Supplementary Table 2A. Clinical efficacy, safety, target-engagement, and evidence-level assessment for POM strategies

Stage	POM strategy	Study/reference	Design and population	OCEBM 2011 level/ evidence maturity	Exposure/ comparator	Key clinical outcome	Key imaging or physiological outcome	Safety	POM interpretation
Prevention	RIC for vascular vulnerability and risk-factor modulation	Orlandi et al.[46]; Guo et al.[47]; RICBP-EH, Yin et al.[48]	Randomized human studies in systemic inflammation, untreated mild hypertension, or essential hypertension	Level 2 — randomized trials; surrogate vascular outcomes	Protocolized upper-limb RIC; sham or usual-care control	Guo et al.[47] showed an additional 24-hour SBP reduction of about 3.6 mm Hg; RICBP-EH showed an SBP-lowering signal	Attenuated inflammation-induced endothelial dysfunction; improved ambulatory BP	Generally well tolerated; no clear serious safety signal	Supports target engagement in vascular vulnerability and hypertension; stroke-event reduction is unproven
Prevention	IH for cardiovascular and metabolic adaptation	Serebrovska et al.[56]; Panza et al.[49]; van Meijel et al.[57]	Small human studies in prediabetes, OSA with hypertension, or overweight/obesity	Level 2 — small randomized/ crossover studies; indirect surrogate outcomes	Repeated mild IH; partly combined with CPAP; normoxic or crossover control	Panza et al. reported an approximately 11-mm Hg reduction in awake 24-hour SBP; stroke events were not assessed	Improved glucose homeostasis and hypoxia tolerance; increased HIF-related gene expression; increased glycolysis and carbohydrate oxidation without improved insulin sensitivity	Short-course protocols were generally tolerable; symptomatic hypoxemia and arrhythmia require monitoring	Indirect nonstroke evidence; effects depend on dose, phenotype, and endpoint
Prevention/ periprocedural	RIC for hemodynamic targets	An et al.[43]; Li et al.[45]; RIC-CCT, Liu et al.[44]	PET/CT-guided RCT (n=23), prospective ICA/MCA occlusion cohort, and randomized carotid-stenting trial	Level 2 — RCTs plus cohort evidence; mainly surrogate endpoints	Repeated upper-limb RIC; short preprocedural or long-term treatment	Long-term delivery was feasible; recurrent-stroke or functional benefit remains unconfirmed	Improved ipsilateral CBF and glucose metabolism; reduced high-risk ischemic tissue; shortened cerebral circulation time; less postprocedural contrast staining	Generally well tolerated; adherence requires assessment	Supports phenotype enrichment based on impaired cerebrovascular reserve or hypoperfusion; outcomes are mainly imaging or physiological surrogates
Secondary prevention	RIC for recurrent-stroke prevention	RICA, Hou et al.[42]	Multicenter, double-blind, randomized sham-controlled trial; n=3,033; recent stroke/ TIA with 50%–99% intracranial stenosis	Level 2 — large randomized trial; neutral hard endpoint	Long-term bilateral upper-limb RIC; sham control	Ischemic stroke occurred in 16.9% vs. 19.0% over 3.5 years; no significant difference	No hemodynamic or subgroup signal sufficient to change the neutral conclusion	Long-term treatment was generally safe	Large negative hard-endpoint trial; anatomical stenosis alone may be insufficient for selection
Acute	Routine low-flow oxygen	SO2S, Roffe et al.[27]	Multicenter pragmatic RCT; n=8,003; broad acute stroke population	Level 2 — large pragmatic randomized trial; neutral	Nasal oxygen at 2 L/min continuously for 72 hours or nocturnally for 3 nights; no routine oxygen control	No improvement in 90-day mRS, death, or disability; common OR about 0.97	No consistent prespecified subgroup or physiological benefit	No clinically important difference in serious adverse events	Does not support routine oxygen in nonhypoxemic, unselected acute stroke
Acute	Moderate-concentration NBO	Chiu et al.[41]	Nonrandomized comparative study; n=46; severe MCA stroke	Level 3 — nonrandomized comparative study	Venturi mask FiO_2 40%, started at a mean of 13.7 hours and continued for a median of 96 hours; control 2 L/min nasal oxygen	In-hospital mortality was 6% vs. 24% (P=0.12); no overall statistically significant mortality benefit was demonstrated	No imaging or physiological target-engagement endpoint was reported	Pneumonia occurred in 6% vs. 21% (P=0.18) and respiratory failure in 18% vs. 28% (P=0.45); no clear oxygen-toxicity signal was reported	Small, nonrandomized comparative study; suggests possible reductions in mortality and complications, but confirmatory randomized evidence is required

