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Review

Ischaemic Stroke Keeps Time: A Critical Review of Circadian Biology from Thrombus Formation to Translational Failure

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Abstract

Ischaemic stroke does not occur at random hours. Onset clusters in the morning, and several physiological correlates of that pattern are well described: an endogenous circadian peak in circulating plasminogen activator inhibitor-1, platelets that aggregate more readily in the hours after rising, and the morning surge in blood pressure. What remains unsettled is whether the hour of onset also influences how quickly brain tissue is lost and how well it responds to treatment. This critical narrative review draws together molecular, experimental and clinical evidence and organises it as a Three-Clock Model: a trigger clock that sets when vessels occlude, a tissue clock that governs the pace of infarct growth, and a treatment clock that modulates the response to reperfusion and to adjunctive or neuroprotective therapy. Human cohorts have reported larger ischaemic cores and faster infarct growth after night-time onset or during night-time interhospital transfer, the latter measured directly with serial diffusion-weighted imaging, and time-of-day differences in thrombectomy outcome, but these associations are vulnerable to confounding by uncertain onset times, out-of-hours care and the gap between clock time and internal circadian phase. In rodents, three neuroprotective strategies reduced infarction when given during the animals' inactive phase but not during the active phase, a mismatch that may have contributed to failed translation; other experiments disagree about which phase is more damaging. Large pragmatic trials of bedtime antihypertensive dosing have been neutral. We propose a ten-item CHRONO-STROKE minimum reporting dataset, which is author-proposed and unvalidated and intended to supplement existing consensus data elements, a clock-time-stratified design for trials of adjunctive therapy, and five testable predictions, as a means of establishing whether circadian biology deserves a place in acute stroke decision-making.

Keywords: ischaemic stroke; circadian rhythm; chronobiology; thrombolysis; endovascular thrombectomy; neuroprotection; plasminogen activator inhibitor-1; blood–brain barrier; chronotherapy; translational research

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1. Introduction

Clinicians who provide acute stroke care are familiar with the morning clustering of presentations, and the published data confirm the impression. A meta-analysis of 31 publications covering 11,816 strokes found onset to be 49% more frequent than expected

between 06:00 and noon, and 29% less frequent between midnight and 06:00 [1]. Cardiologists had described much the same morning peak for myocardial infarction more than a decade earlier [2].

For years the morning peak came with a concise explanation. On rising, blood pressure climbs and platelets become more reactive, so the risk of occlusion rises with them [3,4]. Much of that account has held up. What it does not address is what happens once the artery has occluded. Circadian clocks run in peripheral tissues throughout the body [5,6], including the vessel wall [7] and the immune system [8], and there is no obvious reason to suppose that the ischaemic brain, alone among tissues, is indifferent to the hour.

In 2020 that question moved from speculation to experiment. Esposito and colleagues pointed out that rodents are nocturnal and humans diurnal, so that daytime rodent models represent the animals' inactive phase, whereas most strokes in clinical trials happen during the human active phase. Three neuroprotective strategies reduced infarction in daytime (inactive-phase) rodent models but not in night-time (active-phase) models [9]. A commentary that followed suggested that this mismatch may help to explain why neuroprotection has failed in the clinic [10].

Broad reviews have since mapped the territory [11,12]. The aims of this review are narrower and more critical. First, we set out to separate three variables that can be folded into a single exposure called "time of day": when the vessel occludes, how fast tissue is lost, and how treatment works. Second, we examine how far the human time-of-day data published since 2021 can be explained by confounding rather than by circadian biology. Third, we propose a minimum reporting standard and a trial design that would allow the next generation of studies to distinguish the two. Each of the three arguments ends in a prediction that could be shown to be wrong.

