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Factors Contributing to an Efficacious Endovascular Treatment for Acute Ischemic Stroke in Asian Population

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Although randomized control trials about endovascular treatment (EVT) of emergent large vessel occlusion (LVO) have demonstrated the success of mechanical thrombectomy as the choice of treatment, a wide range of caveats remain unaddressed. Asian patients were rarely included in the trials, thereby raising the question of whether the treatment could be generalized. In addition, there remains a concern on the feasibility of the method with respect to its application against intracranial atherosclerosis (ICAS)-related LVO, frequently observed in the Asian population. It is important to include evidence on ICAS LVO from Asian countries in the future for a comprehensive understanding of LVO etiology. Besides the issues with EVT, prognostic concerns in diabetes patients, acute kidney injury following EVT, neuroprotective management against reperfusion injury, and other peri-EVT issues should be considered in clinical practice. In the current article, we present an in-depth review of the literature that revises information pertaining to such concerns.

Key Words: Cerebral infarction; Endovascular procedures; Intracranial atherosclerosis; Diabetes mellitus; Acute kidney injury; Reperfusion injury

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INTRODUCTION

Randomized control trials (RCTs) on endovascular treatment (EVT) have contributed to a considerable level of understanding, which must be drawn from when establishing specific treatment guidelines. Not all clinical studies can be done through RCTs because a prospective, multinational, multicenter study entails high costs that are required to ensure the safety of the participants. The success of several RCTs with respect to EVT against acute ischemic stroke (AIS) has contributed to a better prognosis of many patients around the world. However, Asians were rarely included in such RCTs for EVT, which led to doubts about whether these treatments could be generalized and used in Asian countries. In particular, mechanical thrombectomy (MT) involving the removal of a thrombus is unlikely to mitigate intracranial atherosclerotic stenosis (ICAS)-associated large vessel occlusion (LVO), which is widely prevalent amongst the Asian population. Interestingly, single-center or multicenter registry studies have suggested that the results of the research conducted in Western countries could

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also be applied to the Asian population. In addition, available studies on ICAS LVO could be used to guide the necessary course of treatment.

There are lots of factors that contribute to EVT outcomes. Efficacious time management, including times from door to puncture (in-hospital process) and from puncture to reperfusion (EVT procedure), leads to better outcomes. In addition, a fast EVT procedure and complete reperfusion can lead to a reduction in stroke volume, as reflected by diffusion reversal. Diabetes mellitus and contrast media may work as risk factors toward poorer outcomes. On the other hand, to widen the therapeutic indication of EVT, especially for patients with large stroke burden, reperfusion injury should be a concern, and neuroprotection has been revisited in the current EVT era.

The Acute Stroke due to Intracranial Atherosclerotic occlusion and Neurointervention Korean Retrospective (ASIAN KR) registry (January 2011–February 2016) from 3 Korean stroke centers not only provided a general perspective on EVT along with essential cues about ICAS LVO but also analyzed factors contributing to EVT outcomes.[1-14] The present article is based on the substudies from the ASIAN KR registry and provides a comprehensive review on EVT that would aid physicians in devising specific treatment regimens. In part I, we review EVT outcomes in Asian countries and outcomes in patients with ICAS LVO. In addition, evolving EVT techniques are briefly described. In part II, we review various factors that contribute to EVT outcomes for patients with AIS and LVO. We hope readers can widen their understanding of EVT for the Asian population and associated factors related to its outcomes.

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PART I. OUTCOMES AND TECHNIQUES IN EVT FOR LVO

Comparable real-world outcomes of EVT

The past several years have witnessed dynamic developments in the field of EVT with respect to AIS. While 3 RCTs for EVT (IMS-3, MR RESCUE, and SYNTHESIS Expansion studies) failed in 2013,[15-17] the next EVT trial, MR CLEAN, was successful in 2014.[18] Besides this trial, other successful trials in 2015, including ESCAPE, SWIFT PRIME, EXTEND IA, and REVASCAT, emphasized the efficacy of EVT when compared with conventional stroke treatment.[19-22] The success of these studies could be attributed to the development of better imaging protocols for appropriate patient selection, advancements in thrombectomy devices, and reduced time from door to treatment.[23] The treatment guidelines for AIS were amended by the American Stroke Association, and new guidelines were compiled by the Korean Stroke Society, Korean Society of Interventional Neuroradiology, and Society of Korean Endovascular Neurosurgeons.[24,25] Although these developments were encouraging, there were specific concerns regarding the extensiveness of the studies. Notably, the successful trials that were performed in Western countries rarely included Asian patients. Clinical trials of therapeutic drugs, such as non-vitamin K antagonist oral anticoagulants, usually involve a substantial proportion of Asian patients.[26-29] Asian populations have also been included in many clinical trials regarding coronary percutaneous intervention. Moreover, several RCTs from Korea have provided evidence that percutaneous coronary intervention can replace coronary bypass surgery in patients with coronary artery disease.[30-32]

As for studies on the efficacy of EVT for Asian patients with LVO, underlying ICAS has been regarded as a challenging hurdle. Thus, a lack of studies involving Asian subjects necessitates a comprehensive review involving a single-center or multicenter registry. In Table 1, the outcomes from major RCTs and representative Korean registry studies have been documented.[1,18-20,33-39] Overall, the outcomes of EVT from multicenter registry studies in Korea were comparable to those of major RCTs. Furthermore, good clinical outcomes, defined by a modified Rankin Scale (mRS) of 0–2 at 3 months, were 50–52% in the anterior circulation, compared to 33% to 60% in the major RCTs.[1,37,39] The data from the ASIAN KR registry revealed that the rates of good clinical outcomes improved after Solitaire FR, Trevo, and the second-generation Penumbra system were approved in Korea.[1]

Recently, RCTs, including the BEST and BASICS trials, for LVO in the posterior circulation failed to prove the efficacy of EVT when compared with the best medical treatment.[35,36] In the BEST trial, the low rates of good outcomes (33%) might be due to the relatively low rates of successful reperfusion (71%).[35] In the BASICS trial, presented in the European Stoke Organisation and World Stroke Organization (ESO-WSO) 2020 Joint Meeting, the rates of good clinical outcomes as a secondary outcome were also low (35%), although the information regarding reperfusion rates was absent in the presented material.[36] It is suspected that the high prevalence of underlying ICAS in the posterior circulation might affect the outcomes.[40,41] With respect to EVT techniques and clinical outcomes, it is more challenging for physicians to treat ICAS LVO in the posterior circulation.[42] It is believed that clinical outcomes would be better in future trials on the posterior circulation occlusion if the EVT strategy is stratified by a predictor of ICAS combined with baseline infarct volume and a time window to groin puncture.[2,3]

After the RCTs for a late time window were successful,[33,34] new guidelines were reported.[43,44] Based on the single-center or multicenter registry studies in addition to RCTs, it is reasonable to perform EVT for LVOs of the anterior circulation in both early and late time windows and to cautiously try EVT for LVOs of the posterior circulation as per the revised guidelines.