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Supplementary Table 2A. Continued

Stage	POM strategy	Study/reference	Design and population	OCEBM 2011 level/ evidence maturity	Exposure/ comparator	Key clinical outcome	Key imaging or physiological outcome	Safety	POM interpretation
Acute	HBOT	Chen et al.[81]	Single-center prospective nonrandomized comparative study; n=50 (25 HBOT and 25 age- and sex-matched disease controls); first-event acute non-cardioembolic ischemic stroke	Level 3—nonrandomized comparative evidence	HBOT at 2.5 ATA with intermittent 100% O_2; total treatment time 100 min; HBOT plus antiplatelet therapy vs. antiplatelet therapy alone	At 1 month, NIHSS, Barthel Index, and mRS improved within the HBOT group; after adjustment, the between-group difference was significant only for Barthel Index (P=0.048), not NIHSS (P=0.810) or mRS (P=0.325)	KDR+/CD34+ endothelial progenitor cells increased within the HBOT group; adjusted between-group EPC differences were not significant	Safety outcomes were not systematically reported	Provides preliminary functional and target-engagement signals; the nonrandomized design and small sample preclude efficacy conclusions
Acute	HBOT evidence synthesis	Li et al.[37]	Systematic review and meta-analysis of 8 randomized controlled trials; n=493; acute ischemic stroke	Level 1—systematic review/meta-analysis; limited by heterogeneous, generally small trials	Adjunctive HBOT versus non-HBOT or sham HBOT; protocols varied in pressure, initiation timing, treatment frequency, session duration, and treatment course	No significant pooled differences in NIHSS or Barthel Index; a statistically significant pooled difference in modified Rankin score was reported, but the overall evidence did not support routine HBOT for acute ischemic stroke	No significant pooled differences in TNF-α, sICAM, sVCAM, sE-selectin, or CRP	Adverse-event incidence was lower in the HBOT group at the end of treatment (OR, 0.42; 95% CI 0.19–0.94), whereas no significant difference was observed during follow-up of ≤6 months (OR, 0.98; 95% CI 0.25–3.79)	Current pooled evidence does not support routine HBOT for acute ischemic stroke; heterogeneous protocols and generally small trials support further standardized evaluation of treatment timing and patient selection
Peri-EVT	Proof-of-concept NBO	OPENS-1, Li et al.[29]	Single-center assessor-blinded RCT; n=86; AIS treated with EVT	Level 2 — small randomized trial; proof-of-concept	100% O_2 at 10 L/min by face mask for 4 hours, started before recanalization or around puncture	Signal toward improved 90-day functional outcome	Smaller early infarct volume	No clear serious harm; underpowered for safety	Supports feasibility and early efficacy signal for time-limited peri-EVT NBO
Peri-EVT	NBO dose-time exploration	Temporal-gradient trial, Li et al.[30]	Open-label, blinded-endpoint, dose-escalation RCT; n=100	Level 2 — randomized dose-escalation trial	Control 1 L/min for 4 hours; NBO 10 L/min for 2, 4, or 6 hours	Functional outcomes trended favorably	The 4- to 6-hour regimens showed stronger 72-hour infarct-volume reduction than the 2-hour regimen	No clear increase in serious adverse events	Suggests duration may matter; the optimal exposure window remains undefined
Peri-EVT	Multicenter randomized NBO	OPENS-2, Li et al.[28]	Multicenter, randomized, single-blind, sham-controlled trial; n=282; anterior-circulation LVO within 6 hours undergoing EVT	Level 2 — multicenter randomized trial	100% O_2 at 10 L/min for 4 hours after femoral puncture; sham 1 L/min	Median 90-day mRS 2 vs. 3; improved mRS distribution; adjusted common OR, 1.65	Signal for smaller infarct volume; feasible integration with EVT workflow	Death 10% vs. 12%; serious adverse events 20% vs. 23%	Strongest positive peri-EVT NBO evidence; external replication and responder phenotyping are needed
Pre-EVT bridging	High-dose NBO	PROOF phase IIb[59,60]	International randomized phase IIb trial; imaging target mismatch and anterior-circulation occlusion planned for EVT	Level 2 — phase IIb randomized trial; neutral	High-flow NBO before EVT; standard-care control	Stopped for futility at interim analysis; no improvement in 90-day mRS	No improvement in 24-hour core growth or early NIHSS change	Benefit-risk signal did not support continuation	Key neutral RCT; differences from OPENS highlight delivery, timing, and workflow issues