Throughout, we distinguish clock time, the local time recorded in clinical notes and registries, from circadian phase, the position of a person's internal biological clock, which can be displaced from clock time and which almost none of the stroke studies reviewed here measured. We also distinguish reperfusion (intravenous thrombolysis and endovascular thrombectomy) from adjunctive therapy, under which we include neuroprotective agents and other drugs given alongside or instead of reperfusion. Where a statement applies to one and not the other, we say so.

2. Literature Search and Scope

This is a critical narrative review, not a systematic review, and no protocol was registered. The evidence was assembled in two steps. First, we identified relevant human, experimental and chronotherapy studies from our own knowledge of the field and from two recent reviews of circadian biology and stroke [11,12]. Second, on 3 October 2026 we searched the OpenAlex and Crossref bibliographic databases, with a general web search engine as a supplement, for studies relevant to each strand of the review and in particular for work published after those two reviews. Principal queries combined one term from {circadian, diurnal, time of day, time of onset, chronotherapy, clock gene, BMAL1, shift work, daylight saving} with one term from {stroke, cerebral ischaemia, infarct growth, thrombolysis, thrombectomy, neuroprotection, thrombosis, blood–brain barrier, neutrophil}. No publication-date limits were applied; the cited work spans 1985 to 2026. Only English-language reports were considered. MEDLINE and PubMed were not searched directly. OpenAlex and Crossref index MEDLINE-listed journals but are not equivalent to a MEDLINE search, and a formal MEDLINE or Embase search could have retrieved studies that we did not identify. Two studies cited in the revised version, a serial-imaging study of infarct growth [13] and a consensus statement on data elements [14],

were brought to our attention during peer review and were not retrieved by our original search; we regard that as evidence of the limitation just described.

Selection was purposive. We gave priority to four groups: (i) human cohort studies, registries and randomised trials with at least 200 participants that related clock time, shift work or sleep disruption to stroke occurrence, imaging-defined tissue status or treatment outcome; (ii) human physiological studies that used controlled protocols to separate circadian from behavioural influences, which are necessarily small; (iii) experimental studies that manipulated clock genes or circadian phase in models of cerebral or myocardial ischaemia, thrombosis, vascular function, blood–brain barrier function or leukocyte timing; and (iv) randomised chronotherapy trials with vascular or platelet outcomes. Reviews and gene-expression atlases were cited for biological context, landmark earlier studies were retained whatever their size, and where studies disagreed both sides were included. Bibliographic details of every cited source were checked against Crossref or OpenAlex records. Every quantitative statement was checked against the abstract or, where it was accessible, the full text of the original report; in this revision, every figure attributed to the thrombectomy and thrombolysis studies in Section 4.3 was re-checked against the full text or abstract of its source. One trial is cited together with the Expression of Concern and the subsequent Editor's Note published about it. No formal risk-of-bias scoring was undertaken; the consequences of that choice are considered in Section 9.

Generative artificial intelligence (Claude, Anthropic, San Francisco, CA, USA) was used in preparing this manuscript: to run the database and web searches described above and screen the results against the stated priorities; to verify bibliographic details and quantitative statements against their sources; to draft and restructure text and tables, including the proposed frameworks; to generate the plotting code for Figure 1; for language editing; and to prepare revisions in response to editorial and peer-review comments. The authors directed the scope and the arguments, reviewed, revised and verified all output, and take full responsibility for the content (see Acknowledgments).

3. The Clock in the Neurovascular Unit

3.1. Architecture of the Mammalian Clock

Mammalian circadian clocks are cell-autonomous oscillators built on a transcription–translation feedback loop. The CLOCK–BMAL1 complex drives expression of the *Period* and *Cryptochrome* genes, whose protein products then repress their own transcription over a cycle of roughly 24 h [15]. The suprachiasmatic nucleus of the hypothalamus is the principal clock [16], coordinating semi-autonomous clocks in peripheral tissues [5].