Comparable ICAS-LVO outcomes

In terms of stroke subtypes according to the trial of ORG 10172 in acute stroke treatment (TOAST) classification, among the general population with AIS, large artery atherosclerosis is relatively more prevalent than cardioembolism in Asian countries, while the opposite is true in western countries.[45] In addition, compared to extracranial atherosclerosis, intracranial atherosclerosis is more prevalent in Asian patients than in Western patients.[45-48] With this background, stroke physicians in Asian countries have worried about potential treatment difficulties in MT despite successful reports from Western countries.

Fortunately, the prognosis of ICAS LVO has been reported to be comparable to that of embolic LVO in the anterior circulation. In most cases, ICAS LVO accounted for around 15–20% of all intracranial LVOs of the anterior circulation, although its definition is a bit varied.[4,49] The rates of good clin-

Table 1. EVT prognosis of major randomized control trials and Korean multicenter registry studies

Studies	Study period	No.	Brain territory	Age (mean)	Initial NIHSS (median)	EVT time window (range or mean)	mTICI 2b/3	mRS 0–2 at 3 m
Major randomized control trials								
MR CLEAN[18]	Dec 2010–Mar 2014	233	Anterior	66*	17	Up to 6 h	59%	33%
ESCAPE[19]	Feb 2013–Oct 2014	165	Anterior	71*	16	Up to 12 h	72%	53%
SWIFT PRIME[20]	Dec 2012–Nov 2014	98	Anterior	65	17	Up to 6 h	88%	60%
DAWN[33]	Sep 2014–Feb 2017	107	Anterior	69	17	6 h to 24 h	84%	49%
DEFUSE 3[34]	May 2016–May 2017	92	Anterior	70	16	6 h to 16 h	76%	45%
BEST[35] (failed)	Apr 2015–Sep 2017	66	Posterior	62	32	Up to 8 h	71%	33%
BASICS[36] (failed)	Dec 2011–Dec 2019	154	Posterior	67	21	Up to 6 h	–	35%
Korean multicenter registry studies								
Kim et al.[37]	Sep 2010–Dec 2015	690	Anterior	68	15	234 min	80%	50%
SECRET[38]	Jan 2012–Dec 2017	500	Anterior	70	15	324 min	81%	52%
ASIAN KR[1]	Jan 2011–Feb 2016	635	Anterior	68	16	261 min	76%	52%
Kang et al.[39]	Jan 2011–Aug 2017	212	Posterior	71	17	242 min	92%	45%
SECRET[38]	Jan 2012–Dec 2017	85	Posterior	72	15	365 min	80%	45%
ASIAN KR[1]	Jan 2011–Feb 2016	72	Posterior	67	19	298 min	86%	42%

NIHSS, National Institute of Health Stroke Scale.
For the data from the SECRET and ASIAN KR registry studies, outcomes were recalculated in the anterior and posterior circulations, for appropriate comparison to other studies. The data of the SECRET was sent by Dr. Young Dae Kim.
*A median value.

ical outcomes were substantial (over 45%) after EVT for ICAS LVO.[4,49] These outcomes were comparable to embolic LVO, in which the rates of good clinical outcomes were 46–55%.[4,49] Previous studies showed that patients were younger, the initial severity was milder, and baseline infarct volume was smaller, while collaterals were more abundant in ICAS LVO than in embolic LVO.[50] From these confounding factors, ICAS LVO was shown to be less associated with good outcomes when major confounding factors were adjusted and embolic LVO was referenced.[4] With respect to ICAS LVO in the posterior circulation, while recent studies reported a substantial portion of good clinical outcomes (46–60%),[51,52] previous studies reported worse clinical outcomes in comparison to embolic LVO (11% *vs.* 38%).[42]

In a meta-analysis study regarding ICAS LVO, the successful reperfusion rate was 88% (95% confidence interval [CI], 84–92%), and good clinical outcomes were seen in 52% (95% CI, 47–56%) of patients.[53] Another meta-analysis study showed no difference in successful reperfusion rate (odds ratio [OR], 0.67; 95% CI, 0.36–1.27) and good clinical outcomes (OR, 1.16; 95% CI, 0.85–1.58) between ICAS and non-ICAS LVOs.[54] It is believed that the prognosis of ICAS LVO has substantially improved over time and is expected to have a higher rate of good clinical outcomes with methodological advancements and device development for EVT.

Evolving EVT devices and techniques

Before the RCTs for intracranial LVO were successful, the use of the Merci device or intra-arterial fibrinolytic drug infusion was the mainstay of treatment, but they did not have a sufficient reperfusion rate.[15] Presently, it is a base using current standard thrombectomy devices such as stent retrievers and contact-aspiration catheters, which had improved reperfusion grade, thereby rendering the RCTs successful.[55-58] In addition, evidence shows that the use of a balloon guide catheter improved the rate of complete reperfusion and good clinical outcomes with either stent retrievers or contact aspiration devices.[59-62] A new occlusion in the Willisian collateral supply, which often occurs during the MT procedure, was associated with grave outcomes.[5] The use of a balloon catheter may help to prevent new embolization during the procedure.[63] For overcoming a tortuous cervical vessel, intermediate or distal delivery catheters might be useful tools.[64] Also, for challenging supra-aortic access, a modified use of a balloon guide catheter can be helpful.[64] While removing a fibrin clot in a bifurcation, which is well known to be resistant to stent retrieval,[65] a double stent-retriever technique has been tried, although safety issues should be considered accordingly.[66,67]