Supplementary Table 2A. Continued

Stage	POM strategy	Study/reference	Design and population	OCEBM 2011 level/ evidence maturity	Exposure/ comparator	Key clinical outcome	Key imaging or physiological outcome	Safety	POM interpretation
Peri-EVT/post-reperfusion	RIC	SERIC-EVT, Guo et al.[95]	Multicenter, participant-blinded, randomized sham-controlled trial; n=498; mITT n=488	Level 2 — multicenter randomized trial	Upper-limb cuff 200 mm Hg twice daily for 7 days; sham 60 mm Hg	90-day mRS 0–2: 61.1% vs. 48.9%; RR, 1.25; early neurological deterioration at 7 days: 4.2% vs. 10.3%	Perfusion imaging was not the primary target-engagement endpoint	No increase in sICH, hemorrhagic transformation, or 90-day death	Supports peri-reperfusion ischemic conditioning; a parallel POM strategy rather than direct oxygen delivery
Post-reperfusion	Hyperoxemia exposure and de-escalation	López et al.[31]; Romero-Garcia et al.[32]	Successful-EVT observational cohort and systematic review/ meta-regression in acute brain injury	Level 3 — observational cohort and nonrandomized evidence synthesis	Serial systemic oxygen assessment after EVT; hyperoxemia defined in López et al.[31] as PaO_2 >120 mm Hg	Hyperoxemia was associated with poor functional outcome and mortality in observational analyses	No validated dose–response threshold or tissue-level oxygen target was established	Confounding by illness severity, ventilation status, and reperfusion injury remains likely	Supports post-reperfusion reassessment and rapid de-escalation of nonindicated hyperoxia; PaO_2 >120 mm Hg should be regarded as a warning signal rather than a validated universal ceiling
Chronic rehabilitation	IH paired with training	Hornby et al.[35]; upper-limb case series, Pearcey et al.[80]	Phase II double-blind randomized crossover trial (n=35; 28 completed) plus small case series	Level 2 — phase II randomized crossover trial	Fifteen 8%–9% O_2/normoxia cycles over about 30 min followed by 1 hour high-intensity gait training	Self-selected gait-speed gain 0.14 vs. 0.05 m/s; fastest speed, treadmill speed, and gait symmetry improved; short-term upper-limb strength signal	Improved motor performance and retention; upper-limb evidence remains exploratory	One hospitalization for supraventricular tachycardia; case series reported no clear intervention-related events	Most direct randomized rehabilitation-stage IH signal; requires cardiovascular screening and larger trials
Chronic rehabilitation	Early randomized HBOT	Efrati et al.[82]	Randomized prospective controlled study in chronic stroke	Level 2 — randomized controlled study; high risk of bias	100% O_2 at about 2 ATA for 90 min/session, 5 sessions/week, 40 sessions	Improved neurological function, activities of daily living, and quality of life	Improved SPECT brain activity	Generally tolerable	Lack of credible sham limits causal interpretation
Chronic rehabilitation	Recent negative randomized HBOT	Harrison et al.[83]	Randomized study; n=34; 6–36 months after stroke	Level 2 — small randomized study; underpowered	Planned approximately 40 HBOT sessions; early trial period used sham HBOT	No clinically meaningful benefit in the Stroke Impact Scale-16	No stable improvement in function or activity outcomes	No new major safety concern was identified	Under-recruitment and protocol changes limit inference, but this is an important recent negative study

