sites included the subcortical white matter (36%; n=39) and the putamen (64%; n=69). Each patient in the surgical arm underwent an open craniotomy, followed by a 15-20 mm dural incision. Early (i.e., within 8 hours) control of blood pressure (BP) was recommended if any of the following conditions were present: systolic BP of more than 180, diastolic BP of more than 105 mmHg, or mean arterial pressure of more than 130. In addition, 45 patients (83%) received operative treatment between 6 and 8 hours post ictus, whereas 9 patients (17%) were operated between 3 and 5 hours after onset.

Rebleeding occurred in 22% of the patients operated between 3 and 5 hours, compared with 9% of the patients operated between 6 and 8 hours after ictus. Two of 54 best medical treatment group patients required secondary surgery – one an external ventricular drainage for intraventricular extension of the putaminal hemorrhage done at day 0 and the other a clot removal done at day 3 because of clinical deterioration.[6]

Benefits and harms

<u>Good functional outcome</u>

Any surgical treatment was associated with better functional outcomes at 3 months compared to best medical therapy (RR 1.4 [95%CI 1.19 to 1.65]; 4 RCTs, N=593; low certainty). The same effect was seen at 6 months (RR 1.32 [95%CI 1.20 to 1.45]; 13 RCTs, N=2,807; moderate certainty) and 12 months (RR 1.20 [95%CI 1.02 to 1.42]; 3 RCTs; N=839; moderate certainty).

There was a better functional outcome with minimally invasive surgery compared to best medical therapy at 3 months (RR 1.40 [95%CI 1.19 to 1.65]; I^2=75%; 2 RCTs; N=472; very low certainty),

6 months (RR 2.56 [95%CI 1.99 to 3.31]; I^2=14%; 8 RCTs; N=1,115; moderate certainty) at 12 months (RR 1.20 [95%CI 1.01 to 1.42]; I^2=76%; 2 RCTs; N=731; low certainty).

Ultra-early surgery was also associated with better functional outcomes compared to best medical therapy (RR 4.9 [95%CI 1.66 to 14.43]; 1 RCT; low certainty).

Mortality

Any surgical treatment lowered the risk of death (RR 0.77 [95%CI 0.68 to 0.85]; $I^{2=}$ 21%; 21 RCTs; N=4,232; high certainty) at the time of follow up. Minimally invasive surgery also lowered the risk of death (RR 0.68 [95%CI 0.56 to 0.83]; I^2=14%; 13 RCTs; high certainty) at the time of follow-up.

Safety outcomes

Evidence suggested no conclusive difference between surgery and best medical management in terms of rebleeding (RR 0.86 [95%CI 0.66 to 1.12]; I^2=74%; 13 RCTs; N=1,683; very low certainty), severe systemic infection (RR 1.29 [95%CI 0.95 to 1.74]; I^2=75%; 5 RCTs; N=1,156; very low certainty), operative site infection (RR 1.53 [95%CI 0.39 to 5.97]; I^2=0%; 5 RCTs; N=719; low certainty), seizure (RR 1.40 [95%CI 0.58 to 3.59]; I^2=17%; 5 RCTs, N=719; low certainty). The risk of having to undergo secondary surgery (e.g., external ventricular draining, hemicraniectomy, etc.) on top of clot evacuation with any surgery was significant less compared to best medical management (RR 0.31 [95%CI 0.24 to 0.40]; I^2=69%; 11 RCTs; N=3,034; very low certainty).

Certainty of evidence

The certainty of evidence is rated from very low to moderate low due to issues on inconsistency, imprecision, and risk of bias.

Other considerations

Cost and cost-effectiveness

No local study has explored the costs associated with disability resulting from a stroke when a good functional outcome is not achieved. However, the expenses related to surgical intervention for ICH are considerable. These may encompass admission costs to an Acute Stroke Unit/Intensive Care Unit (ranging from nil to PHP 100,000 per day), professional fees for the neurosurgical team (ranging from nil to PHP 500,000), and fees for the intensive care team (ranging from nil to PHP 5,000 per day). In resource-limited settings, ASU or ICU care may either be unavailable or expensive. Moreover, in many hospitals, neurosurgical services may not be accessible or could be costly.

Patient's values and preferences, equity, acceptability, and feasibility

Many Filipinos are averse to neurosurgery, deeming it extreme, especially for the elderly. Because consent from the patient or his/her family is necessary in any surgical procedure, it may be easier to get consent for surgery using guideline-based recommendations.

Recommendations from other groups

Table Q12.1. Summary of findings: surgery versus best medical management for supratentorial ICH.

Outcomes	Basis	Effect Estimate (95% CI)	Interpretation	Overall Certainty of Evidence
Any surgery vs. best medical management				
Good functional outcome at 3 months	4 RCTs (n=593)	**RR 1.40** (1.19, 1.65)	Favors surgery	LOW[a,d] ⊕⊕◯◯
Good functional outcome at 6 months	13 RCTs (n=2,807)	**RR 1.32** (1.20, 1.45)	Favors surgery	MODERATE[a] ⊕⊕⊕◯
Good functional outcome at 12 months	3 RCTs (n=839)	**RR 1.20** (1.02, 1.41)	Favors surgery	MODERATE[a] ⊕⊕⊕◯
Rebleeding	13 RCTs (n=1,683)	**RR 0.86** (0.66, 1.12)	Inconclusive	VERY LOW[a,c,d] ⊕◯◯◯
Severe systemic infection	5 RCTs (n=1,156)	**RR 1.29** (0.95, 1.74)	Inconclusive	VERY LOW[a,c,d] ⊕◯◯◯
Operative site infection	5 RCTs (n=719)	**RR 1.53** (0.39, 5.97)	Inconclusive	LOW[a,c] ⊕⊕◯◯
Seizure	2 RCTs (n= 652)	**RR 1.44** (0.58, 3.59)	Inconclusive	LOW[a,c] ⊕⊕◯◯
Secondary surgery (EVD, hemicraniectomy, etc)	11 RCTs (n=3,034)	**RR 0.31** (0.24, 0.40)	Favors surgery	LOW[a,c] ⊕⊕◯◯
Minimally invasive surgery vs. best medical management				
Good functional outcome at 3 months	2 RCTs (n=472)	**RR 1.40** (1.19, 1.65)	Favors surgery	LOW[a,d] ⊕⊕◯◯
Good functional outcome at 6 months	8 RCTs (n=1,115)	**RR 2.56** (1.99, 3.31)	Favors surgery	MODERATE[a] ⊕⊕⊕◯
Good functional outcome at 12 months	2 RCTs (n=731)	**RR 1.20** (1.01, 1.42)	Favors surgery	LOW[a,d] ⊕⊕◯◯
Ultra-early surgery vs. best medical management				
Mortality	1 RCT (n=108)	**RR 0.84** (0.59, 1.20)	Inconclusive	MODERATE[c] ⊕⊕⊕◯
Good functional outcome	1 RCT (n=108)	**RR 4.9** (1.66 to 14.43)	Favors surgery <8 hrs	MODERATE[a] ⊕⊕⊕◯

a. Downgraded due to risk of bias
b. Downgraded due to indirectness
c. Downgraded due to imprecision
d. Downgraded due to inconsistency

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Recommendations from other groups

The European Stroke Organization concludes that there is no evidence to support routine surgical intervention to improve outcome after supratentorial ICH when compared to conservative management, but early surgery may be beneficial for patients with a GCS of 9 to 12.[7] According to the American Heart Association/American Stroke Association (AHA/ASA), minimally invasive approaches for evacuating supratentorial ICHs and intraventricular hemorrhages have lower mortality rates than medical management alone. The clinical trial evidence supporting the improvement of functional outcomes with these procedures is neutral.[8]

Table Q12.2. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation and certainty of evidence
ESO 2014[7]	Improvement in outcome for adults with supratentorial ich who underwent surgical hematoma evacuation compared with conservative management	Weak recommendation, moderate certainty
AHA/ASA 2022[8]	For patients with supratentorial ICH of >20- to 30-mL volume with GCS scores in the moderate range (5—12), minimally invasive hematoma evacuation with endoscopic or stereotactic aspiration with or without thrombolytic use can be useful to reduce mortality compared with medical management alone.	Class 2a (moderate strength of recommendation), level of evidence B-R (moderate)
	For patients with supratentorial ICH of >20- to 30-mL volume with GCS scores in the moderate range (5—12) being considered for hematoma evacuation, it may be reasonable to select minimally invasive hematoma evacuation over conventional craniotomy to improve functional outcomes.	Class 2b (weak recommendation), level of evidence B-R (moderate)
	For patients with supratentorial ICH of >20- to 30-mL volume with GCS scores in the moderate range (5—12), the effectiveness of minimally invasive hematoma evacuation with endoscopic or stereotactic aspiration with or without thrombolytic use to improve functional outcomes is uncertain.	Class 2b (weak recommendation), level of evidence B-R (moderate)
	For most patients with spontaneous supratentorial ICH of moderate or greater severity, the usefulness of craniotomy for hemorrhage evacuation to improve functional outcomes or mortality is uncertain.	Class 2a (moderate strength of recommendation), level of evidence A (high)
	In patients with supratentorial ICH who are deteriorating, craniotomy for hematoma evacuation might be considered as a lifesaving measure.	Class 2b (weak recommendation), level of evidence C-LD (limited data)

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Decompressive hemicraniectomy

Q13. Should we do decompressive hemicraniectomy on top of medical therapy among patients with malignant MCA infarction?

RECOMMENDATION 13A:

Among adult patients aged 60 years or younger with malignant MCA infarction, surgical decompression on top of medical management may be considered.

Overall Level of Certainty: **Moderate** ⊕⊕⊕◯
Strength of Recommendation: **Weak**

RECOMMENDATION 13B:

Among adult patients aged > 60 years with malignant MCA infarction, surgical decompression on top of medical management may be considered.