Concomitantly, the MT methods against ICAS LVO have been the first-line in the absence of a standardized method to differentiate ICAS and embolic occlusion on the basis of baseline angiography. Stent retrievers, such as Solitaire, have been shown to be effective and safe for ICAS LVO.[6,68] Contact aspiration techniques have also been shown to be feasible, although miscontact or dissection risks have been reported.[7,69,70] The next step for remnant stenosis following mechanical thrombectomy could include antiplatelet agent infusion and angioplasty with or without intracranial stenting. Because *in situ* thrombosis is the main mechanism in ICAS LVO,[40] stabilization with local antiplatelet infusion is reasonable. In an earlier study, the local infusion of abciximab, an antiplatelet agent, was reported to be effective in preventing reocclusion in a specific case series.[71,72] However, abciximab potentially has a bleeding risk due to its irreversible action. As such, tirofiban, a reversible antiplatelet agent, has been more frequently applied in EVT situations. Until now, tirofiban intra-arterial (IA) treatment has been reported to be effective in stabilizing remnant stenosis and preventing reocclusion in several cases.[8,73,74] In the context of blood-brain barrier breakdown, additional antiplatelet infusion has been considered for intracerebral hemorrhage (ICH) development. However, IA tirofiban infusion has a protective effect to prevent ICH that results from a reduction in the final infarct volume.[8] Intracranial stenting has also been extensively reported with studies showing its feasibility against ICAS LVO.[75,76] Although it is a powerful recanalization method, stenting requires antiplatelet pretreatment for successful long-term deployment, and the density of post-EVT strong antiplatelet administration may induce symptomatic ICH, especially in patients with IV thrombolysis. Lastly, recent studies have shown that stenting improves clinical outcomes compared with management without stenting in patients with failed MT with or without underlying ICAS.[77-79] However, this result should not be generalized to ICAS LVO because failed MT does not always indicate underlying ICAS.[9,78] On the other hand, emergent stenting for extracranial atherosclerotic lesions on ICA has been reported in several studies, which showed its efficacy and safety.[80-82] However, extracranial stenting for tandem occlusions resulted in frequent post-EVT ICH, thereby making antithrombotic treatment for stroke prevention difficult.[10] If antithrombotic treatment cannot

be applied due to hemorrhages, a recurrence of stroke or reocclusion of recanalized vessels would increase in clinical practice. The decision for deployment of foreign material in the vessel should be cautious.

PART II. FACTORS CONTRIBUTING TO EVT OUTCOMES

Onset-to-door *vs.* in-hospital time

While it is often considered that time is brain,[83] it might seem strange that onset-to-door time is no longer considered a prognostic factor.[1,84] This discrepancy is attributable to patient selection for EVT among patients with highly-varied collateral grades. Patients with poor collaterals could be denied EVT if rapid infarct growth or poor clinical outcomes are predicted.[85-88] In addition, recent RCTs studied the effect of an elongated treatment time window for good clinical outcomes.[33,34] If door-to-randomization time is assumed to be short, the time from last normal to door was around 10 to 12 hours, but patients who underwent EVT showed 44% to 49% of good clinical outcomes in the late-window trials.[33,34] Despite the inconsistency between onset-to-door time and prognosis, all systematic efforts should be continued for a patient with emergent LVO to reach a thrombectomy center.[89] In real practice, many patients could not undergo EVT because they arrived late at centers and lost an opportunity for EVT. The number of these patients is substantial, but they are underestimated in most studies.

It is believed that patients with ICAS LVO could be treated in this late time window. Pre-existing stenosis develops abundant collaterals, and a smaller stroke volume could be maintained in such cases. From the ASIAN KR registry study, it was evident that the probability of good clinical outcomes was well maintained for up to 24 hours in the ICAS LVO group, whereas the probability continuously decreased in the embolic LVO group.[4] In a recent study, the prognosis of EVT was acceptable (39% of good outcomes at 3 months) even beyond 24 hours after stroke onset, and patients with ICAS LVO were the most predominant (46%), followed by those with tandem occlusion (33%) and cardioembolism (21%).[90] There is an increasing need to perform clinical trials for the treatment of ICAS LVO in the near future.

Based upon appropriate patient selection, in-hospital time is the main prognostic factor. From the ASIAN KR registry, short door-to-puncture time and short procedure time were found to be independently associated with good clinical outcomes in multivariable analyses.[1] Among RCTs, the ESCAPE trial only showed a significant decrease in mortality.[19] This trial had strict criteria for in-hospital pre-EVT time. The image-to-puncture time of over 1 hour was considered as an exclusion criterion.[91] On this ground, a short door-to-puncture time is the responsibility of each thrombectomy center, and all efforts should be focused on a reduction of the time.[92-94]

Diffusion reversal: a goal toward rapid complete reperfusion

Diffusion reversal was observed in a portion of patients with acute ischemic stroke and EVT, as evident from the evaluation of pretreatment and post-treatment magnetic resonance imaging (MRI) scans from the ASIAN KR registry. When the diffusion volume was subjected to a blinded evaluation, 63 (15.5%) of 404 patients showed a decrease in volume.[11] The diffusion reversal was independently associated with good clinical outcomes (OR, 2.5; 95% CI, 1.1–5.9).[11] Among various factors, complete reperfusion (modified treatment in cerebral ischemia [mTICI] 3) and short time from imaging to reperfusion were proven to be associated with diffusion reversal on multivariable analysis.[11] A change of diffusion-weighted MRI due to a reduction of the apparent diffusion coefficient (ADC) of water is known to represent early cytotoxic edema owing to a failure in cellular energy.[95] An animal study in which cerebral ischemia was induced showed that ATP and glucose were depleted and severe lactic acidosis was sustained in animals without any recovery in the values of ADC.[96] In contrast, the result of diffusion reversal suggested that brain tissue can also be salvaged with EVT. Indeed, an early study showed that ATP and glucose are replenished to near normal range, and lactic acidosis is substantially reversed in animals with a recovery in the ADC values.[96]

In the clinical setting, however, physicians should be cautious about diffusion volume. Diffusion volume can be variously calculated according to each threshold of the ADC value.[97] If the diffusion volume is strictly defined with a very low ADC threshold, diffusion reversal might happen less because of the initial smaller volume. Infarct volume by manual evaluation on the diffusion-weighted imaging (DWI) map was twice that of the threshold ADC value at 600×10^{-6} mm^2/s.[97] Although a wide variation of diffusion reversal rate has been reported in the clinical settings, the frequency appears to

increase in EVT when compared with intravenous (IV) thrombolysis.[98]

The results of diffusion reversal indicate that the goal of EVT should be the achievement of a first-pass effect (FPE) and complete reperfusion (mTICI 2c/3) rather than successful reperfusion (mTICI 2b/3). Recent reports regarding FPE and mTICI2c/3 are in line with the results of diffusion reversal, which suggest technical and device improvement.[99-104] It is believed that all the efforts of stroke physicians and neurointerventionists with all the best and evolving devices would shorten the image to reperfusion time and increase the complete reperfusion rate.