Peripheral clocks have measurable consequences. In a mouse atlas of 12 organs, 43% of protein-coding genes showed circadian transcription in at least one organ; the same study reported that 56 of the 100 top-selling drugs and 119 of the 250 medicines on the World Health Organization essential medicines list act on the products of rhythmic genes [6]. In 13 human tissues from 632 donors, nearly half of all genes cycled in at least one tissue, and about 1000 of them encode drug targets, transporters or drug-metabolising enzymes [17]. Two consequences follow for stroke. Circadian phase and clock time can drift apart, as they do in shift work [18], and ischaemic stroke itself disrupts endogenous circadian rhythms [19]. When a dataset records "time of day", it therefore records a proxy for a biological state that was not measured. In humans, circadian phase is best estimated with dedicated laboratory protocols that separate endogenous rhythms from behaviour and environment, such as those used in the studies cited below [20,21]; in laboratory animals the light–dark schedule defines the active and inactive phases and the zeitgeber time at which an insult or a treatment is delivered.

3.2. Vessel Wall, Platelets and Fibrinolysis

The vascular evidence is consistent. *Bmal1*-knockout and *Clock*-mutant mice show increased pathological vascular remodelling, and aortas from *Clock* mutants show endothelial dysfunction [22]; *Per2*-mutant mice have impaired endothelium-dependent relaxation [23]. After photochemical vascular injury, the time to occlusion in wild-type mice varies across the day; *Clock* mutation abolishes that rhythm, *Npas2* deletion alters it, and *Bmal1* deletion prolongs the time to occlusion [24]. These observations have been drawn together in reviews of vascular and cardiovascular clocks [7,25].

In people, the clearest evidence concerns plasminogen activator inhibitor-1 (PAI-1). In the diurnal study of Angleton and colleagues, PAI-1 activity was higher in the morning than in the evening, tissue-type plasminogen activator activity moved inversely with it, and the authors attributed the variation in tissue-type plasminogen activator activity to changes in PAI-1 rather than to changes in the secretion of tissue-type plasminogen activator itself [26]. In 12 healthy adults studied under a protocol designed to separate endogenous circadian influences from behaviour and environment, circulating PAI-1 concentration showed a circadian peak at about 06:30 that was independent of the sleep–wake cycle and much larger than the changes produced by standardised behavioural stressors [20]. Using forced desynchrony in a further 12 adults, the same group found plasma cortisol peaking at a circadian phase corresponding to about 09:00, plasma catecholamine concentrations highest during the biological day, and the greatest exercise-induced vagal withdrawal at about 09:00 [21].

Platelets have both an endogenous and a behavioural rhythm, and the two differ in timing. In 15 healthy men, aggregability to adenosine diphosphate or adrenaline was higher at 09:00, an hour after rising, than at 03:00; in a second group the morning increase disappeared when the subjects stayed supine and inactive [3]. In a forced-desynchrony study of 12 adults, flow-cytometric markers of platelet activation (including surface-activated glycoprotein IIb/IIIa) peaked at a circadian phase corresponding to 08:00–09:00, whereas whole-blood aggregability and plasma adrenaline peaked later, at a phase corresponding to 15:00–20:00 [27]. The morning prothrombotic state therefore has at least two components: an endogenous circadian one, of which PAI-1 is the clearest example, and a behavioural one that accompanies rising and activity. The distinction matters when the chronotherapy trials are read (Section 7).

3.3. Barrier and Immune Clocks

Two less familiar clocks may matter for what happens after occlusion. The first is at the blood–brain barrier. In mice, nervous-system deletion of *Bmal1* caused barrier hyperpermeability with an age-dependent loss of pericyte coverage [28]. In *Drosophila*, a clock in the perineurial glia of the barrier drives rhythmic efflux of xenobiotics; brain permeability is higher at night, and night-time phenytoin was more effective in a seizure model [29]. These are invertebrate data and should be interpreted with corresponding caution. If a comparable rhythm operates at the human barrier, however, brain exposure to an adjunctive drug would depend on the hour of dosing as well as on the dose. This consideration applies to neuroprotective and other adjunctive agents that must cross the barrier; it has no direct bearing on mechanical thrombectomy, and its relevance to thrombolytic drugs, which act within the vessel lumen, is uncertain. None of the studies reviewed here has tested it.