Overall Level of Certainty: **Low** ⊕⊕◯◯
Strength of Recommendation: **Weak**

CONSENSUS ISSUES

The recommendations supporting decompressive hemicraniectomy for patients with malignant middle cerebral artery (MCA) infarction are based on its observed benefits in reducing mortality rates. However, the application of these recommendations across different healthcare settings faces several challenges.

Firstly, while the procedure increases survival rates, it often results in diminished functional outcomes, imposing significant costs and affecting the quality of life for both patients and their families. Optimizing rehabilitation services after surgery is crucial in maximizing functional recovery. Secondly, healthcare providers must sufficiently discuss to families the expected benefits and risks of decompressive hemicraniectomy, which includes exploring patients' values and preferences regarding survival versus quality of life and function. Thirdly, there is a need to strengthen community-based rehabilitation services, such as expanding facilities and ensuring an adequate number of qualified staff. Involving family medicine physicians before discharge can facilitate the transition to rehabilitation and ongoing care. Furthermore, ensuring insurance coverage for decompressive hemicraniectomy is essential to mitigate disparities in access to this treatment option, thereby ensuring equitable healthcare provision. Lastly, given the differing impacts of decompressive hemicraniectomy on functional outcomes based on age, separate recommendation statements were issued for younger and older patients.

BACKGROUND

Malignant MCA infarction can lead to life-threatening brain edema, occurring in 2% to 8% of patients within the first 4 days after stroke onset.[1-4] Conservative treatment alone has been associated with death rates of up to 80%,[5,6] as reported in randomized clinical trials and intensive care–based series. Surgical decompression, involving a large hemicraniectomy and duraplasty, consistently lowers the risk of death in clinical trials and enhances the likelihood of a favorable outcome.[15,17]

SUMMARY OF THE EVIDENCE

Evidence considered

This guideline recommendation is based on evidence from eight randomized trials (RCTs),[7-14] which were also part of previous systematic reviews and meta-analyses.[15-17] The trials involved 362 adult patients, with ages ranging from 43 to 70 years, experiencing malignant MCA infarctions within 48–96 hours of stroke onset. The definition of malignant MCA infarction was consistent across the RCTs, incorporating clinical signs, stroke severity, and imaging findings.

The majority of the trials specified baseline stroke severity, indicating severe strokes with mean NIHSS ranging from 20 to 24. Notably, one RCT by Zhao et al. used CT scan findings, defining malignant MCA as ischemic signs involving at least 2/3 of the MCA territory with a decrease in consciousness to a Glasgow Coma Scale (GCS) score of <9 within 48 hours.

Early RCTs (DECIMAL, DESTINY, HAMLET)[7-9] included patients up to 60 years old, while later RCTs (Zhao et al., Slezins et al., HeADDFIRST, HeMMi)[11-14] extended the age inclusion criterion up to and including 80 years. The treatment window varied, with some trials (HAMLET, HeADDFIRST, and HeMMI)[8,12,13] allowing intervention up to 48 hours after symptom onset and others permitting treatment beyond 48 hours. All trials enrolled previously independent patients (i.e., mRS ≤ 2) with very severe strokes and infarcts involving two-thirds or more of the MCA territory.

Benefits and harms

<u>30-day mortality</u>

Decompressive hemicraniectomy has shown to significantly reduce the risk of death compared to medical therapy alone at 30 days, 6 months, and 1 year follow-up in adult patients of all ages with malignant middle cerebral artery (MCA) infarction, provided the intervention is initiated within 48 hours of stroke onset. In younger patients (≤60 years old), this mortality reduction benefit is observed at 1 month, 6 months, and 1 year when surgery is performed within 48 hours of stroke onset. However, if the intervention is delayed beyond 48 hours, decompressive hemicraniectomy does not show significant superiority over medical therapy alone in terms of mortality.

For older patients (>60 years old), a similar mortality benefit is observed at 6 months and 1 year follow-up if the procedure is conducted within 48 hours of stroke onset. There are no available data on the effect of this intervention if started beyond 48 hours on this older population at 6 months follow up. Overall, early initiation of decompressive hemicraniectomy within 48 hours of stroke onset appears to be associated with better outcomes in terms of mortality reduction, especially in younger patients.

<u>Functional outcome at 6 months</u>

Decompressive hemicraniectomy demonstrates significant efficacy in reducing the risk of poor functional outcomes, defined by a modified Rankin Scale score > 3, among patients aged 18 to 60 years when initiated within 48 hours of stroke onset. A meta-analysis of five randomized controlled trials (DESTINY, DECIMAL, HeADDFIRST, HeMMI, Zhao et al.) comprising 122 patients in this age group showed a notable absolute risk reduction of 16% at 6 months (RR 0.81, 95% CI 0.66 to 0.99, $p < 0.05$, I2=0%). However, no significant benefit was observed beyond 48 hours post-stroke onset or among patients over 60 years old.

Contrarily, among patients aged over 60 years, decompressive hemicraniectomy did not show significant efficacy in reducing the risk of poor functional outcomes at 6 months, regardless of the timing of intervention within 48 hours. A meta-analysis of two RCTs (DESTINY II, Zhao et al.) involving 141 patients in this age group revealed no statistically significant difference in outcomes at 6 months (RR 0.96, 95% CI 0.89 to 1.04, $p = 0.29$).

Safety outcomes

Serious and other major adverse events

Based on moderate certainty of evidence from 6 RCTs (N=283), it was inconclusive whether decompressive hemicraniectomy resulted in significantly more serious adverse events than medical treatment alone. Most commonly reported adverse events included brain herniation, myocardial infarction, symptomatic epidural hemorrhage. Some trials, such as the DESTINY II, HEADDFIRST, and the Slezins concluded no significant difference in the incidence of these adverse events between the treatment groups.

Certainty of evidence

The overall certainty of evidence was low across critical outcomes. Reasons for downgrading included serious risk of bias and/or imprecision associated with confidence intervals. Most RCTs were small and suffered from a certain amount of bias. Blinding of participants and personnel to the procedure could not be performed in any trial, and often blinding of the procedure in outcome assessment was not applied or was unclear in many trials. In addition, allocation concealment was not always clear, and several trials were stopped early.

Table Q13.1. Summary of findings: decompressive hemicraniectomy for patients with malignant MCA infarction.

Outcomes	Stroke onset	Basis	Effect Estimate (95%CI)	Interpretation	Certainty of Evidence
Patients ≤ 60 years old					
Mortality reduction (30 days)	< 48 hrs	2 RCTs (N=42)	**RR 0.25** (0.08, 0.79)	Favors DHC plus medical treatment	HIGH ⊕⊕⊕⊕
	> 48 hrs	1 RCT (N=14)	**RR 0.75** (0.14, 3.90)	Inconclusive	MODERATE[a] ⊕⊕⊕◯
Mortality reduction (6 months)	< 48 hrs	6 RCTs (N=122)	**RR 0.43** (0.27, 0.69)	Favors DHC plus medical treatment	HIGH ⊕⊕⊕⊕
	> 48 hrs	1 RCT (N=14)	**RR 1.13** (0.27, 4.76)	Inconclusive	MODERATE[a] ⊕⊕⊕◯
Mortality reduction (1 year)	< 48 hrs	4 RCTs (N=145)	**RR 0.42** (0.28, 0.61)	Favors DHC plus medical treatment	HIGH ⊕⊕⊕⊕
Risk of poor outcome (mRS >3)	< 48 hrs	4 RCTs (N=122)	**RR 0.81** (0.66, 0.99	Favors DHC plus medical treatment	MODERATE[b] ⊕⊕⊕◯
	> 48 hrs	5 RCTs (N=151)	**RR 0.75** (0.60, 0.94)	Favors DHC plus medical treatment	MODERATE[b] ⊕⊕⊕◯
Patients > 60 years old					
Mortality reduction (6 months)	< 48 hrs	2 RCTs (N=141)	**RR 0.40** (0.21, 0.76)	Favors DHC plus medical treatment	HIGH ⊕⊕⊕⊕
Mortality reduction (1 year)	< 48 hrs	2 RCTs (N=138)	**RR 0.47** (0.21, 0.88)	Favors DHC plus medical treatment	HIGH ⊕⊕⊕⊕
Risk of poor outcome (mRS >3)	< 48 hrs	2 RCTs (N=141)	**RR 0.96** (0.89, 1.04)	Inconclusive	LOW[a,b] ⊕⊕◯◯
	> 48 hrs	2 RCTs (N=138)	**RR 0.97** (0.89, 1.06)	Inconclusive	LOW[a,b] ⊕⊕◯◯

a Downgraded due to imprecision
b Downgraded due to risk of bias
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio; **MD**: mean difference

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Other considerations

Cost and cost-effectiveness

When comparing hospitalization costs for patients with malignant MCA infarction undergoing decompressive hemicraniectomy plus medical treatment versus those receiving medical

treatment alone, various factors, including hospitalization days, ICU duration, medication expenses, and more, must be considered. Estimating these costs is challenging. However, PhilHealth insurance covers decompressive hemicraniectomy for ischemic stroke at a rate of PHP 37,800, compared to PHP 28,000 for ischemic stroke without surgery. In private hospitals, neurosurgeon fees typically range from PHP 150,000 to PHP 300,000, and anesthesiologist fees range from PHP 100,000 to PHP 200,000. Regardless of surgery, daily charges from neurologists, cardiologists, and other specialists range from PHP 1,000 to P3,500. Naturally, decompressive hemicraniectomy entails higher costs than medical therapy alone.

Patient's values and preferences, equity, acceptability, and feasibility

The primary goal of surgery is to reduce increased intracranial pressure and herniation, not to reverse the neurological deficits caused by the stroke. According to the findings of this evidence review, decompressive hemicraniectomy increases the chances of survival but also the likelihood that surviving patients will be severely disabled. This should be thoroughly explained to patients or their legal guardians before treatment decisions are made.