Is diabetes mellitus a risk factor for EVT?

Diabetes mellitus is not only a risk factor for the occurrence of acute ischemic stroke and the development of atherosclerosis but also a prognostic factor of acute ischemic stroke and a predictor of early neurological deterioration.[105-108] Whereas occurrence issues are a preventive concern, prognostic issues are an emergent treatment concern. For IV thrombolytic treatment, a combination of the history of stroke and diabetes used to be a contraindication on the European label.[109] While most contraindications focus on the risk of ICH following thrombolytic treatment, the combined risk factors were based on a less-favorable benefit/risk ratio.[110] In reality, the combined risk factors were not associated with an increase of symptomatic ICH among patients with IV thrombolysis within a 3–4.5 hours window as observed in the data from the Get With The Guidelines-Stroke Registry.[111] Nevertheless, diabetes mellitus (DM) is a risk factor for ICH in patients with acute ischemic stroke who undertook IV or intra-arterial thrombolysis.[112-114] In the PROACT II study, which was a successful RCT for EVT,[113] the frequency of symptomatic ICH was higher in the thrombolysis group than in the control group, and the prognosis was worse in patients with symptomatic ICH.[114] Blood glucose level >200 mg/dL was the only factor associated with symptomatic ICH in the study.[114]

It is well known from animal studies that DM or hyperglycemia is associated with the rapid growth of cerebral infarction and increased chances of hemorrhagic transformation even without thrombolysis, mediated by perfusion deficit and free radicals.[115,116] The animal models had undergone

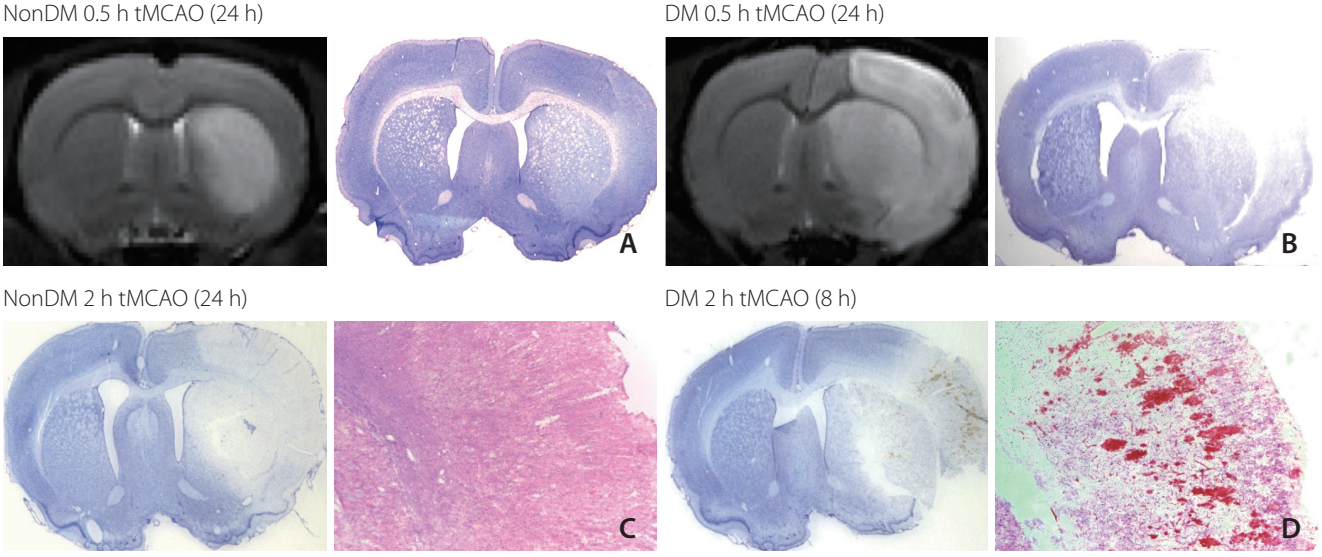

Fig. 1. Representative images of infarct volume and hemorrhagic transformation among rat models with cerebral ischemia in the presence or absence of diabetes mellitus (DM) induction. (**A, B**) Models of 30-minute ischemia and reperfusion in the unilateral middle cerebral artery with a thread (0.5 hours transient middle cerebral artery occlusion [tMCAO], sacrificed 24 hours after reperfusion); T2-weighted imaging by 9.4T magnetic resonance imaging taken in the Institute for Basic Science (Suwon, Korea) (left) and cresyl violet staining (right). (**A**) In a non-DM rat, the cerebral infarction is relatively small. (**B**) In a DM rat, the infarction is evident on the entire middle cerebral artery (MCA) territory induced only by 30-minute ischemia. (**C, D**) Models of 2 hours ischemia and reperfusion in the MCA (2 hours tMCAO, sacrificed 24 and 8 hours after reperfusion in non-DM and DM rats, respectively); cresyl violet (left) and hematoxylin and eosin staining (right). (**C**) The evident territorial infarction is induced by 2 hours tMCAO, the most common rodent model of cerebral ischemia, in a non-DM rat. (**D**) The territorial infarction is evident in the early time point, and prominent hemorrhagic transformation is shown in a DM rat with 2 hours tMCAO. The serum HbA1c was around 10–11%, 4 weeks after intraperitoneal streptozotocin injection in the DM rats. Materials are from the corresponding author's own laboratory (JSL; Suwon, Korea). Low magnification, ×6.7. High magnification, ×400.

transient occlusion and reperfusion procedures, which highly correspond to patients with LVO and reperfusion by MT. Representative features of the resultant infarct volume and hemorrhagic transformation from animal models are shown in Fig. 1A–D.