Evidence levels follow the OCEBM 2011 Levels of Evidence for treatment/prevention questions and are design-based rather than a formal GRADE certainty assessment. For rows containing multiple studies, the level reflects the highest directly relevant human evidence, with endpoint directness and major limitations summarized in the same row. RIC is included as a conditioning strategy with shared adaptive pathways rather than a direct oxygen-exposure intervention.

POM, precision oxygen modulation; OCEBM, Oxford Centre for Evidence-Based Medicine; RIC, remote ischemic conditioning; RICBP-EH, Efficacy of Remote Ischemic Conditioning on Blood Pressure in Essential Hypertension; SBP, systolic blood pressure; BP, blood pressure; IH, intermittent hypoxia; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; HIF, hypoxia-inducible factor; RIC-CCT, Effect of Remote Ischemic Preconditioning on Cerebral Circulation Time in Patients With Severe Carotid Artery Stenosis; PET/CT, positron emission tomography/computed tomography; RCT, randomized controlled trial; ICA, internal carotid artery; MCA, middle cerebral artery; CBF, cerebral blood flow; RICA, Chronic Remote Ischemic Conditioning in Patients With Symptomatic Intracranial Atherosclerotic Stenosis; TIA, transient ischemic attack; SO2S, Stroke Oxygen Study; mRS, modified Rankin Scale; OR, odds ratio; NBO, normobaric oxygen; FiO_2, fraction of inspired oxygen; HBOT, hyperbaric oxygen therapy; ATA, atmosphere absolute; KDR+, kinase insert domain receptor-positive; CD34+, cluster of differentiation 34-positive; EPC, endothelial progenitor cell; TNF-α, tumor necrosis factor-alpha; sICAM, soluble intercellular adhesion molecule; sVCAM, soluble vascular cell adhesion molecule; sE-selectin, soluble E-selectin; CRP, C-reactive protein; CI, confidence interval; OPENS-1, Safety and Efficacy of Normobaric Hyperoxia Combined With Reperfusion for Acute Ischemic Stroke; AIS, acute ischemic stroke; EVT, endovascular thrombectomy; OPENS-2, Normobaric Hyperoxia Combined With Endovascular Treatment in Patients With Acute Ischemic Stroke; LVO, large-vessel occlusion; PROOF, Penumbral Rescue by normobaric O=O administration in patients with ischemic stroke and target mismatch proFile; OPENS, Normobaric Hyperoxia Combined With Reperfusion for Acute Ischemic Stroke; SERIC-EVT, Safety and Efficacy of Remote Ischemic Conditioning Combined With Endovascular Thrombectomy for Acute Ischemic Stroke Due to Large Vessel Occlusion of Anterior Circulation; mITT, modified intention-to-treat; RR, risk ratio; sICH, symptomatic intracranial hemorrhage; PaO_2, arterial oxygen tension; SPECT, single-photon emission computed tomography; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

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Supplementary Table 2B. Independent human evidence supporting POM patient selection, target identification, and monitoring