Recommendations from other groups

Table Q13.2. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation and certainty of evidence
2021 ESO[17]	In adult patients ≤ 60 yrs with space-occupying hemispheric infarction who can be treated within 48 hours of stroke onset we recommend surgical decompression to reduce the risks of death or a poor outcome.	Strong recommendation, moderate certainty of evidence
	In patients aged 61 years or older with space-occupying infarction who can be treated within 48 hours of stroke onset we suggest considering surgical decompression to reduce the risk of death. Surgery should only be done after a shared decision process including a careful discussion with the patient or his/her representatives about the risk of survival with substantial disability.	Weak recommendation, low certainty of evidence
2019 AHA/ASA[18]	In patients ≤ 60 years of age who deteriorate neurologically within 48 hours from brain swelling associated with unilateral MCA infarctions despite medical therapy, decompressive craniectomy with dural expansion is reasonable.	Class 2a (moderate strength of recommendation), level of evidence A (high)
	In patients > 60 years of age who deteriorate neurologically within 48 hours from brain swelling associated with unilateral MCA infarctions despite medical therapy, decompressive craniectomy with dural expansion may be considered.	Class 2a (moderate strength of recommendation), level of evidence A (high)
2022 Canadian Stroke Best Practice Recommendations [19]	For patients aged ≤60 yrs old, hemicraniectomy should be considered as a life-saving measure for patients in the early stages of extensive (malignant) middle cerebral artery (MCA) territory ischemic stroke (defined as infarction size >50% MCA territory on visual inspection, or an ischemic lesion volume >150 cm^3 and concomitant clinical features) if patients or their substitute decision-makers are willing to accept a significant risk of living with a degree of disability that may leave them dependent on others for their activities of daily living.	Strong recommendation, high certainty of evidence
	Hemicraniectomy could also be considered for patients aged 60 – 80 years.	Weak recommendation,

	moderate certainty of evidence

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Neuroprotective agents

Q14. Should we routinely give edaravone as an add-on therapy among patients with acute stroke?

RECOMMENDATION 14A:

Among patients with acute ischemic stroke, we do not recommend the routine use of edaravone as add-on therapy.

Overall Level of Certainty: Low ⊕⊕◯◯
Strength of Recommendation: **Strong**

RECOMMENDATION 14B:

Among patients with acute intracerebral hemorrhagic stroke, we do not recommend the routine use of edaravone as add-on therapy.

Overall Level of Certainty: Low ⊕⊕◯◯
Strength of Recommendation: **Strong**

CONSENSUS ISSUES

The routine use of edaravone was not recommended primarily since the current available evidence suggests no conclusive benefit or harm for patients with acute ischemic and hemorrhagic stroke. In addition, costs of edaravone is substantial and may not be accessible to most Filipino stroke patients. The variability in the standard of care used in the included trials added to the uncertainty about the effects edaravone. As with other neuroprotectants, the impact of edaravone on improving function as well as its associated adverse events require clarification in subsequent international or local trials.

BACKGROUND

Stroke may lead to a myriad of damaging pathological processes which include inflammation, excitotoxicity, oxidative stress, apoptosis, and cerebral edema resulting from damages to the blood-brain-barrier. For patients with intracerebral hemorrhage, physical damage resulting from the mass of collected blood as well as the cytotoxicity of the components contribute to the insult.[1]

There are considerable number of novel treatments intended to protect the brain from damages resulting from stroke although still with limited evidence of success, one of which is edaravone. Edaravone (MCI-186, 3-methyl-1-phenyl2-pyrazoline-5-one) is a novel free radical scavenger, which, in in-vitro studies, prevents vascular endothelial injury, delays neuronal death in transient cerebral ischemia and ischemic brain edema, and inhibits activation of lipoxygenase pathway in the arachidonic acid cascade and peroxidation of the phosphatidylcholine liposomal membrane.[2]

This review synthesized evidence on the effects of edaravone as an add-on therapy to routine care on various outcomes, such as improvement in the neurological impairment, all-cause mortality, and safety/adverse events among adult patients with acute stroke.

SUMMARY OF THE EVIDENCE

Evidence considered

A total of 13 randomized controlled studies (RCTs) regarding the use of edaravone in acute stroke were reviewed: 7 RCTs for acute ischemic stroke (AIS) and 6 RCTs for acute intracerebral hemorrhagic stroke (AICHS).

Edaravone for acute ischemic stroke

Evidence came from 7 RCTs that included a total of 745 acute ischemic stroke patients who received either edaravone or placebo/standard of care.[1-7] The first and the landmark trial (Otomo 2003)[5] for edaravone was the biggest study involving 250 participants in Japan. While most of the studies[1-3,6] were done between 2010 to 2019. Only two Chinese studies[4,7] were published 2020 onwards.

Most of the studies used the standard dosing of edaravone 30mg intravenously twice a day given from a range of 7-14 days except for the study of Kaste[1] which used a loading dose and a weight-based infusion of edaravone for 72 hours. Most of the studies compared edaravone versus a placebo while the studies of Sun 2019[4], Li 2020a[3], and Li 2020b[2] compared combination of edaravone with ASA/ ligustrazine, ASA/tPA and ASA alone, respectively. Standard of care varied across trials. Studies also did not mention if thrombectomy was done among the study participants.

Assessment of outcomes on neurologic function were pegged at the end of study and during the 90th day post intervention as these were the most common follow-up period among the included studies. The studies of Otomo 2003[5] and Sharma 2011[6] were pooled to investigate the effect of edaravone on mortality. Three RCTs[1,5,6] were pooled to investigate edaravone's role in neuroprotection and 4 RCTs[1,3,5,6] were pooled to investigate its safety.

Edaravone for acute hemorrhagic stroke

A total of 6 RCTs were included involving 440 participants.[8-13] The original articles were not retrieved as the studies are not available on public domain and are written in Chinese. Data which the evidence reviewers considered as important were extracted from the available meta-analyses.[14,15] All studies were done in China and included patients with AICHS diagnosed clinically and proven with cranial CT scan. In all of the above RCTs, patients who were considered as "non-surgical" as those requiring surgery were excluded. The intracerebral hemorrhage volume and location of the bleed were not mentioned in the available references.

All trials compared edaravone at 30mg twice daily plus routine treatment versus routine treatment alone given for 14 days except for the study of Li 2005[16] and Geng 2004[17] which extended the treatment duration to 19 days and 28 days, respectively. The accurate timing of the start of treatment after stroke, however, was not reported. For the evaluation of improvement in

neurological impairment using NIHSS, 4 trials[8-10, 18] were included with the assessment done ranging from 28 to 90 days.

Benefits and harms

Table Q14.1. Summary of outcomes: edaravone for acute stroke.

Outcomes	Basis	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Edaravone in acute ischemic stroke				
Mortality at 90 days	2 RCTs (n=300)	**RR 0.86** (0.29, 2.49)	Inconclusive	LOW[a,b] ⊕⊕◯◯
Neurologic deficit improvement at 90 days[+]	3 RCTs (n=322)	**RR 1.23** (0.95, 1.59)	Inconclusive	LOW[a,b] ⊕⊕◯◯
Incidence of any treatment-related adverse event	5 RCTs (n=762)	**RR 0.82** (0.58, 1.17)	Inconclusive	MODERATE[b] ⊕⊕⊕◯
Edaravone in acute intracerebral hemorrhagic stroke				
Mortality at 90 days	1 RCT (n=79)	**RR 0.93** (0.20, 4.32)	Inconclusive	LOW[a,b] ⊕⊕◯◯
Incidence of any treatment-related adverse event	4 RCTs (n=199)	**RR 2.09** (0.71, 6.19)	Inconclusive	LOW[a,b] ⊕⊕◯◯

[+] Improvement defined as an mRS score of <2
a Downgraded due to risk of bias
b Downgraded due to imprecision
***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio; **MD**: mean difference

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Edaravone for acute ischemic stroke

Mortality at 90 days

No significant difference was observed between edaravone and placebo in terms of 90-day mortality among acute ischemic stroke patients (RR 0.86 [95%CI 0.29 to 2.49]; 2 RCTs; n=300; low certainty).

Neurologic deficit improvement at 90 days

There is no difference between those who received edaravone over standard of care in improving neurologic deficit as measured by a modified Rankin scale sore <2 at 90 days post-ictus (RR 1.23 [95%CI 0.95 to 1.59]; 3 RCTs; n=322; low certainty).

Safety outcomes

Nausea, skin rash and elevated liver enzymes were the top treatment-related adverse effects. Overall, there is no significant difference in the incidence of any treatment-related treatment side-effects among those given edaravone versus placebo (RR 0.82 [95%CI 0.58 to 1.17]; 5 RCTs; n=762; moderate).

Edaravone for acute intracerebral hemorrhagic stroke

Improvement of neurological impairment

None of the studies used mRS as a measure of the functional outcome. The MESSS, though the data are available in some studies, cannot be used as a surrogate outcome as it measures the quantity (severity) of the neurological impairment and not the degree of disability or dependence in daily activities after the stroke as measured by mRS.

Mortality at 90 days

Based on 1 RCT involving 79 patients, no significant reduction in mortality was observed for edaravone (RR 0.93; 95%CI 0.20 to 4.32, P = 0.92). There were 3 deaths among 41 participants (7%) in the edaravone group and 3 deaths among 38 participants (8%) in the control group. There is no significant reduction in mortality with edaravone (RR 0.93 [95%CI 0.20 to 4.32]; low certainty).

Safety outcomes

Meta-analysis of the 3 trials revealed that there was no significant difference between the two groups in terms of adverse events during the scheduled treatment (RR 2.09 [95% CI 0.71 to 6.19]; N=199; low certainty).

Three RCTs[8,12,13] including 199 patients reported the incidence of adverse events during the treatment. Four patients out of 66 participants (6.06%) in the treatment group and 2 patients out of 65 participants (3.08%) in the control group were reported with mild impairment of kidney function.[12,13]

Four patients out of 100 participants (4%) in the treatment group and 2 patients out of 65 participants (2%) in the control group were reported with mild impairment of kidney function.[12,13] One patient out of 36 participants (3%) with skin irritation was reported in the treatment group only.[13]

Certainty of evidence

Edaravone for acute ischemic stroke

Most of the studies only have low to uncertain risk of biases. However, the overall certainty of evidence across the different outcomes is rated low due to serious risk of bias (i.e., inconsistency with regards to duration of follow-up and the variety of treatment and control as well as to blinding in allocation concealment and the blinding of participants), and imprecision.