The second is the innate immune system. Leukocyte recruitment to tissues follows circadian rules [8]. In mice, BMAL1 regulates a CXCL2–CXCR2 pathway that drives the daily ageing of circulating neutrophils; in mice engineered for constitutive neutrophil ageing, persistence of aged neutrophils in the circulation predisposed the animals to thrombo-inflammation and death [30]. Whether a comparable daily shift affects how a

cerebral infarct evolves was not tested in the studies reviewed here. One experimental observation is consistent with it. In a thromboembolic mouse model, deoxyribonuclease I (DNase-I) lowered levels of neutrophil extracellular traps and reduced infarct volume without causing bleeding or haemorrhagic transformation with tissue plasminogen activator; chronic aspirin pretreatment increased the haemorrhagic transformation induced by tissue plasminogen activator but did not change the protective effect of DNase-I. The protection appeared only when DNase-I was given during the daytime (inactive) phase, not overnight [31].

4. The Three-Clock Model

The Three-Clock Model splits time of day into three exposures, each with its own biology, its own body of human evidence and its own characteristic way of being confounded (Figure 1; Table 1).

- Trigger clock: The timing of vessel occlusion, associated with the morning convergence of PAI-1 [20,26], platelet reactivity [3,27], the blood-pressure surge [4] and the cortisol peak [21]. Its clinical relevance lies in prevention and in the timing of preventive drugs.
- Tissue clock: The pace at which threatened tissue becomes infarct once the vessel has closed, potentially shaped by barrier integrity, inflammation and neuronal tolerance. Its clinical relevance lies in prognosis and in imaging-based selection.
- Treatment clock: The way the brain responds to reperfusion and to adjunctive therapy, including haemorrhagic transformation and drug delivery. Its clinical relevance lies in how trials are interpreted and how studies of adjunctive agents are designed.

The separation is worth making because the three clocks need not run in phase. A morning excess of occlusions carries no information about whether tissue tolerates ischaemia better or worse at that hour. A treatment outcome that varies across the day could reflect the biology of the tissue being treated, the biology of the treatment itself, or neither: it could simply reflect who is treated at that hour and how. Two further distinctions are needed when the treatment clock is read. The first is between studies that time the onset of stroke and studies that time the administration of treatment; these are correlated but not interchangeable. The second is between an association between treatment time and outcome, which is what the available studies report, and evidence that the effect of treatment itself differs by time. The latter requires a comparison of treated with untreated patients, ideally randomised, across the day, and none of the studies reviewed here provides it. The closest is a registry of patients who all received thrombectomy, which tested whether the association between successful recanalisation and outcome differed by time of day [32]; that is an observational interaction within treated patients, not a test of whether the benefit of thrombectomy itself varies with the hour.