In the modern thrombectomy era, DM or high admission glucose levels were shown to affect the prognosis and the occurrence of ICH.[12] Overall, a moderate to high admission glucose level (>110 mg/dL) was associated with a lower rate of good clinical outcomes after EVT, and overt hyperglycemia (>170 mg/dL), which was closely related to the history of DM, also was significantly associated with a higher rate of the occurrence of parenchymal hematoma.[12] Similarly, these associations were reported in a previous RCT, MR CLEAN.[117] When the authors defined admission hyperglycemia as >7.8 mmol/L (141 mg/dL) and impaired fasting glucose as >5.5 mmol/L (99 mg/dL), those factors were associated with a higher symptomatic ICH and a lower rate of good clinical outcomes, respectively.[117]

From point of view of mechanisms, the distinction between normal, moderate, and overt hyperglycemia is reasonable (Fig. 2). Moderate hyperglycemia did not directly affect the occurrence of parenchymal hematoma but negatively affected prognosis in the ASIAN KR study. Worse prognosis in hyperglycemic or diabetes patients might be related to poor collaterals in the hyperglycemic environment, resulting in infarct volume growth.[118] A higher rate of ICH might be related to higher levels of free radicals and advanced glycation products in a sustained very high glucose exposure in the circulation systems or enlarged infarct volume itself, in which blood-brain barriers are vulnerable.[118]

Despite the worse prognosis, EVT for patients with moderate to overt hyperglycemia or DM should not be discouraged. In the above registry study, the ratio of good clinical

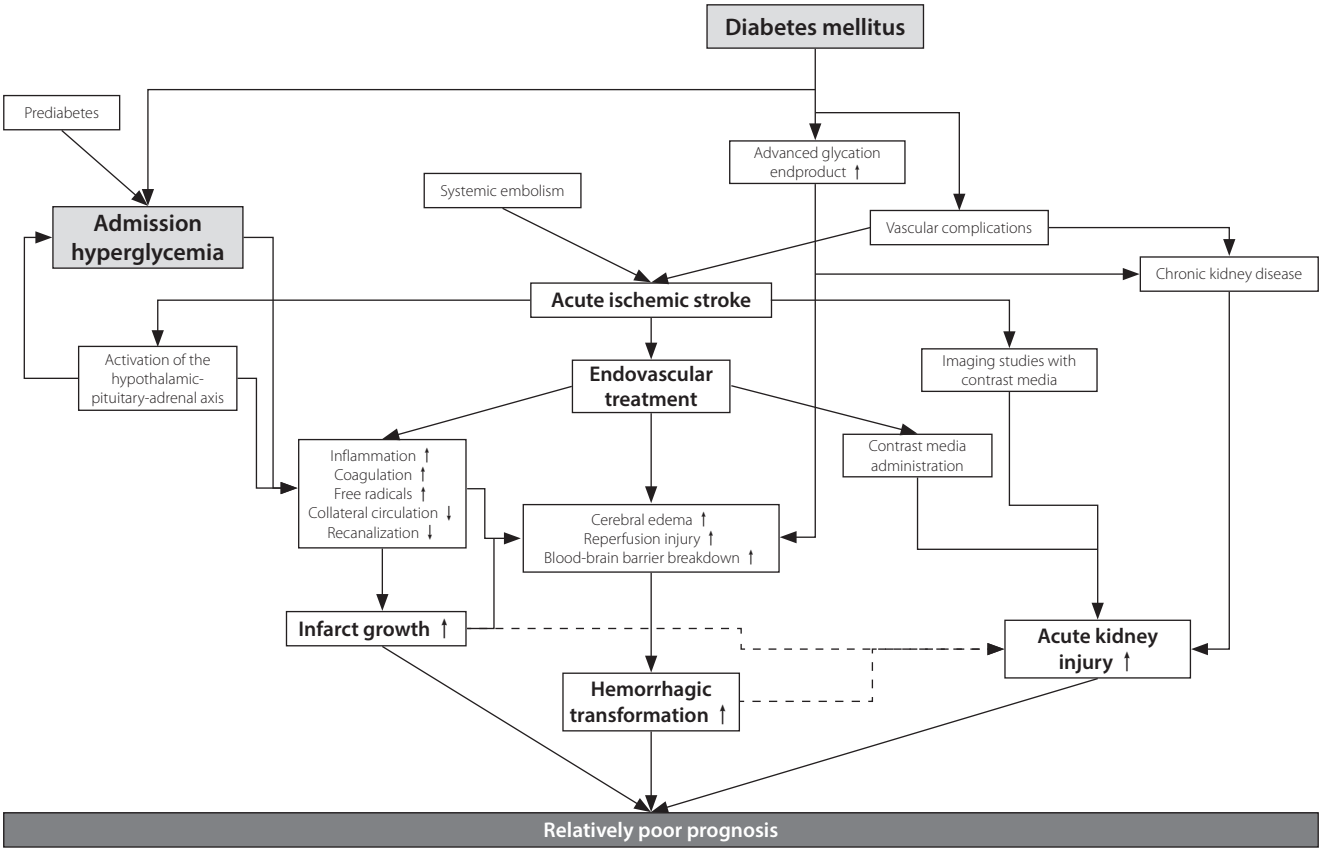

Fig. 2. The possible pathomechanism of poor prognosis in patients with diabetes mellitus or admission hyperglycemia who have acute ischemic stroke and endovascular treatment. Although there are overlapped features among the representative complications, including infarct growth, hemorrhagic transformation, and acute kidney injury, the main contributing factors seem to be somewhat distinctive. Infarct growth may be attributable to admission hyperglycemia especially upon recanalization failure. Although hemorrhagic transformation and acute kidney injury share a common factor, diabetes mellitus, different factors seem to respectively affect each complication. Hemorrhagic transformation more likely occurs after reperfusion injury. Severe stroke might indirectly affect the occurrence of acute kidney injury (dashed line).