Stage	Evidence question	Study/reference	Population and methods	Main human finding	Candidate indicators	POM use	Main limitation
Post-reperfusion	Residual hypoperfusion and no-reflow after successful reperfusion	Sperring et al.[33]; Sun et al.[34]; Horie et al.[61]; Ter Schiphorst et al.[63]	Angiographic, early MRI/perfusion imaging, and inflammatory-marker studies after successful EVT	Macrovascular reperfusion does not ensure tissue reperfusion; some eTICI 2c–3 patients have residual hypoperfusion, delayed inflow/outflow, or continued infarct growth associated with worse outcomes	CTP/MR perfusion deficit, venous outflow, distal flow, infarct growth, inflammatory markers	Identify candidates with residual tissue oxygen-delivery targets and guide continued monitoring or oxygen de-escalation	POM reversal of no-reflow is unproven; imaging thresholds are not standardized
Acute/post-reperfusion	BBB injury and hemorrhagic-transformation risk	Inzitari et al.[77]; Jha et al.[78]; Rosell et al.[79]	Post-thrombolysis circulating markers, MRI FLAIR, and human brain tissue studies	Higher MMP9 is associated with hemorrhagic transformation, basement-membrane degradation, and death; MMP9-positive neutrophil infiltration is associated with BBB breakdown and basal lamina type IV collagen degradation	Circulating MMP9, FLAIR hyperintensity, type IV collagen degradation, neutrophil infiltration	Safety biomarker panel for peri-reperfusion POM and BBB-risk stratification	Mainly prognostic associations; not oxygen-dose specific
Rehabilitation	Neural-repair potential	Human BDNF studies, Stanne et al.[109]	Associations between circulating BDNF and long-term recovery after stroke	Lower BDNF is associated with poorer recovery or long-term outcome	Serum or plasma BDNF	Candidate response and target-engagement marker in rehabilitation IH or HBOT trials	Predictive value for POM response is unproven; timing and thresholds vary
Repair phase	HBOT-related progenitor-cell mobilization	Thom et al.[16]	Circulating stem/progenitor cells before and after human HBOT exposure	HBOT can mobilize circulating stem/progenitor cells	Circulating CD34+ or endothelial progenitor cells	Target-engagement measure for HBOT-related neurovascular repair	Mostly nonstroke populations; functional relevance is uncertain
Long-term implementation	Adherence to repeated-course POM	Zhao et al.[96]	Adherence survey in ischemic stroke patients receiving long-term RIC	Treatment beliefs, burden, family support, and device convenience influence completion	Completion rate, interruption reasons, device logs, patient-reported outcomes	Supports adherence and implementation assessment in preventive repeated-course POM	Does not assess biological efficacy; generalizability may vary by setting

This table summarizes independent human evidence supporting candidate POM phenotypes, target identification, safety monitoring, and implementation measures. The listed indicators are proposed for phenotype-enriched study design and are not validated oxygen-dose selection criteria. Reference numbers correspond to the revised manuscript.

POM, precision oxygen modulation; MRI, magnetic resonance imaging; EVT, endovascular thrombectomy; eTICI, expanded Treatment in Cerebral Ischemia; CTP, computed tomography perfusion; MR, magnetic resonance; BBB, blood–brain barrier; FLAIR, fluid-attenuated inversion recovery; MMP9, matrix metalloproteinase-9; BDNF, brain-derived neurotrophic factor; IH, intermittent hypoxia; HBOT, hyperbaric oxygen therapy; CD34+, cluster of differentiation 34-positive; RIC, remote ischemic conditioning.