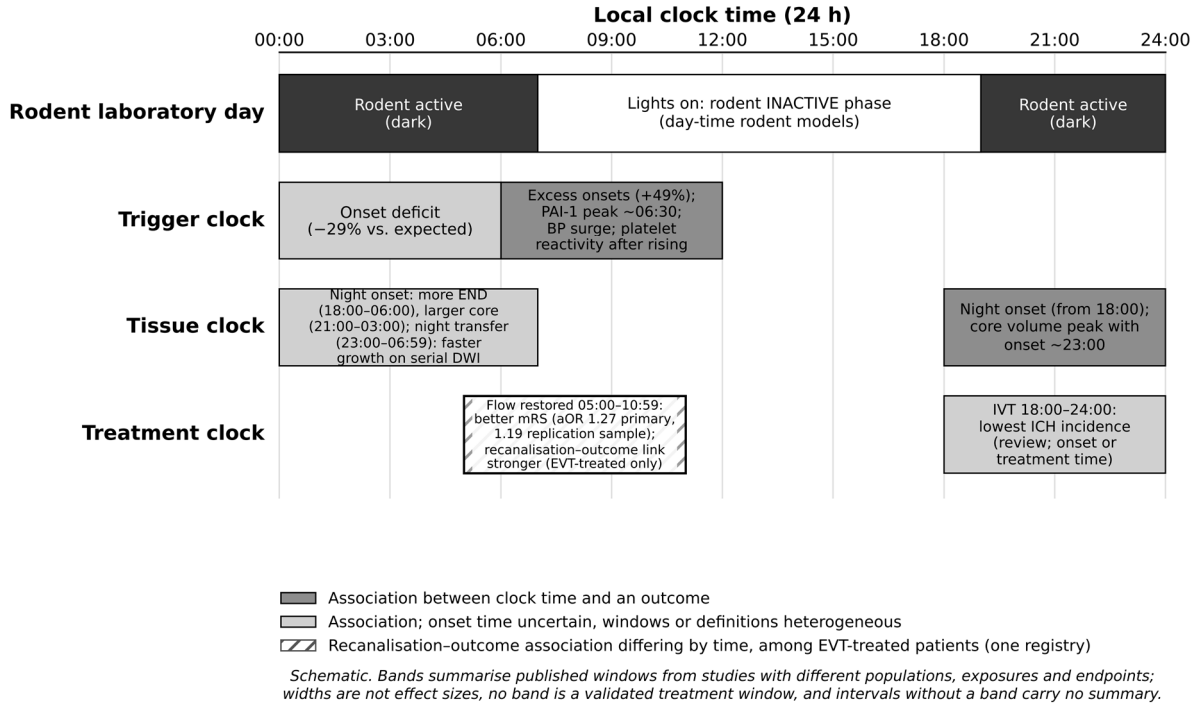


Figure 1. The Three-Clock Model of circadian influence in ischaemic stroke. The top row shows the mismatch between daytime rodent models, which fall in the rodent inactive phase, and the human active phase in which most strokes in clinical trials occur [9]; light–dark timings are illustrative. The trigger clock summarises the morning excess of onsets and its prothrombotic correlates [1,4,20]; the tissue clock, the reported night-time excess of core volume, infarct growth and early deterioration [13,33,34]; and the treatment clock, the reported associations between time of treatment and thrombectomy outcome [32] and between time of onset or treatment and thrombolysis-associated haemorrhage [35]. All bands are schematic. Each combines studies with different populations, exposures (onset time in some, treatment time in others), time windows and endpoints, and none represents a validated treatment window. Band positions summarise the published windows and band widths are not effect sizes. Solid bands denote associations between time of day and an outcome. The hatched band marks the single registry of thrombectomy-treated patients in which the association between successful recanalisation and outcome differed by time of treatment [32]; this is an observational interaction within treated patients and does not show that the benefit of thrombectomy itself varies by time of day. Intervals without a band carry no summary; they do not indicate an absence of data or of effect. BP, blood pressure; EVT, endovascular thrombectomy; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; PAI-1, plasminogen activator inhibitor-1.

Table 1. Selected human evidence for the trigger, tissue and treatment clocks in stroke. The column "Exposure timed by" states whether the study analysed the clock time of stroke onset or the clock time of treatment. Effect estimates are given with 95% confidence intervals where the original report provides them, and for comparisons between time blocks the reference category is stated. Haemorrhagic transformation (HT) and symptomatic intracranial haemorrhage (sICH) are as defined by each study.