Edaravone for acute intracerebral hemorrhagic stroke

In general, the studies have low but mostly unclear risk of bias. Some articles were not retrieved as they are not available in the public domains and are written in Chinese. However, the data for all included studies were available for extraction and analysis. The risk of bias was done through triangulation between the assessment of the authors of the published meta-analyses and our assessment as the current evidence reviewers.

The quality of the included trials is generally poor due to following factors: the method of allocation was not reported, the blinding of outcome assessors were not reported, the functional neurological outcome of mRS and NIHSS at long term follow-up should have been directly measured, and the small number of participants.

However, the overall certainty of evidence (across the different outcomes) is rated low due to serious risk of bias (i.e., inconsistency with regards to duration of follow-up and the variety of treatment and control as well as to blinding in allocation concealment and the blinding of participants), and imprecision.

Other considerations

Cost and cost-effectiveness

Since its launch in the Philippines in November 2022, edaravone is available at a suggested retail price (SRP) of PHP 2,000 to 2,800 per vial. Currently, it is not yet included in the Philippine National Drug Formulary and as such, the expenses for this treatment will have to be shouldered by the patient out-of-pocket. The recommended schedule dosing of edaravone is 30 mg in 100 ml of normal saline infused over 60 minutes twice daily up to a duration of 14 days. This translates to a total cost of treatment for the medication alone of PHP 56,000 to 78,400, excluding the cost of materials and other miscellaneous expenses such as infusion fees.

Patient's values and preferences, equity, acceptability, and feasibility

No relevant studies were found.

Recommendations from other groups

The Japan Stroke Society[21] has grade B recommendation to add edaravone as a reasonable neuroprotective adjunct in acute ischemic stroke. There is no mention yet of edaravone in the American and the European stroke guidelines.

Table Q14.2. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation and certainty of evidence
Japan Stroke Society 2021[21]	In patients with acute ischemic stroke, edaravone is reasonable.	Grade B (moderate strength of recommendation), moderate level of evidence

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Neuroprotective agents

Q15. Should we give citicoline as an add-on therapy for adult patients with acute stroke?

RECOMMENDATION 15:

Among patients with acute stroke, we do not recommend the use of citicoline as an add-on therapy.

Overall Level of Certainty: **Moderate** ⊕⊕⊕◯
Strength of Recommendation: **Strong**

CONSENSUS ISSUES

A strong recommendation against giving citicoline for acute stroke patients was made by the panel due to the moderate to high certainty of evidence showing that it offers no additional benefit to placebo in terms of improving functional outcomes and stroke severity. This recommendation also was based on the high certainty of evidence suggesting that citicoline is associated with more central nervous system adverse events. Examples of these were hemorrhagic stroke transformation, carotid artery stenosis, decrease in level of consciousness, and dyskinesia. The panel also acknowledged that practitioners have been prescribing citicoline for several decades unsupported by evidence. The panel believes that this recommendation may encourage clinicians to focus more on other existing standard treatments for acute stroke and minimize the costs borne by patients for a drug that confers no clear benefit.

BACKGROUND

Citicoline is one of the various treatments being investigated to salvage the ischemic penumbra. Citicoline is the exogenous form of cytidine-5'-diphosphocholine (CDP-choline), a key intermediary in the generation of phosphatidylcholine, which is a major brain phospholipid.[2] Phospholipids are essential constituents of cells and have a high turnover rate, which requires continuous synthesis to ensure cell membrane integrity.[3] Impaired phospholipid metabolism as well as cell membrane damage have been implicated in the pathophysiology of cerebral ischemia. Choline precursors, such as citicoline, is said to promote the maintenance, repair and de novo formation of cell membrane phospholipids.[4] An important component of the neuroprotective effect of citicoline in an injured brain is said to be its ability to improve phosphatidylcholine synthesis in the injured brain.[4]

In experimental stroke models, citicoline has been found to reduce the size of the infarcted region, brain edema, decrease free fatty acid concentration, and improve neuronal survival.[5] These models have also shown that citicoline simultaneously inhibits different steps of the ischemic cascade, hence protecting the injured tissue against early and delayed mechanisms of glutamate-mediated ischemic brain injury as well as facilitate recovery by increasing neuroplasticity and facilitating synaptic growth.[6,7]

SUMMARY OF THE EVIDENCE

Evidence considered

A total of 9 randomized controlled trials fulfilled the inclusion criteria: 1 RCT on acute hemorrhagic stroke and 8 RCTs on acute ischemic stroke. For the risk of bias assessment, triangulation of the assessment of the authors in the most recent meta-analysis by Marti-Carvajal et al[8] and those of the current evidence reviewers' assessment was performed.

Citicoline for Acute Ischemic Stroke

Eight randomized controlled trials (RCTs) conducted from 1988 to 2022, involving 4,556 participants, were reviewed. Most studies on citicoline in acute ischemic stroke had low risk of bias with moderate quality of evidence due to imprecision. The study by Tazaki et al.[9] data were extracted from the meta-analysis by Marti-Carvajal et al.[8] All participants were clinically diagnosed with stroke, supported by radiographic evidence of ischemic stroke. Participants were primarily over 60 years old, mostly male, and had baseline NIHSS scores ranging from 11 to 18.[10-12] Six trials reported left hemisphere involvement in the majority of strokes, and four trials[12-15] identified large vessel atherosclerosis as the predominant stroke mechanism.

All RCTs compared citicoline with placebo, usual care, or other interventions, except Ghosh et al.[10], which combined citicoline with standard stroke therapy. Two trials included intravenous thrombolysis as an intervention. [14,15] The treatment duration was typically 6 weeks, with a follow-up period of up to 12 weeks. All-cause mortality was reported by all 8 RCTs[5,12-16], and adverse events were reported by 5 RCTs.[9,12-15]

Functional outcomes were assessed using outcomes from three scales: modified Rankin Scale (mRS), Barthel Index (BI), and National Institute of Health Stroke Scale (NIHSS) at 90 days. Four RCTs reported these scales. The assessment of all-cause mortality at 90 days involved 4 RCTs[9-11,16] with different primary outcomes—level of consciousness using the Japanese Coma Scale[9], change in lesion volume on diffusion-weighted MRI from baseline to 12 weeks[11], and Barthel Index alone.[10,16] The study characteristics and methodologies varied across trials, with some lacking sufficient information for bias assessment.

Citicoline for acute hemorrhagic stroke
A 2006 trial conducted in Spain investigated the impact of citicoline on 38 patients experiencing acute hemorrhagic stroke. This randomized, double-blind, placebo-controlled pilot study took place across four university hospitals. The inclusion criteria involved previously independent individuals aged 40 to 85 years, admitted within 6 hours of stroke onset, with neuroimaging confirmation of an acute supratentorial hemispheric cerebral hemorrhage. Exclusion criteria comprised intraventricular or subarachnoid hemorrhage, hemorrhage secondary to anticoagulant or other pathologies, coma, no motor deficits on NIHSS, INR greater than 1.7, any condition or treatment at baseline that would interfere with efficacy or safety assessments, and a life expectancy of less than 3 months. Baseline characteristics, risk factors, concomitant treatments, and comorbidities were similar between the two groups.
The primary endpoint focused on safety, while the efficacy endpoint assessed the proportion of independent participants at 3 months (mRS 0 to 2). Secondary efficacy endpoints included neurologic function measured by NIHSS and the volume of the residual lesion.

Benefits and harms

Most of the studies on citicoline in acute ischemic stroke did not show a significant difference in outcomes compared to placebo in terms of modified Rankin Scale, Barthel Index and National Institute of Health Stroke Scale score after 90 days of follow up. Even among participants who received recombinant tissue plasminogen activator, there was no significant difference in outcome between citicoline and placebo groups.

Severe adverse events were reported but there were no significant differences between the citicoline and placebo groups in terms of cardiovascular, respiratory, musculoskeletal, renal, and urologic and hematologic events. There was a significant difference in terms of central nervous system events but there was substantial heterogeneity among studies.

Degree of disability (mRs score)

A favorable outcome in terms of degree of disability or dependence in daily activities at 90 days was reported as a score of 0 to 2 on the modified Rankin Scale (mRS). There were 4 RCTs with a total of 3,690 participants, which reported this outcome. In the citicoline group, 433 of the 1,917 participants had a favorable outcome. On the other hand, 360 participants out of 1,773 had a favorable outcome in the placebo group. There was no heterogeneity among the RCTs included in the assessment ($I^2 = 0\%$). There was no significant difference in outcome in terms of mRS among those who received citicoline compared to placebo (RR 1.10; 95%CI 0.97 to 1.24; $I^2 = 0\%$; P = 0.15).

Functional recovery (Barthel Index) / neurological function (NIHSS)

For acute stroke cases, there was no significant difference between the citicoline and placebo groups in terms of favorable outcomes in the Barthel Index (RR 1.03, 95% CI 0.94 to 1.13, $I^2 = 5\%$, p = 0.57). Similarly, there was no significant difference in outcome on the NIHSS at 90 days between those who received citicoline and placebo (RR 1.09; 95%CI 0.98 to 1.23; $I^2 = 0\%$; P = 0.12). In a subgroup analysis among patients (n = 1,113) who received recombinant tissue plasminogen activator (rt-PA), there was no significant difference in outcome between those who received citicoline and placebo (RR 1.00; 95% CI 0.92 to 1.09, $I^2 = 0\%$, p = 0.97).

For acute hemorrhagic stroke, no significant impact of citicoline was noted compared to in terms of the proportion of patients having no disability (mRS $\leq$2) at 3 months (OR 5.38; 95% CI 0.55 to 52.4). NIHSS scores changed from 10.6 $\pm$ 6.2 at baseline to 5.2 $\pm$ 5.7 in the citicoline group whereas in the placebo group, scores were from 13.2 $\pm$ 6.5 to 7.8 $\pm$ 6.8 at 3 months. There was significant improvement in both groups (p <0.01) in the evolution of NIHSS scores (change) between baseline and 3 months without differences between groups.