Table 2. Nephropathic complications in various clinical situations

Studies	Study period	No.	Definition	Contrast media	Main risk factors	AKI/ARF	Dialysis/ replacement
Cervicocerebral contrast CT protocol							
Josephson et al.[120]	Apr 2000–Oct 2004	1,075 (no disease information)	A rise in serum creatinine >0.5 mg/dL within 1 week	150 mL of IV iohexol (CTA+CTP)	NA	4.8%	0.2%
Krol et al.[121]	Apr 2002–Apr 2005	481 (with an acute stroke syndrome)	A rise in serum creatinine >25% within 5 days	Ioversol (mostly for CT angiography)	NA	3%	0%
Hopyan et al.[122]	Jan 2003–Aug 2007	198 (suspected acute stroke)	A rise in serum creatinine >25% within 3 days	Iodixanol, iohexol (mostly for CTA±CTP)	NA	2.9%	0%
Cervicocerebral and spinal digital subtraction angiography							
Prasad et al.[123]	Jan 2011–Feb 2013	158 (no definite renal disease)	A rise in serum creatinine >0.3 mg/dL or >50% within 48 h	Iohexol	DM plus high-dose contrast	2.5%	0%
Overall acute stroke							
Covic et al.[124]	Jan 2005–Jan 2006	1,090 (hemorrhagic stroke in 14.5%)	Any rise in serum creatinine value or fall in GFR	Iodixanol (contrast only used in necessary cases)	Old age, low GFR, CHF, hemorrhagic stroke	14.5%	1% (F group of RIFLE classification)
Tsagalis et al.[125,126]	Jan 1993–Dec 2007	2,155	A rise in serum creatinine >0.3 mg/dL or >50% within 48 h	NA	Baseline stroke severity & GFR	27%	NA
Rowe et al.[127]	Jun 2012–Jan 2016	209 (ischemic stroke only)	A rise in serum creatinine >0.5 mg/dL or >25% within 72 h of CTA	NA	DM	14.8%	NA
Percutaneous coronary interventions							
McCullough et al.[128]	Dec 1993–Aug 1994	1,869	A rise in serum creatinine >25% within 5 days	Diatrizoate (55%), ioxaglate meglumine (33%), both (12%)	Baseline CrCl, DM, contrast dose	14.5%	0.8%
Rihal et al.[129]	Jan 1996–May 2000	7,586	A rise in serum creatinine >0.5 mg/dL within 48 h	Iopamidol	Baseline Cr >2.0, DM with Cr <2.0, old age, CHF, contrast volume	3.3%	0.3%
Gruberg et al.[130]	NA (published in 2000)	439 (baseline Cr >1.8)	A rise in serum creatinine >25% within 48 h	Ioxaglate meglumine	Blood transfusion, low ejection fraction, contrast volume	37%	7%
Marenzi et al.[131]	Jan 2002–Sep 2007	561 (STEMI)	A rise in serum creatinine >25% within 72 h	Iomeprol or iohexol	Contrast volume	20.5%	2.5%

Table 2. Continued

Studies	Study period	No.	Definition	Contrast media	Main risk factors	AKI/ARF	Dialysis/ replacement
Endovascular treatment for acute ischemic stroke							
Loh et al.[132]	Sep 2002–Jan 2008	99	A rise in serum creatinine >0.3 mg/dL or >50% within 48 h	Iohexol	No adjusted data	3%	0%
Sharma et al.[133]	Jan 2006–Jan 2011	194	A rise in serum creatinine >0.3 mg/dL or >50% within 48 h	Ioversol	No adjusted data	1.5%	0%
Diprose et al.[134]	Mar 2011–Mar 2019	333	A rise in serum creatinine >0.3 mg/dL or >50% at 24–72 h	Iohexol	Low GFR, DM	3.3%	0%
Jia et al.[135]	Sep 2016–Sep 2017	94 with CTA+EVT (87 in CTA group)	A rise in serum creatinine >25% within 48 h of CTA	Iodixanol	NA	7.4% (2.3% in CTA group, P=0.172)	
ASIAN KR[13]	Jan 2011–Feb 2016	601	A rise in serum creatinine >0.3 mg/dL within 48 h or >50% within 7 days	Iodixanol, Iopamidol	DM, contrast dose, unsuccessful reperfusion	9.8%	0.8%

AKI, acute kidney injury; ARF, acute renal failure; CT, computed tomography; IV, intravenous; CTA, computed tomographic angiography; CTP, computed tomographic perfusion; NA, not available; DM, diabetes mellitus; GFR, glomerular filtration rate; CHF, congestive heart failure; RIFLE, Risk, Injury, Failure, Loss, and End-stage Kidney; CrCl, creatinine clearance; Cr, creatinine; STEMI, ST-elevation myocardial infarction; EVT, endovascular treatment; ASIAN KR, Acute Stroke due to Intracranial Atherosclerotic occlusion and Neurointervention Korean Retrospective.

outcomes was over 50% in the moderate and overt hyperglycemia groups, respectively, whereas it was over 75% in the normal group.[12] EVT would be helpful in patients with hyperglycemia or DM if the EVT is meticulously decided. Nevertheless, stroke physicians and neurointerventionists should recognize these complications when they decide EVT and should warn about the same to the concerned patients and caregivers. Intensive glucose control using insulin did not improve clinical outcomes once stroke occurred; rather, it induced severe hypoglycemia and other adverse events in the SHINE trial.[119] Therefore, further studies should focus on neuroprotection from DM or hyperglycemia besides glucose control.

Contrast-induced acute kidney injury

The manifestation of acute kidney injury (AKI) after EVT was not rare (around 10%), but the occurrence of renal replacement therapy was rare (<1%) in patients with EVT as per the ASIAN KR registry.[13] In a multivariable analysis, however, the occurrence of AKI was independently associated with poor clinical outcomes (modified Rankin Scale 3–6 at 3 months: OR, 5; 95% CI, 2–14) and with a high mortality rate (OR, 8; 95% CI, 4–17).[13] This AKI is generally associated with the use of iodinated contrast media and typically occurs 48–72 hours after the administration of contrast media in patients with an advanced imaging protocol, percutaneous coronary intervention (PCI), and stroke with or without EVT (Table 2).[13,120-135] A substantial dose of contrast media is not only exposed during neurointervention but also administered for baseline angiography and perfusion imaging, especially for EVT candidates with AIS and LVO. These multiple exposures may increase the risk of AKI in patients with AIS and EVT.