Clock	Study (Design, Size)	Exposure Timed by	Principal Finding (95% CI Where Reported)	Outcome Definition	Main Vulnerability
Trigger	Elliott 1998 [1] (meta-analysis; 31 publications, 11,816 strokes)	Onset	Onset 49% more frequent than expected 06:00–12:00; 29% less frequent 00:00–06:00	Timing of onset	Pooled published series

Trigger	Kario 2003 [4] (prospective cohort; 519 older hypertensive adults)	Not applicable (morning BP surge)	Surge ≥ 55 mmHg: clinical stroke 19% vs. 7.3% over 41 months; RR 2.7 after matching (p = 0.04; CI not reported)	Clinical stroke; silent infarcts on MRI	Hypertensive older adults only; top-decile cut-off
Trigger	Pariona-Vargas 2023 [36] (FAST-MAG trial cohort; 1615, 76.5% ischaemic)	Onset	Ischaemic onset plateau 10:00–21:59; ICH peaks at 09:00 and 19:00	Timing of onset	Trial-enrolled population
Tissue	Reidler 2023 [33] (pooled cohorts; 583 anterior LVO with CT perfusion)	Onset	Night (21:00–03:00) vs. day (09:00–15:00; reference) onset: larger admission core (median 40.2 vs. 33.8 mL; adjusted p = 0.008); faster single-scan core growth (adjusted p = 0.01)	Core volume; core volume ÷ onset-to-imaging time	Growth derived from recorded onset time
Tissue	Seners 2023 [13] (transferred LVO patients with paired DWI; 225)	Interhospital transfer (window)	Night transfer (23:00–06:59; n = 31) vs. day transfer (07:00–22:59; n = 194; reference): median growth 4.3 vs. 1.4 mL/h (p < 0.001)	Difference between two DWI volumes ÷ scan interval	Doubly selected cohort; small night subgroup
Tissue	Ryu 2022 [34] (registry; 17,461 witnessed onsets within 6 h)	Onset	Onset 18:00–06:00 vs. 06:00–18:00 (reference): END 14.4% vs. 12.8% (adjusted; p = 0.006); aOR 0.88 (0.79–0.98) for favourable 3-month outcome	END; 3-month mRS 0–2	Residual confounding; outcome partly mediated by care
Treatment	Cappellari 2014 [37] (cohort; 476 IVT)	Treatment	HT: OR 0.29 (0.12–0.67) for 12:00–18:00 and 0.26 (0.11–0.62) for 18:00–24:00 vs. 00:00–06:00 (reference)	HT (ECASS definition) within 24 h	Small; several time blocks compared
Treatment	Lorenzano 2014 [38] (SITS-ISTR; 21,513 IVT)	Treatment	Day-hours treatment (08:00–19:59) vs. night (20:00–07:59; reference): aOR 1.12 (1.04–1.21) for 3-month mRS 0–2	mRS 0–2; mortality; sICH	Day/night dichotomy; registry
Treatment	Stan 2023 [35] (systematic review; 6 studies, 33,365)	Onset and treatment (mixed)	Lowest ICH incidence with onset or treatment 18:00–24:00; highest 06:00–12:00	ICH; definitions vary	Few studies (n = 6); onset and treatment timing pooled; heterogeneous definitions
Treatment	Wang 2022 [39] (cohort; 438 EVT)	Onset	Favourable outcome 58.6% (onset 00:00–06:00) to 30.5% (18:00–24:00). Reference 18:00–24:00:	3-month mRS 0–2; sICH not associated	Single cohort; wide CIs

			aOR 4.01 (1.02–15.80) for 00:00–06:00; 3.24 (1.09–9.64) for 06:00–12:00. Onset time as a single variable: aOR 0.61 (0.40–0.93), coding not stated		
Treatment	Granja Burbano 2023 [32] (German Stroke Registry; 9357 EVT-treated patients)	Time of flow restoration (primary); onset (secondary, no association)	Morning (05:00–10:59) vs. all other times combined (reference): aOR 1.27 (1.08–1.47) for better 90-day mRS in primary sample (2015–2019; n = 5025) and 1.19 (1.01–1.41) in replication sample (2020–2021; n = 4332). Recanalisation–outcome association stronger in morning than evening (interaction p = 0.046 in abstract, 0.049 in results)	90-day mRS (ordinal); association of successful recanalisation with outcome	Observational; all patients treated; recanalisation not randomised; selection, staffing and process times; single interaction test