Mortality

Eight RCTs with a total of 4,463 participants reported on all-cause mortality at 90 days of follow-up.[9-15] There was no significant reduction in mortality among those who received citicoline compared to placebo (citicoline 17.2% versus placebo 18.7%; RR 0.93; 95% CI 0.82 to 1.05; $I^2 = 0\%$; P = 0.24). In the only trial included for acute hemorrhagic stroke, only 1 death was reported the citicoline (n=19) and placebo group (n=19).[17]

Safety outcomes

For acute ischemic stroke

Five RCTs reported the severe adverse events in their trials (n = 3,957), classified into the organ system involved. Among those who received citicoline, the following are the number of participants who were reported to have severe adverse events: 165 participants (4.6%) with cardiovascular events, 254 participants (6.9%) with central nervous system events, 123 participants (3.3%) with respiratory events, 29 participants (2.2%) with gastrointestinal events, 10 participants (0.8%) with musculoskeletal events, 3 participants (0.8%) with hepatic events, 30 participants (1.8%) with renal and urologic events and lastly, 10 participants (0.6%) with hematologic events.

No significant differences between citicoline and placebo groups were found in terms of the different types of serious adverse events: cardiovascular (RR 1.04; 95% CI 0.84 to 1.29; $I^2 = 0\%$; P = 0.70), respiratory (RR 1.0; 95% CI 0.77 to 1.29; $I^2 = 0\%$; P = 0.97), musculoskeletal (RR 1.52; 95% CI 0.50 to 4.06; $I^2 = 0\%$; P = 0.46), renal and urologic (RR 1.76; 95% CI 0.91 to 3.41; $I^2 = 0\%$; P = 0.09) and lastly, hematologic (RR 1.27; 95% CI 0.46 to 3.51; $I^2 = 0\%$, P = 0.65).

In those who reported central nervous system events, there was a significant difference between those who received citicoline and placebo (favoring placebo), although there is substantial heterogeneity between the studies in the comparison (RR 1.30; 95%CI 1.07 to 1.58; $I^2 = 89\%$; P = 0.008). For those who reported gastrointestinal events, there was no significant difference between those who received citicoline and placebo and there is also substantial heterogeneity between the 2 studies (RR 0.61; 95%CI 0.38 to 0.96; $I^2 = 82\%$; P = 0.03).

For acute hemorrhagic stroke

There were 4 patients in each group who reported adverse events during the study. None of these were related to the active drug. There were no statistically significant differences between groups in the frequency of adverse events.

Certainty of evidence

The certainty of evidence is moderate for most outcomes due to serious imprecision.

Other considerations

Cost and cost-effectiveness

The total cost of a full treatment course of citicoline is estimated at PHP 10,287.00 based on current retail price of the drug in its intravenous and oral forms. Although there are no published economic studies yet related to neuroprotectants in the Philippines, these interventions are likely to post a substantial economic burden for low- and middle-income families. The current Philhealth package rate for stroke (ischemic or hemorrhagic) does not cover the cost of treatment as the drug is not currently included in the Philippine National Drug Formulary.

Table Q17.1. Summary of outcomes.

Outcomes	Intervention	Control	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence

mRS 0-2 at 90 days (4 RCTs, n=3,960)	433/1917 (22.5%)	360/1773 (20.3%)	**RR 1.10** (0.97, 1.24)	No significant difference	MODERATE ⊕⊕⊕◯
Barthel Index ≥ 95 at 90 days (5 RCTs, n=3,949)	684/2111 (32.4%)	559/1838 (30.4%)	**RR 1.03** (0.94, 1.13)	No significant difference	MODERATE ⊕⊕⊕◯
NIHSS 0-2 at 90 days (5 RCTs, n=3,949)	516/2111 (24.4%)	410/1838 (22.3%)	**RR 1.09** (0.98, 1.23)	No significant difference	MODERATE ⊕⊕⊕◯
All-cause mortality at 12 weeks (8 RCTs, n=4,463)	400/2324 (17.2%)	400/2139 (18.7%)	**RR 0.93** (0.82, 1.06)	No significant difference	MODERATE ⊕⊕⊕◯
Cardiovascular adverse events (3 RCTs, n=3,591)	7.8%	8.1%	**RR 1.04** (0.84, 1.29)	No significant difference	MODERATE ⊕⊕⊕◯
Central nervous system adverse events (4 RCTs, n=3,690)	8.9%	11.6%	**RR 1.30** (1.07, 1.58)	Favors control	HIGH ⊕⊕⊕⊕
Respiratory adverse events (4 RCTs, n=3,690)	5.9%	5.9%	**RR 1.00** (0.77, 1.28)	No significant difference	MODERATE ⊕⊕⊕◯
Gastrointestinal adverse events (2 RCTs, n=1,293)	6.1%	3.7%	**RR 0.61** (0.38, 0.96)	Favors citicoline	HIGH ⊕⊕⊕⊕

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio; **MD**: mean difference

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table Q17.2. Estimated costs associated with citicoline.

Parameter	Estimated cost
Unit cost of treatment	Citicoline 1 gram ampule – P 245.50 Citicoline 1 gram tablet – P 102.75 to P 113.00
Dosing frequency	1 gram IV q 12 for 3 days then 1 gram tab BID
Duration of therapy	6 weeks
Total cost of treatment	PHP 10,287.00 for a full course

Patient's values and preferences, equity, acceptability, and feasibility

No evidence was found on the social impact, including stigma of treatment, of citicoline among stroke patients in the Philippines and other countries.

Recommendations from other groups

No specific pharmacologic and non-pharmacologic neuroprotective agents are currently recommended for patients with acute ischemic stroke and transient ischemic attack by the American Heart Association/American Stroke Association 2019 (Class II, Level A) and European Stroke Organization 2008 (Class 1, Level A).

Table Q15.2. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation and certainty of evidence
American Heart Association / American Stroke Association 2019	At present, pharmacological or nonpharmacological treatments with putative neuroprotective actions are recommended.	Class 2b (weak recommendation), level of evidence A (high)
European Stroke Organization 2008	Currently, there is no recommendation to treat ischemic stroke with neuroprotective substances.	Class 1 (strong recommendation), level of evidence A (high)

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Neuroprotective agents

Q16. Should we give Cerebrolysin® as an add-on therapy for patients with acute ischemic stroke?

RECOMMENDATION 16:

Among patients with acute ischemic stroke, we do not recommend the use of Cerebrolysin® as an add-on therapy.

Overall Level of Certainty: **Low** ⊕⊕◯◯
Strength of Recommendation: **Strong**

CONSENSUS ISSUES

The panel has reached a consensus not to recommend the use of Cerebrolysin® due to the lack of clear evidence supporting its benefits and the potential for higher risk of non-fatal serious adverse events in patients. They stress the importance of conducting new studies to establish clearer evidence regarding the effectiveness and safety of Cerebrolysin® for neuroprotection in acute ischemic stroke patients. Additionally, identifying the optimal dosage of Cerebrolysin® should be a priority for future trials.

BACKGROUND

Cerebrolysin®, a unique neurotrophic peptide preparation derived from porcine brain tissue, has garnered attention as a potential treatment for acute ischemic stroke due to its proposed mechanisms of action, which include the stimulation of neurotrophic factors and potential attenuation of secondary injury cascades. Despite promising results in animal models, clinical trials of neuroprotective agents in humans, including cerebrolysin, have not yielded consistent efficacy.[3]

Nevertheless, cerebrolysin has been widely used in Russia, Eastern Europe, and Asia for the management of acute ischemic stroke. Given the need for a comprehensive review of the evidence, this study aims to provide an updated analysis of the efficacy and safety of cerebrolysin in patients with acute ischemic stroke.

SUMMARY OF THE EVIDENCE

Evidence considered

Eight articles were included in this review.[2-9] A total of 1,833 study participants were included in randomized controlled trials spanning from 2005 to 2017, investigating the efficacy and safety of cerebrolysin as an add-on agent in the treatment of acute ischemic stroke. The studies employed diverse treatment regimens, such as 30 mL for 10 days, 30 mL for 21 days, 50 mL for 21 days, and 30 mL for 7 days followed by 10 mL, 5 days a week for 3 weeks. Efficacy outcomes encompassed all-cause death, functional outcomes assessed through various scoring systems,

and severity scores. Safety outcomes included adverse events, serious adverse events, as well as fatal and non-fatal serious adverse events.

Benefits and harms

All-cause deaths

Cerebrolysin, when used as an add-on therapy in patients with acute ischemic stroke, does not decrease all-cause deaths compared with placebo (RR 0.80 [95% CI 0.53 to 1.20]; 7 RCTs; N=1,749; low certainty). This effect was observed across different treatment regimens (30ml for 10 days, 30ml for 21 days, 50ml for 21 days, and 30mL for 7 days then 10mL, 5 days a week for 21 days). Certainty of evidence was rated low due to serious risk of bias and imprecision.

Functional outcome

Five randomized controlled trials (RCTs) involving 1,557 total participants reported functional outcomes using the modified Rankin Scale (mRS), but the reporting of mRS varied among the studies, precluding the pooling of data for this specific outcome.

In 2012, the CASTA study[8] found no difference in responder rates based on mRS between the cerebrolysin group (37.6%) and the placebo group (38.5%). In the same year, the CERE-LYSE-1 trial[7] reported the proportion of patients based on mRS scores but did not specify the degree of improvement from baseline. In 2015, the CARS trial[2] reported cumulative percentages of 8.65 vs. 2.97 with mRS 0 and 42.31 vs. 14.85 with mRS 1, favoring the cerebrolysin group at day 90. Gharagozli et al. (2017)[6] reported a substantial difference in mRS scores between the cerebrolysin and placebo groups from baseline to day 30, with 51% of the cerebrolysin group (versus 20.4% in placebo) showing a median improvement of ≥ 2 points. Similar findings were observed by Stan et al. (2017)[3], who reported a mean improvement in mRS at day 30 of -2.4 +/- 0.76 in the cerebrolysin group compared to -1.6 ± 0.91 in the placebo group. The certainty of evidence was rated low due to a serious risk of bias and heterogeneity.