Supplementary Table 2C. Preclinical and experimental mechanistic evidence for POM strategies

Stage	POM strategy or mechanistic question	Study/reference	Model and exposure	Functional or histological findings	Mechanisms and candidate markers	Opposite effect or safety boundary	Translational meaning
Prevention/ rehabilitation	IH dose, cycling pattern, and adaptive responses	Mechanistic studies and reviews, Liu et al.[13]; Zhang et al.[25]; Yuan et al.[36]	Repeated hypoxia-normoxia cycles varying oxygen level, bout duration, recovery interval, number of cycles, and course length	Enhanced tolerance to subsequent hypoxia or hypoperfusion; some models show metabolic and motor-plasticity effects	HIF, EPO, GLUT1, VEGF, glycolysis, mitochondrial homeostasis; candidate 5-HT and BDNF pathways	Excessive depth, duration, or inadequate recovery may convert IH into injurious exposure	IH must be specified by full dose-time parameters, not labeled simply as hypoxia
Prevention	IH vs. sustained hypoxia	Guan et al.[51]	Moderate IH vs. sustained hypoxia in animals followed by distal MCAO or hypoxic-ischemic injury	IH increased CBF and brain oxygen saturation, promoted functional angiogenesis, preserved BBB integrity, and reduced infarct volume and deficits; sustained hypoxia did not show the same protection	HIF-VEGF signaling, perfused vessel density, brain oxygenation, BBB integrity	Protection depends on intermittent pattern and moderate hypoxic dose	Direct support for pattern-specific rather than total-dose-based prevention-stage POM
Prevention/ acute	IH-derived plasma and PF4-dependent paracrine protection	Liu et al.[52]	Two-week IH (13% O_2; 5-min intervals; 10 cycles/day) generated IH-derived plasma; plasma or recombinant PF4 was tested before/ after dMCAO and tMCAO in young, female, and aged mice	IH-derived plasma reduced infarct and atrophy volumes and improved sensorimotor/cognitive recovery; PF4 depletion abolished and recombinant PF4 reproduced protection	Plasma proteomics, circulating PF4, BBB integrity, IgG extravasation, endothelial ZO-1	Poststroke benefit varied by reperfusion model; systemic PF4 dosing and thrombotic safety require validation	Identifies PF4 as a causal circulating mediator and candidate biomarker or pharmacological surrogate of IH
Prevention/ acute	RIC antioxidant, immune, and humoral adaptation	Experimental RIC evidence, Zhao et al.[26]; Xu et al.[50]; Ren et al.[53]	Transient limb ischemia-reperfusion; some studies combined pharmacological modulation with tMCAO	Reduced oxidative injury and neurological deficits; enhanced endogenous antioxidant defense	Nrf2-related defense, NO, inflammatory mediators, immune and humoral signaling	Stimulation site, cuff intensity, cycle number, and cotreatments may alter efficacy	Supports RIC as ischemic conditioning within POM, mechanistically distinct from direct oxygen delivery
Prevention/ peri-reperfusion	RIC augmentation of leptomeningeal collaterals	Saito et al.[54]; Zhang et al.[55]	Mouse MCAO with preischemic RIC or immediate remote ischemic postconditioning	Enhanced leptomeningeal anastomoses and collateral flow; reduced early ischemic lesion and final infarct volume	Collateral flow, leptomeningeal anastomoses, microcirculatory perfusion	Mainly young rodent models; clinical EVT timing is not fully represented	Supports collaterals and microcirculation as target-engagement endpoints for RIC
Acute occlusion	NBO preservation of penumbral oxygenation and energy metabolism	Liu et al.[65]; Sun et al.[67]	Transient or focal cerebral ischemia in rats with early NBO	Preserved penumbral oxygen tension; reduced infarct volume and deficits; improved energy metabolism	Tissue oxygen tension, ATP and metabolites, ionic homeostasis, cytotoxic edema	Delayed start, absent residual perfusion, or prolonged exposure may reduce benefit	Supports early NBO in patients with residual flow and salvageable tissue
Thrombolysis/ reperfusion	NBO with tPA for BBB protection	Liang et al.[64]; Liu et al.[66]	Rat MCAO models with early NBO during ischemia combined with delayed tPA before reperfusion	Reduced neurovascular complications, BBB disruption, and hemorrhagic-transformation signals; extended the experimental tPA window	MMP9, BBB permeability, basement membrane, hemorrhagic transformation	Effects depend strongly on NBO and tPA timing	Supports time-paired oxygen and reperfusion treatment with prespecified BBB safety endpoints