aOR, adjusted odds ratio; BP, blood pressure; CI, confidence interval; CT, computed tomography; DWI, diffusion-weighted imaging; ECASS, European Cooperative Acute Stroke Study; END, early neurological deterioration; EVT, endovascular thrombectomy; FAST-MAG, Field Administration of Stroke Therapy–Magnesium; HT, haemorrhagic transformation; ICH, intracerebral haemorrhage; IVT, intravenous thrombolysis; LVO, large vessel occlusion; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; OR, odds ratio; RR, relative risk; sICH, symptomatic intracranial haemorrhage; SITS-ISTR, Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register.

4.1. The Trigger Clock

The trigger clock has the deepest evidence base. In the Elliott meta-analysis the morning excess held across stroke types: 55% for ischaemic stroke, 34% for haemorrhage and 50% for transient ischaemic attack [1]. Among 1272 patients enrolled in the Trial of Org 10172 in Acute Stroke Treatment (TOAST), more than half of ischaemic strokes were either present on awakening or began between 06:00 and noon; lacunar strokes were present on awakening in 31.6%, although the difference between subtypes fell short of significance (p = 0.07) [40]. Among 519 older hypertensive patients, a morning surge in systolic blood pressure of 55 mmHg or more, defined as the mean of the 2 h after waking minus the mean of the hour containing the lowest sleeping pressure, identified those with more multiple silent infarcts at baseline (57% vs. 33%) and more clinical strokes over an average of 41 months of follow-up (19% vs. 7.3%; relative risk 2.7 after matching for age and 24 h pressure, p = 0.04) [4].

Wake-up strokes accounted for 14.3% of ischaemic strokes in a population-based study and differed little from other strokes clinically [41]. Studies of disrupted circadian timing and sleep also suggest that the timing system matters, although most of the effects reported are modest. In Finland, ischaemic stroke admissions rose in the first two days after daylight saving time transitions (relative risk 1.08), an effect that was diluted across the whole week [42]. Among 80,108 nurses, each five years of rotating night shifts carried a 4% higher risk of ischaemic stroke [43], and a meta-analysis of 2,011,935 people found a relative risk of 1.05 for ischaemic stroke with shift work [44]. In 1022 patients, obstructive sleep apnoea was associated with stroke or death from any cause (adjusted hazard ratio

1.97) [45]; it is for this reason that sleep-disordered breathing is included in the reporting dataset proposed in Section 8.1.

Two cautions are warranted. The shift-work associations are small enough that residual confounding could account for them entirely. And the shape of the morning peak may be less fixed than the older literature implies. Among 1615 patients from the Field Administration of Stroke Therapy–Magnesium (FAST-MAG) prehospital trial, 76.5% of whom had cerebral ischaemia and 23.5% intracerebral haemorrhage, ischaemic onset showed a broad plateau from 10:00 to 21:59, while intracerebral haemorrhage peaked at 09:00 and again at 19:00 [36]. Differences in how onset was defined, and in who was enrolled, may explain part of the discrepancy with older series; that problem is the subject of Section 5.

4.2. The Tissue Clock

Direct human evidence for a tissue clock is recent, and it comes from two different methods of measuring infarct growth, which should be kept apart. The first method estimates growth from a single scan: core volume on admission divided by the recorded interval from onset to imaging. In 583 patients with anterior large vessel occlusion imaged with computed tomography perfusion, onset at night (21:00–03:00) rather than by day (09:00–15:00) was associated with larger ischaemic cores on admission (median 40.2 vs. 33.8 mL; adjusted $p = 0.008$); core volumes peaked with onset at about 23:00, and calculated core growth was faster at night (adjusted $p = 0.01$), whereas penumbral volume did not vary across the day [33]. Because this estimate depends on the recorded onset time, any systematic tendency to record night-time onsets later than they truly occurred would inflate apparent growth directly.