Serious adverse events

Cerebrolysin, when used as an add-on therapy in patients with acute ischemic stroke, does not increase the incidence of any serious adverse events compared with placebo (RR 1.06 [95% CI 0.76 to 1.50]; 5 RCTs; N=1,643; low certainty). This effect was observed in all treatment regimens. Certainty of evidence was rated low due to serious risk of bias and imprecision.

When classified according to either fatal or non-fatal SAEs, cerebrolysin did not significantly differ with placebo for fatal SAEs (RR 0.90 [95% CI 0.59 to 1.38]; 3 RCTs; N=1,335; low certainty) but increased the risk of non-fatal SAEs (RR 2.13 [95% CI 1.04 to 4.36]; 3 RCTs; N=1,335; moderate certainty).

Table Q16.1. Summary of findings: Cerebrolysin® for acute ischemic stroke.

Outcomes	Regimen	Basis	Effect Estimate	Interpretation	Overall Quality of Evidence
All-cause deaths	30mL for 10 days	4 RCTs (N=1,295)	**RR 0.88** (0.56, 1.39)	Inconclusive	LOW ⊕⊕◯◯
	30mL for 21 days	1 RCT (N=208)	**RR 0.11** (0.01, 2.04)	Inconclusive	LOW ⊕⊕◯◯
	50mL for 21 days	1 RCT (N=146)	**RR 0.87** (0.29, 2.58)	Inconclusive	LOW ⊕⊕◯◯
	30mL for 7 days then 10mL, 5 days a week for 21 days	1 RCT (N=100)	**RR 0.50** (0.05, 5.34)	Inconclusive	LOW ⊕⊕◯◯
Functional outcome	Varied	5 RCTs (N=1,557)	Not pooled; no significant difference with placebo	Inconclusive	LOW ⊕⊕◯◯
Serious adverse events (SAEs)	30mL for 10 days	2 RCTs (N=1,189)	**RR 1.23** (0.83, 1.81)	Inconclusive	LOW ⊕⊕◯◯
	30mL for 21 days	1 RCT (N=208)	**RR 0.43** (0.11, 1.61)	Inconclusive	LOW ⊕⊕◯◯
	50mL for 21 days	1 RCT (N=146)	**RR 0.75** (0.26, 2.12)	Inconclusive	LOW ⊕⊕◯◯
	30mL for 7 days then 10mL, 5 days a week for 21 days	1 RCT (N=100)	**RR 1.00** (0.15, 6.82)	Inconclusive	LOW ⊕⊕◯◯
Fatal SAEs	30mL for 10 days	2 RCTs (N=1,189)	**RR 0.90** (0.57, 1.44)	Inconclusive	LOW ⊕⊕◯◯
	50mL for 21 days	1 RCT (N=146)	**RR 0.87** (0.29, 2.58)	Inconclusive	LOW ⊕⊕◯◯
Non-fatal SAEs	30mL for 10 days	2 RCTs (N=1,189)	**RR 2.87** (1.24, 6.69)	Harm	MODERATE ⊕⊕⊕◯
	50mL for 21 days	1 RCT (N=146)	**RR 0.29** (0.01, 7.03)	Inconclusive	LOW ⊕⊕◯◯
	30mL for 7 days then 10mL, 5 days a week for 21 days	1 RCT (N=146)	**RR 1.00** (0.15, 6.58)	Inconclusive	LOW ⊕⊕◯◯

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Certainty of evidence

The overall certainty of evidence is low due to serious risk of bias, inconsistency, and/or imprecision.

Other considerations

Cost and cost-effectiveness

Cerebrolysin at a dose of 215.2mg/mL (10mL vial) ranges from PHP 910 to PHP 1,357.47 per vial. For a 10-day treatment protocol, it will cost PHP 9,100 to PHP 13,574.70.

Patient's values and preferences, equity, acceptability, and feasibility

There are currently no local studies evaluating the patient's values and preference, equity, acceptability, and feasibility of using cerebrolysin versus placebo in acute ischemic stroke.

Recommendations from other groups

The European Academy of Neurology weakly recommends using cerebrolysin (30mL, intravenous) for moderate-severe stroke cases when initiated within 7 days, citing potential benefit and acceptable safety profile for this specific clinical population.[10]

Table Q16.2. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation and certainty of evidence
EAN 2021[10]	Based on low and high quality of evidence across primary and secondary critical outcomes, a weak recommendation for Cerebrolysin (30 ml, intravenous, minimum 10 days) is given for early motor neurorehabilitation after moderate–severe ischemic stroke.	Weak recommendation, low-to-high certainty of evidence across outcomes

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Neuroprotective agents

Q17. Should we give NeuroAiD™ as an add-on therapy for adult patients with acute ischemic stroke?

RECOMMENDATION 17:

Among patients with acute ischemic stroke, we do not recommend the use of NeuroAiD™.

Overall Level of Certainty: **Very Low** ⊕◯◯◯
Strength of Recommendation: **Strong**

CONSENSUS ISSUES

A consensus decision was reached not to recommend NeuroAiDTM for acute ischemic stroke patients due to the lack of conclusive evidence of benefit. Despite effect estimates being reported with very low certainty, the high cost of the intervention was considered a significant factor that could financially burden patients, particularly those who currently access this intervention through out-of-pocket payments. Further research on MLC901, its current available formulation, is needed to establish its net effects for acute ischemic stroke patients.

BACKGROUND

Aside from organized stroke care systems, decompression surgery, and rapid reperfusion treatments such as intravenous thrombolysis and endovascular thrombectomy, there are relatively few therapies that have been shown to minimize disability and death in acute stroke.[1] Patients' dissatisfaction with poststroke rehabilitation has driven many to explore untested alternative therapies such as acupuncture, herbal drugs, and traditional Chinese medicine (TCM).[2]

NeuroAiD™, also known as MLC601 or Danqi Piantan Jiaonang, is a TCM that has been recognized by the Chinese FDA since 2001 and is commonly used to aid in stroke rehabilitation. MLC601 contains extracts from nine herbal (radix astragali, radix salviae miltorrhizae, radix paeoniae rubra, rhizoma chuanxiong, radix angelicae sinensis, Carthamus tinctorius, Prunus persica, radix polygalae and rhizoma acori tatarinowii) and 5 animal (Hirudo, Eupolyphaga seu Steleophaga, calculus bovis artifactus, Buthus martensii, and cornu saigae tataricae) components.[3] Since 2018, MLC601 is no longer marketed and has been replaced by a simpler formulation (MLC901 or NeuroAiD II™) that contains 9 herbal components.[4]

Animal studies or in vitro models have demonstrated that NeuroAiD reduces neuronal cell death,[5] reduces infarction volume,[6] and promotes neurogenesis and neurite outgrowth.[7,8] MLC901 has also been found to inhibit neuroinflammation by reduction of neutrophil recruitment, microglia activation, and production of pro-inflammatory mediators (TNFα, IL6, IL1β, CCL2).[9] According to TCM theory, the components in NeuroAiD capsules restores Qi and invigorates blood after stroke.[10]

SUMMARY OF THE EVIDENCE

Evidence considered

Ten studies comprised the evidence base for this guideline recommendation.[12-20] Eight were RCTs,[12-18] 2 were observational, case-control studies, [19,20] and 1 was a prospective cohort registry for safety data. [22] Most of these trials have also been included in previous systematic reviews published in 2013,[23] 2016,[24], 2017,[25] and a 2020 umbrella review on various ischemic stroke therapies. [65] A total of 2,359 adult patients with average ages between 59 to 76 years were included. In trials that specified baseline stroke severity,[12,13,16,17,20] most involved moderate-to-severe strokes.

The largest placebo-controlled RCT on MLC601 was the CHIMES (CHInese Medicine Neuroaid Efficacy on Stroke recovery [NCT00554723]) trial, which enrolled 1,099 patients with moderately severe[1] acute ischemic stroke across several Asian countries, including the Philippines.[16] The long-term effects of MLC601 (i.e., 6, 12, 18, 24 months) were assessed in the extension of the CHIMES RCT (CHIMES-E), involving 880 of the original 1,099 patients.[21] Four other placebo-controlled RCTs were performed in 2009 in Singapore (TIERS) [13] and 2011-2014 in Iran.[14,15,17] One Chinese RCT in 2009 (n=605) [12] compared 1-month use of MLC601 with another approved TCM for stroke (Buchang Naoxintong Jiaonang), while another RCT in Iran (n=40) assessed the effects of 3-month use of MLC601 on visual field defect recovery versus piracetam.[18] No RCTs were found on MLC901 / NeuroAiD II. Only the EPICA 2020 case-control study in Spain reported data on clinical outcomes of patients who took MLC901 versus those who did not.[20]

Primary efficacy outcomes in the included studies were motor recovery after 1 to 3 months (i.e., Fugl-Meyer Assessment scores)[13,15] and functional outcome after 1 to 3 months (i.e., proportion of patients who had functional independence or had no-to-slight disability),[12-14,16,19] visual field defect recovery after 3 months.[18] Functional independence was assessed using different outcome measures such as modified Rankin Scale (mRS 0-2),[12,16,19] Barthel Index (BI ≥ 65),[14] or Functional Independence Measure (FIM raw scores).[13] Safety data were reported in 6 RCTs.[12-17]

Benefits and harms

Mortality reduction

No significant difference was noted between MLC601 (6.3%) and placebo (6.7%) with regard to mortality rates after a 24-month follow-up period (RR 0.94 [0.57 to 1.55]; N=880) based on the CHIMES-E RCT.[21] Certainty of evidence for this outcome was moderate due to imprecise interval estimates.