These risk factors and poor clinical outcomes associated with EVT for AIS are similar to those in PCI. In an early PCI study, acute renal failure (ARF) occurred in around 14% of the 1,869 patients with PCI, among which dialysis was needed

in less than 1%.[128] However, high in-hospital mortality and poor long-term survival were especially associated with the cases of ARF that required dialysis.[128] The risk factors of ARF occurrence included diabetes mellitus and contrast dose, as well as baseline renal function estimated from creatinine clearance.[128,136,137] Besides the above risk factors, dehydration, congestive heart failure, and old age are known to be associated with contrast-induced nephropathy (CIN).[138] To reduce the chance of CIN after EVT, adequate hydration is necessary in patients without congestive heart failure.[138] In addition, a less nephrotoxic contrast agent should be selected.[138] In 2006, the US Food and Drug Administration (FDA) database reported iopamidol and iodixanol to be the lowest and iohexol to be the highest toxic agents associated with CIN.[139] Furthermore, meta-analysis studies have supported that iodixanol or other low-osmolar contrast media, except iohexol, might be good choices for interventional treatment.[140,141] In the results from the ASIAN KR registry study, the use of iodixanol accounted for around 72% of the included patients and iopamidol for 28%.[13] Nevertheless, AKI after EVT is not induced only by contrast media. A severe stroke type, hemorrhagic stroke, which does not require much contrast media for brain evaluations, was independently associated with AKI in a study including both ischemic and hemorrhagic stroke patients.[124]

Again, it is imperative to focus on patients with diabetes (Fig. 2). Patients who have baseline diabetic nephropathy would be the most vulnerable to the manifestation of CIN.[138,142,143] Diabetic patients without nephropathy are also classified into the high-risk group.[144] On this ground, sufficient warning to patients and their caregivers and appropriate hydration alongside emergent stroke treatment should be given. Although sufficient hydration and minimal use of contrast, and high-dose atorvastatin are suggested to prevent CIN in patients who undergo contrast imaging or endovascular procedures,[145,146] further studies are warranted

Table 3. Enrolled populations and outcomes in representative studies for neuroprotective treatment

Studies	Treatment	Study design	Enrolled population	Endpoint	Outcomes	Comments
SAINT II[148]	NXY-059	RCT, phase III	Overall AIS	mRS	Ineffective	Reperfusion not considered. A wide range of severity.
ESCAPE-NA1[149]	Nerinetide (NA1)	RCT, phase III	LVO and EVT	mRS	Insignificant	ASPECTS criteria: 5–10. Overall high rate of good outcomes upon modern EVT.
SONIC[150]	Neu2000	RCT, phase II	LVO and EVT	mRS	Enrollment finished	ASPECTS criteria: 6–10. Treatment upon modern EVT.
ICTuS-2[151]	TTM (33.0°C for 24 h)	RCT, phase II/III	Overall AIS and IV rtPA	mRS	Ineffective	Reperfusion not considered. A wide range of severity.
Neugebauer et al.[152]	TTM (33.0°C for 72 h)+hemicraniectomy	RCT	Unilateral MCA infarction with early hemicraniectomy within 48 h from symptom onset	Mortality	Ineffective	Malignant stroke profile (>2/3 of MCA territory+basal ganglia). Early termination due to safety concern.
HARIS[153]	TTM (34.5°C for 48 h)	Retrospective, case-control	Reperfused LVO (mTICI 2b–3) by EVT within 6 h	mRS, CT, MRI	More favorable	Moderate to severe stroke severity (median ASPECTS 6). Treatment upon modern EVT.
ASIAN KR[14]	TTM (34.5°C for 48 h)	Retrospective case-control	LVO and EVT	mRS	More favorable in the malignant trait subgroup	Malignant trait subgroup (ASPECTS <6). Treatment upon modern EVT.

RCT, randomized control trial; AIS, acute ischemic stroke; mRS, modified Rankin Scale; LVO, large vessel occlusion; ASPECTS, Alberta stroke program early CT score; EVT, endovascular treatment; TTM, targeted temperature management; IV, intravenous; rtPA, recombinant tissue plasminogen activator; MCA, middle cerebral artery; CT, computed tomography; MRI, magnetic resonance imaging; ASIAN KR, Acute Stroke due to Intracranial Atherosclerotic occlusion and Neurointervention Korean Retrospective.

to prevent unwanted effects in those patients.

Reperfusion injury and neuroprotection study

In terms of the pathobiology of cerebral infarction, a cascade of cellular changes, including excitotoxicity, peri-infarct depolarization, inflammation, and apoptosis, are involved.[147] Glutamate release *via* the N-methyl-D-aspartate (NMDA) receptor and free radicals, which are related to reperfusion injury, is known as an essential pathophysiologic mechanism in ischemia/reperfusion models, and is a target for neuroprotective treatment.[147] In the era of modern thrombectomy, reperfusion injury might be masked due to improved clinical outcomes, and neuroprotective treatment might be necessary in specific situations. Various representative neuroprotective studies for patients with acute stroke, which were performed before and after the EVT era, are summarized in Table 3.[14,148-153]

Previously, NXY-059, a neuroprotective agent with free radical-trapping properties showed a huge protective effect on rodent models with cerebral ischemia.[154] A clinical trial, SAINT I study, showed an improvement of mRS in the NXY-059 group whereas change from baseline in total National Institute of Health Stroke Scale (NIHSS) score, another co-primary endpoint, did not differ from the placebo group.[155] Finally, the next SAINT II study failed to prove the neuroprotective effect between the NXY-059 and placebo groups.[148] After this failure, all neuroprotective studies and investments were discouraged. It is suspected that the inconsistent results of neuroprotective treatment came from differences between animal studies and clinical settings. In the SAINT trials, patients were enrolled if they had acute ischemic stroke.[148,155] The population, however, was highly heterogeneous because they were not differentiated based on the severity of the stroke and the size of occlusive vessels. Thus, the study would include diverse subjects with mild, moderate, or severe stroke, and the occlusion of the cerebral artery might occur in small branches or large vessels. In addition, only a small portion of the LVO was reperfused in the pre-MT era. In contrast, LVO is mostly involved in the proximal middle cerebral artery (MCA) through the ICA and is always completely recanalized and reperfused within a few hours (mostly 2 hours) in rodent models.[156] Furthermore, very young animals were used for the experiments.[157] It is believed that these differences had contributed to the inconsistent result and the failure in clinical trials. However, it is time for neuroprotection to be revisited. In the current thrombectomy era, successful reperfusion among patients with LVO is much more frequent than that in the pre-MT era, although complete reperfusion is still challenging.[65,158-160] Now, the characteristics of patients with LVO are more similar to those of cerebral ischemia animal models.