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Supplementary Table 2C. Continued

Stage	POM strategy or mechanistic question	Study/reference	Model and exposure	Functional or histological findings	Mechanisms and candidate markers	Opposite effect or safety boundary	Translational meaning
Post-reperfusion	Hyperoxia and reoxygenation injury	Experimental/mechanistic evidence, Sun et al.[34]; Stoll et al.[70]; Singer et al.[73]	Ischemia-reperfusion, high-FiO_2, or sustained hyperoxia models	May worsen oxidative stress, mitochondrial dysfunction, inflammation, microvascular impairment, and BBB injury	ROS, mitochondrial function, MMPs, NETs, leukocyte-platelet aggregation, endothelial injury	Effect depends on exposure intensity, duration, tissue viability, and reperfusion quality	Mechanistic basis for upper oxygen bounds, reassessment, and de-escalation
Acute/reperfusion	HBOT effects on BBB and edema	Veltkamp et al.[17]	Transient focal cerebral ischemia with acute HBOT	Reduced BBB permeability and brain edema	Tight junctions, vascular permeability, brain water content	Pressure, timing, and exposure duration determine benefit-risk balance	Supports acute barrier-protective potential, but clinical window remains undefined
Acute/reperfusion	HBOT metabolic and inflammatory regulation	Hu et al.[15]; Zhao et al.[19]	Hyperglycemic MCAO and ischemia-reperfusion animal models	Reduced infarct volume, hemorrhagic transformation, and reperfusion injury	ATP/NAD+/SIRT1; SIRT1-mediated HMGB1 deacetylation; inflammatory and BBB markers	Metabolic state and treatment timing strongly influence effects	Supports testing HBOT in comorbidity models rather than only healthy young animals
Rehabilitation/repair	Delayed repeated HBOT and neurogenesis	MCAO experimental study, Hu et al.[93]	Delayed repeated HBOT after rat MCAO with pathway inhibition	Enhanced endogenous neurogenesis; improved sensorimotor and cognitive function; pathway inhibition attenuated benefit	ROS/HIF-1α/β-catenin, doublecortin, synapsin-1	ROS may serve as repair signal at lower levels but mediate injury at higher exposure	Provides causal mechanistic support and target-engagement markers for rehabilitation-stage HBOT

This table summarizes preclinical and experimental evidence supporting candidate mechanisms, target-engagement markers, and safety boundaries for POM strategies. These findings are intended to guide mechanistic hypotheses and biomarker selection and should not be interpreted as clinical efficacy evidence. Reference numbers correspond to the revised manuscript.

POM, precision oxygen modulation; IH, intermittent hypoxia; HIF, hypoxia-inducible factor; EPO, erythropoietin; GLUT1, glucose transporter 1; VEGF, vascular endothelial growth factor; 5-HT, 5-hydroxytryptamine; BDNF, brain-derived neurotrophic factor; MCAO, middle cerebral artery occlusion; CBF, cerebral blood flow; BBB, blood–brain barrier; PF4, platelet factor 4; dMCAO, distal middle cerebral artery occlusion; tMCAO, transient middle cerebral artery occlusion; IgG, immunoglobulin G; ZO-1, zonula occludens-1; RIC, remote ischemic conditioning; Nrf2, nuclear factor erythroid 2–related factor 2; NO, nitric oxide; EVT, endovascular thrombectomy; NBO, normobaric oxygen; ATP, adenosine triphosphate; tPA, tissue-type plasminogen activator; MMP9, matrix metalloproteinase-9; FiO_2, fraction of inspired oxygen; ROS, reactive oxygen species; MMP, matrix metalloproteinase; NET, neutrophil extracellular trap; HBOT, hyperbaric oxygen therapy; NAD+, nicotinamide adenine dinucleotide; SIRT1, sirtuin 1; HMGB1, high mobility group box 1.