Motor recovery

Pooled results from the Harandi et al. 2011[15] and TIERS 2009[13] RCTs involving 190 moderate-to-severe stroke patients showed no significant difference between MLC601 and placebo in terms of the extent of motor recovery at 1 month (MD 7.31 pts [95%CI -8.06 to 22.69]; I^2=89%] and 2 months (MD 8.02 [95%CI -1.08 to 17.11]; I^2=58%). Only the RCT by Harandi et al. (2011) reported

[1] NIHSS score 6-14

significant motor recovery at 3 months (MD 13.13 pts [95%CI 7.29 to 18.97].[15] In contrast, the TIERS RCT found no significant difference in FMA improvement scores between MLC601 and placebo regardless of stroke severity, site of lesion, or follow-up period.[13] In stroke patients, a change of 12.4 points in FMA was previously identified as the minimal clinically important difference (MCID) in stroke patients with moderate to severe hemiparesis.[27]

Although these results suggest potential benefit, the certainty of evidence for these effect estimates is low due to inconsistency (significant heterogeneity between included trials) and imprecision (95% CI for the change in FMA scores crosses MCID value). Data regarding concurrent physical therapy that may have been given to recruited participants and influenced outcomes were also not reported in the two trials.

Functional outcomes

Short-term (1-3 months)

In 1 Chinese RCT involving 650 patients, the odds of achieving a functional outcome after 1 month (i.e., Diagnostic Therapeutic Effects of Apoplexy Scoring System score of 0) was higher for 1-month course of MLC601 compared to BNJ, another TCM (OR 2.30 [95%CI, 1.19 to 4.42]).[12] At 3-months, MLC601 did not increase the odds of patients exhibiting favorable mRS scores of 0 to 1 (OR 1.11 [95%CI, 0.88 to 1.42]; I^2=0%).[14,16]

Long-term (6-24 months)

In terms of the long-term effects (6-24 months), the CHIMES-E trial showed no significant effect on mRS shift (aOR 1.08 [95%CI, 0.85 to 1.37]).[21] The odds of achieving mRS 0–1 was significantly higher at 6 months (OR 1.49 [95%CI, 1.11 to 2.01]) and 12 months (OR 1.41 [95%CI, 1.05 to 1.90]), but was not different than placebo at 24 months (OR 1.29 [95%CI 0.96 to 1.74]).[21]

Effect of MLC901

Based on very low certainty of evidence from the EPICA study involving 131 patients, use of MLC901 was associated with improvements in mRS scores (Cohen's d = 0.26 [95%CI, -0.11 to 0.62]).[20] Certainty was downgraded due to risk of bias associated with the use of case-control study design, imprecision (Cohen's d ranges from no effect to moderate effect size).

Effect on specific population subgroups

Various post-hoc analyses of the CHIMES trial suggest possible benefit for certain population subgroups (e.g., women, elderly, more severe strokes on baseline, treatment initiation beyond 48 hrs, patients receiving concurrent rehab), although these effects still need to be demonstrated in RCTs specifically designed for this purpose. Particularly on Filipino stroke patients, MLC601 was associated with a higher adjusted odds ratio for a shift in mRS score at month 3 (aOR 1.41 [1.01 to 1.96]) and odds of a favorable functional outcome (i.e., mRS 0-1; aOR 1.68 [1.10 to 2.57]). However, this potential treatment effect was not significant if measured using an mRS 0-2 dichotomy (aOR 1.32 [0.86 to 2.04]) or an NIHSS improvement of ≥ 5 pts (aOR 1.12 [0.75 to 1.68]).[34]

The effect of MLC601 combined with persistent rehabilitation among a subgroup of patients in the CHIMES-E trial (n=807, mean age 61.8 yrs, 36% female) was evaluated by Suwanwela et al. (2018).[37] At 3 months, higher odds for achieving mRS ≤ 1 was noted among patients receiving

rehabilitation (aOR 1.85 [95%CI, 1.18 to 2.91]). This effect was observed throughout all follow-up periods up to month 24 (aOR 1.87 [95%CI, 1.09 to 2.94]).

Safety outcomes

Mild adverse events

Based on 6 RCTs involving 2,422 patients,[12-17] MLC601 was associated with more mild adverse events than placebo (6.24% vs. 4.71%; RR 1.53 [95%CI, 1.00 to 2.36]; I^2=23%). The certainty of evidence for this effect is low due to risk of bias and imprecision. The most common type of reported side effects included nausea,[12,15,17] abdominal pain,[17] and vomiting.[12,15]

Serious adverse events

Based on the same 6 RCTs,[12-17] MLC601 did not significantly increase the risk for SAEs compared to placebo (0.59% vs. 0.57%; RR 1.44 [95%CI, 0.32 to 6.58]; I^2=38%). Only the CHIMES and TIERS RCT have noted MLC601-related SAEs[13,16] such as jaundice (n=1), hypokalemia (n=1), seizures (n=1), recurrent stroke (n=1), [13] and 4 other unspecified SAEs. [16]

Regarding MLC901, long-term safety data (up to 6 months) is currently being collected in the NeuroAiD Safe Treatment Registry (NeST). NeST is targeting to collect data from 2,000 participants with analysis performed after every 500 participants.[30] Preliminary data from a cohort of 98 Eastern European patients (80% were ischemic strokes on concomitant anticoagulants) showed no adverse events associated with the use of MLC901.[22] Similarly, no serious side effects were recorded in another NeST cohort involving 66 Malaysian hemorrhagic stroke patients.[31]

Certainty of evidence

The overall certainty of evidence was very low across critical outcomes. Reasons for downgrading included serious risk of bias, imprecision associated with confidence intervals, or inconsistency in results.

Other considerations

Cost and cost-effectiveness

Since 2011, NeuroAiD II MLC 901 has been sold in the Philippines as an adjunctive Traditionally Used Herbal Product (TUHP) to support the recovery of neurological disorders in post-stroke patients.[46] The published retail price of 1 box containing 180 400 mg capsules equivalent to a 1 month course is USD 677.50 (PHP 37,000).[47] Considering that the latest average annual income of Filipino families is estimated at PHP 307,000 [48] and that costs of stroke treatment are still mainly borne by patients[49], access to NeuroAiD may only be possible for high-income families.

Table Q17.1. Summary of findings: NeuroAiD™ versus placebo in acute ischemic stroke.

Outcomes	Follow-up	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Mortality	24 months	1 RCT (n=880)	**RR 0.94** 0.57, 1.55	Inconclusive	MODERATE ⊕⊕⊕◯
Functional outcome	1 month	1 RCT (n=605)	**OR 2.30** (1.19, 4.42)	Favors NeuroAid	VERY LOW ⊕◯◯◯
	3 months	2 RCTs (n=1,129)	**OR 1.11** (0.88, 1.42)	Inconclusive	LOW ⊕⊕◯◯
	24 months	1 RCT (n=880)	**OR 1.29** (0.96, 1.74)	Inconclusive	LOW ⊕⊕◯◯
Motor recovery	1 month	2 RCTs (n=190)	**MD 7.31 pts** (-8.06, 22.69)	Inconclusive	VERY LOW ⊕◯◯◯
	2 months	2 RCTs (n=190)	**MD 8.02 pts** (-1.08, 17.11)	Inconclusive	VERY LOW ⊕◯◯◯
	3 months	1 RCT (n=150)	**MD 13.13 pts** (7.29, 18.97)	Inconclusive	VERY LOW ⊕◯◯◯
Any adverse events	1-3 months	6 RCTs (n=2,422)	**RR 1.53** (1.00, 2.36)	Inconclusive	LOW ⊕⊕◯◯
Serious adverse events	1-3 months	6 RCTs (n=2,422)	**RR 1.44** (0.32, 6.58)	Inconclusive	LOW ⊕⊕◯◯

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group Certainty of Evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No evidence was found from qualitative or observational studies investigating patients' experiences or perceptions regarding NeuroAiD. As such, it is still unclear how Filipino stroke patients and practitioners view NeuroAiD as a treatment for post-stroke recovery. Many limitations exist in the development and clinical application of TCM theory and Chinese herbal medicine in the Philippines.[50,51]

Nonetheless, MLC601 has been registered in the Philippines since 2006[19] and may be accessed by patients through licensed distributors. Some practitioners prescribe it to post-stroke patients at a dose of 2-4 capsules, 3x per day, for 3 months.[19]

Recommendations from other groups

Latest guidelines from Europe issued a weak recommendation against MLC601 for acute ischaemic stroke due to negligible effect on motor recovery, neurological function, and disability.[40] The CHIMES trial was used as the basis for this recommendation.[16] The American Heart Association and American Stroke Association also recommend against using neuroprotective agents due to absence of benefit.[41] No specific recommendations on neuroprotective agents were made in stroke guidelines from Australia/New Zealand[42] as well as China.[43]

Table Q17.2. Recommendations from other clinical practice guidelines.

Group	Recommendation	Strength of recommendation and certainty of evidence
2021 European Academy of Neurology and European Federation of Neurorehabilitation Societies [40]	Based on low quality of evidence, negligible intervention effect and lack of evidence for the primary critical outcome, a weak recommendation against MLC601 (1200 mg) is given for early motor neurorehabilitation in patients after acute ischaemic stroke.	Weak recommendation, Low quality of evidence
2019 American Heart Association/American Stroke Association Guidelines for the Early Management of Patients With Acute Ischemic Stroke [41]	At present, pharmacological or nonpharmacological treatments with putative neuroprotective actions are not recommended	Class 3 (No benefit) Level of evidence A (high)
2023 Australian and New Zealand Living Clinical Guidelines for Stroke Management [42]	No recommendation	-
2020 Chinese Stroke Association [43]	No recommendation	-

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Chapter 4. RESEARCH GAPS

The following topics were identified as research gaps:

- No studies were found on stroke units particularly in low-income settings. Although it is now considered a treatment for patients with acute stroke, its sustainability and feasibility in low-income countries has not been ascertained.
- Ongoing randomized phase 3 trials are determining whether tenecteplase is superior or non-inferior to alteplase within the 4.5-hour time window, in wake-up stroke, and in combination with endovascular thrombectomy. After these clinical trials are completed, a pooled analysis of data may help identify significant differences between tenecteplase and alteplase in terms of their clinical outcomes and adverse events.
- There are no other ongoing clinical trials on decompressive hemicraniectomy in malignant MCA infarction.
- More research is needed to establish the effectiveness of edaravone as well as other neuroprotectants.
- A Cochrane systematic review protocol on Neuroaid for acute ischemic stroke has been published in 2017; however, results of this review are still pending. There are no ongoing or planned trials on MLC601/MLC901 in acute ischemic stroke. Although MLC601 has not been found to significantly modify hematological, hemostatic, and biochemical parameters in both stroke patients and healthy controls,[32] potential clinically significant drug interactions especially with anticoagulants has been highlighted as a topic that warrants further studies.