The very recent ESCAPE-NA1 trial is an RCT for evaluating the efficacy and safety of a neuroprotective agent in the modern thrombectomy era.[149] NA1 (nerinetide, or Tat-NR-2B9c), used in the trial, interferes with post-synaptic protein 95 and perturbs the interactions between the protein and NMDA receptor, thereby ameliorating the glutamate toxicity of the ischemic brain and reducing infarct volume in both permanent and transient focal ischemia models.[161,162] In the previous ENACT study, a phase II trial, no serious adverse events were reported in 92 patients from the NA1 group, although the lesion volume as observed by MRI did not differ between the NA1 and placebo groups.[163] The final results of the ESCAPE-NA1 trial failed to prove the efficacy of NA1 on clinical outcomes after EVT for patients with AIS and LVO.[149] In a subgroup analysis, an interaction was shown between alteplase and the efficacy of NA1 administration. It appeared that NA1 was effective in patients without alteplase.[149] In reality, alteplase inhibited NA1 levels,[164] and this could be a possible explanation for the failure of the ESCAPE-NA trial.[165] However, it is thought that too good clinical outcomes in the placebo group were the main reason behind the failure. Based upon similar (onset to randomization up to 12 hours) or slightly wider inclusion criteria than that compared with the ESCAPE trial (ASPECTS 5 to 10 in ESCAPE NA1 *vs.* ASPECTS 6 to 10 in ESCAPE), the rate of good clinical outcomes was higher in the ESCAPE-NA1 placebo group than in the ESCAPE treatment group (59.2% *vs.* 53.0%).[19,149] Now, a new successive trial, ESCAPE NEXT, is being launched (ClinicalTrials.gov Identifier: NCT04462536). The candidates will be randomized for nerinetide without alteplase infusion with a protocol similar to that of ESCAPE-NA1. We hope that this will succeed.

Neu2000 (nelonemdaz) is another neuroprotective agent, which is a cocktail regimen with both NMDA antagonistic and antioxidant actions.[166,167] The drug awaits the reports from the phase II trial.[150] We hope additional neuroprotective agents would help in improving the clinical outcomes in serious stroke patients.

Therapeutic hypothermia, a targeted temperature management (TTM), is another neuroprotective method. It is a specified composite of management but does not use a specific drug. The key mechanisms of action include the

inhibition of excitotoxicity, neuroinflammation, apoptosis, free radical production, and so on.[168] A decrease in cerebral energy metabolism is another main mechanism of TTM neuroprotective effects.[169] The TTM has already been approved as a neuroprotective treatment in comatose patients with return of spontaneous circulation after cardiac arrest.[170-172] These patients are in line with the ischemia/reperfusion model. On this ground, TTM has been mentioned as a promising treatment strategy for patients with acute ischemic stroke and has been evaluated in various studies (Table 3).[173] Contradicting our expectations, most RCTs for TTM have failed to prove the improvement of clinical outcomes in patients with acute ischemic stroke.[151,152,174] In contrast, the HARIS study, a case-control study, did show an improvement in clinical outcomes and the reduction of cerebral edema and hemorrhagic transformation in the TTM group versus the control group.[153] The median ASPECTS was 6 in the TTM group, which means that included patients had moderate to severe stroke severity.[153] Interestingly, only patients who had successful reperfusion from EVT were included, similarly as ischemia/reperfusion models.[153] From the ASIAN KR registry, similar results were reported.[14] In the overall population with LVO and EVT, the clinical outcomes did not differ between the TTM and control groups.[14] However, a significantly higher rate of good clinical outcomes (32.1% *vs.* 7.7%) was revealed from TTM in the malignant trait subgroup, which was designated as baseline ASPECTS <6, DWI lesion volume >82 mL, or NIHSS >20.[14]

To summarize the results from neuroprotective studies in a stroke population, essential points for trial success appear to include (1) reperfusion by EVT in patients with emergent LVO and (2) patients with a relatively malignant stroke profile or with poor prognostic factors.

CONCLUSION

The current review article was based on the results of the ASIAN KR registry studies. The most important issues and considerations regarding EVT for emergent LVO were covered. Although Asian patients were rarely included in the RCTs for EVT that were reported earlier, the obtained data from Asian registry studies were found to be comparable to the outcomes of RCTs. Besides, with respect to the Asian subjects, EVT was observed to be more efficacious against ICAS LVO when compared with embolic LVO, which is primarily detected in patients from Western countries. Fast and complete reperfusion should be an ultimate target of EVT since it is closely related to good outcomes as demonstrated by diffusion reversal. Patients with diabetes should be cautiously treated because they have a potential risk of poor clinical outcomes, hemorrhagic transformation, and acute kidney injury after EVT. Treatment of reperfusion injury in patients with poor prognostic factors should be further studied to determine if the prognosis could be improved by both EVT and neuroprotection treatment. Cumulatively, with these factors contributing to EVT outcomes and clinical implications, EVT can lead to a better prognosis in patients with AIS and LVO.

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Ethics Statement

The approval of the institutional ethics committee and informed consents were waived since its nature lies on literature review.

Conflicts of Interest

The authors have no conflicts to disclose.

Author Contributions

Concept and design: JSL. Analysis and interpretation: JSL. Data collection: JSL. Writing the article: JSL. Critical revision of the article: JSL, YH, and SS. Final approval of the article: JSL, YH, and SS. Statistical analysis: JSL. Obtained funding: JSL. Overall responsibility: JSL.

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