Chapter 5. MONITORING AND EVALUATION

Dissemination

The CPG will be submitted to the National Practice Guideline Clearinghouse of the DOH for review, assessment, and approval. The DOH, SSP, and the involved organizations shall also promote the use and uptake of these recommendations nationally through publications, lectures, and other forms of notifications of all possible stakeholders.

Dissemination of the CPG will be done through lectures in various conferences involving different stakeholders, apply for publication locally and internationally, and the output will be available in the Stroke Society of the Philippine, Philippine Neurological Association, and in the Compendium of DOH-Approved Clinical Practice Guidelines (https://doh.gov.ph/dpcb/doh-approved-cpg/).

The Disease Prevention and Control Bureau of DOH will transmit copies of this CPG to the Philippine Health Insurance Corporation, health maintenance organizations, and pharmaceutical industry partners. This CPG will also be presented during conferences and annual conventions of medical societies. Copies of this CPG with the endorsement of relevant medical institutions will be sent to medical schools and libraries to integrate the recommendations in their training curricula, with the support of the faculty members and heads of hospital-based departments, including but not limited to surgery, radiology, pathology, and internal medicine.

The evidence base and the final manuscript will be made available both in print and electronic media through the DOH, the SSP, and the organizations involved in its creation.

Guideline Monitoring and Evaluation

The Task Force will distribute a questionnaire annually, aiming to determine the best practices of relevant stakeholders in terms of diagnosis and management of acute stroke. Monitoring the use of this clinical practice guideline may also be a subject of research by interested parties. For monitoring and auditing, the CPG group will use the final strength of recommendation to determine key performance indicators. Those recommendations voted with “Strong Recommendation” will be used as indicators. These indicators will be identified once the strength of recommendations is finalized for each of the guideline review questions.

Specific operational definitions of how the criteria should be measured will be based on the recommended standards as defined in the DOH Manual for CPG Development. These will also be defined after consultations with the EGMD of the DOH as there is limited local literature on how these are defined.

External Review

External reviewers representing end-users and/or stakeholders, or technical experts were identified and asked to perform a technical review of the draft manuscript. The manuscript of this Clinical Practice Guideline was reviewed by a clinical epidemiologist and primary care physician, and content expert clinicians. A customized template was used and a subset of items were asked per review question as follows:

1. General Response (to the guideline as a whole)
2. Comments/feedback on this specific recommendation
3. What is the level of completeness in terms of:
    a. Search of evidence?
    b. Synthesis and analysis of evidence base?
4. Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.
5. What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.
6. Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)
7. Any comments on the "implementability" of this recommendation?

Comments or feedback gathered from the external review process were used as reference for revisions (as needed).

Implementation and Applicability

The Stroke Society of the Philippines organization is committed to facilitating the nationwide uptake of the newly developed local stroke management guidelines by developing transfer and implementation tools whether de novo or adapted from available resources. These tools which would allow integration of guideline recommendations into daily practice which includes protocols, algorithms, care pathways will be designed to be culturally relevant, ensuring accessibility and practicality across diverse local settings.

Educational resources, such as modules, slides and protocol manuals will be developed. Web-based platforms will be optimized to provide accessible updates and interactive tools for healthcare professionals nationwide. By fostering partnerships with government agencies, academic institutions, and professional organizations, we aim to ensure widespread dissemination and implementation of the guidelines, promoting a unified approach to stroke management that meets the unique needs of Philippine healthcare settings.

The Society shall offer training on monitoring and auditing techniques and encourage benchmarking against national and international standards to drive continuous improvement. Standardized reporting requirements have been developed especially for Acute Stroke Ready Hospitals to ensure a culture of adherence to evidence-based stroke care practices nationwide.

The Society likewise plans to implement feedback mechanisms, gathered via online surveys, email correspondence, or dedicated feedback forms to provide comments, suggestions and experiences which shall serve as valuable insights for continuous improvement of the guidelines and ensure alignment with clinical practice needs.

Auditing And Monitoring Statement

The Stroke Society of the Philippines envisions enhancing the effectiveness of its clinical practice guidelines by creating an implementation checklist, defining key monitoring indicators, and outlining auditing protocols for healthcare facilities to assess compliance.

The Society shall offer trainings on monitoring and auditing techniques, and encourage benchmarking against national and international standards to drive continuous improvement. Standardized reporting requirements have been developed especially for Acute Stroke Ready Hospitals to ensure a culture of adherence to evidence-based stroke care practices nationwide.

The Society likewise plans to implement feedback mechanism, gathered via online surveys, email correspondence, or dedicated feedback forms to provide comments, suggestions and experiences which shall serve as valuable insights for continuous improvement of the guidelines and ensures alignment with clinical practice needs.

Updating of the guidelines

This Stroke CPG will be updated every 3 years (i.e., 2026). The Steering Committee is responsible for initiating such updates or revisions when new evidence from large scale studies become available on certain priority topics or when there are changes in available resources, national policies, approval status of new interventions or health technologies, or values placed on outcomes. The DOH will also regularly assess the relevance and applicability of these guidelines and issue and update if necessary.

The updating of the CPG wil follow the recommended CPG process in the DOH Manual on Practice Guideline Development and the GRADE approach will be used. The GRADE Adolopment (as applicable) and Evidence-to-decision (EtD) framework will be utilized in finalizing the recommendations.

Preparation

The Task Force Steering Committee will set the CPG objectives, scope, target audience, and clinical questions. The Task Force Steering Committee will convene 1. the technical working group involved in creating the evidence base and 2. the consensus panel involved in finalizing the recommendations for each clinical question included. Questions will be prioritized using the criteria set by DOH.

COI Management

All task force members will submit their declaration of conflict of interest (COI) and curriculum vitae. A COI committee will review and evaluate the potential conflicts of interest and give their recommendation on how to manage them. In general, those with financial COI will not be allowed to vote for questions related to the COI. Those with non-financial COIs (such as authorship related to the CPG topic) will be allowed to participate but COIs will be declared during the panel meeting and the final manuscript.

Evidence Synthesis

The clinical questions will be developed using the PICO (population, intervention, comparator and outcome) format.

For each question, we will perform a systematic medical literature search of the MEDLINE (via PubMed), The Cochrane Library, and (OTHER DATABASES). Systematic reviews that will meet our inclusion criteria to answer our clinical questions will be used directly to identify relevant

articles and summary of findings. If no related reviews will be found, we will conduct de novo systematic reviews. We will critically appraise the methodological quality of the included studies using the standard tools such the Cochrane Risk of Bias tool (ROB 2.0) for randomized controlled trials (RCTs), Painless EBM appraisal criteria, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic accuracy studies, and the Newcastle–Ottawa Scale (NOS) for observational studies. We will use the GRADE approach to rate the certainty of evidence and the strength of recommendations.

Evidence to Decision Consensus Approach

In the development of this clinical practice guideline, a diverse range of stakeholders was engaged to capture their views and preferences, particularly those of the target population, including patients and the relevant medical societies. Nominations from various stakeholders were sought and nominees were assessed accordingly through a rigorous Conflict of Interest (COI) deliberation process to ensure transparency and impartiality. After thorough vetting, qualified nominees were selected to serve on the consensus panel. This panel included representatives from different professional societies as well as a patient representative or advocate, ensuring that the guideline reflects a broad spectrum of perspectives and expertise.

The multisectoral consensus panel (CP) was tasked to review the evidence summaries and develop recommendations during the en banc meeting. Prior to the meeting, the CP will prioritize critical and important outcomes.

The CP will be provided with the evidence base for all the clinical questions and a draft recommendation solely based on the trade-offs between benefit and harm and the certainty of evidence. Each CP member will then be asked to complete an EtD questionnaire . The purpose of this questionnaire survey is for each CP member to explicitly incorporate other important factors such as cost-effectiveness, patient values and preferences, applicability, feasibility, appropriateness, equity, and resources in their decision-making.

The direction and strength of each recommendation will be determined by a formal consensus method. Recommendations will be considered to have reached a consensus when 75% or more of the voters agreed on the proposed recommendation. If consensus will not reached initially, two further rounds of voting will be allowed. A modified Delphi methodology is planned in case no consensus will be reached during the en banc meetings. On the rare occasion that no consensus would not be reached, no recommendation would be indicated in the final CPG manuscript.

Barriers and Facilitators

After discussions with the multistakeholder group throughout the CPG development process, information/description of the types of facilitators and barriers have emerged. Additional feedback was sought from other key stakeholders through dialogues or external communications. These methods included the identification of facilitators (i.e., support of government for medications and services, advocacy groups activity) and barriers (i.e., out-of-pocket mode of healthcare payment, availability of specific machines/laboratory tests/reagents, etc.). This information influenced the value judgment of the consensus panel during the discussions and formulation of the recommendation statements and the strength of each recommendation.

Chapter 6. AUTHORSHIP, CONTRIBUTIONS, ACKNOWLEDGEMENT

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Asia Pacific Center for Evidence Based Healthcare (APCEBH)

Critical Care Nurses Association of the Philippines (CCNAPI)

Academy of Filipino Neurosurgeons, Inc. (AFN)

Department of Health (DOH)

Philippine Academy of Family Physicians (PAFP)

Philippine College of Emergency Medicine (PCEM)

Philippine College of Physicians (PCP)

Philippine College of Radiology (PCR)

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Philippine Neurological Association (PNA)

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