The second method measures growth from two scans and does not use the onset time at all. Seners and colleagues studied 225 patients with large vessel occlusion who were transferred from a primary to a comprehensive stroke centre for thrombectomy and who had diffusion-weighted MRI at both centres; interhospital growth was calculated as the difference between the two measured infarct volumes divided by the interval between the scans [13]. Median growth was faster in the 31 patients (14%) whose transfer occurred at night (23:00–06:59) than in the 194 transferred by day (4.3 vs. 1.4 mL/h; $p < 0.001$). This design removes onset misclassification as an explanation, which makes it the most direct human evidence for a tissue clock among the studies reviewed here. It has limitations of its own. The cohort was selected twice over, first by referral and transfer for thrombectomy and then by the availability of paired MRI, so it represents patients who reached a comprehensive centre with persisting occlusion rather than all patients with stroke; the night-time subgroup was small; the time of transfer is a window rather than a point and overlaps the time of onset; and night-time transfer may differ from daytime transfer in duration, haemodynamic management and the proportion of patients with early reperfusion. The finding is nonetheless concordant with the single-scan estimate, and the two methods fail in different ways, which strengthens the case that something beyond measurement error is being observed. The Leducq CIRCA consortium has published consensus data elements and time segmentations intended to make such studies comparable [14].

Clinical correlates have been reported in a large registry. Among 17,461 patients in a Korean cohort restricted to witnessed onset and arrival within 6 h, onset between 18:00 and 06:00 was associated with more early neurological deterioration (adjusted incidence 14.4% vs. 12.8%; $p = 0.006$) and lower odds of a favourable outcome at three months (adjusted odds ratio 0.88, 95% confidence interval 0.79–0.98) [34]. The restriction to witnessed strokes is important, because it means that this particular association cannot be attributed to wake-up strokes with unknown onset times.

Experimental work agrees that time of day matters, but not on which phase is the more dangerous. In rats, which are nocturnal, lesion volume after middle cerebral artery occlusion varied with the time of occlusion and was more than three times larger at 04:00 than at 16:00 [46]. In mice, outcomes were best when ischaemia was induced at zeitgeber time 18, in the middle of the active phase, with greater BMAL1 expression and AKT activation [47], and BMAL1 overexpression protected against transient focal ischaemia while its knockdown or knockout made the injury worse [48]. In mice, weekly advances of the light–dark cycle before occlusion enlarged infarcts and dysregulated the inflammatory cytokine response [49]. Esposito and colleagues reported a narrower penumbra, fewer dying cells and less infarct growth between 12 and 72 h in active-phase mice [9]. The mouse data and the rat data therefore point in different directions, and the differences in species, model and timing deserve a direct head-to-head comparison.

The heart offers the clearest proof of principle. In mice, myocardial ischaemia–reperfusion at the sleep-to-wake transition produced infarcts 3.5 times larger than at the wake-to-sleep transition, and the difference was attenuated or abolished when the cardiomyocyte clock was disabled [50]. In patients undergoing aortic valve replacement, afternoon surgery was followed by less perioperative myocardial injury than morning surgery, in both a propensity-matched cohort and a randomised study, and REV-ERBα deletion or antagonism reduced injury in a mouse model [51]. None of the stroke studies reviewed here combines a human organ, a timed ischaemia–reperfusion insult and a candidate mechanism in this way.

The night-time growth findings are the most important results in this section, and the single-scan estimate is also the most fragile. Night-time onset includes strokes that begin during sleep and are only discovered on waking, whose true timing is unknown [41]. Unless onset is witnessed and timed, faster apparent growth from a single scan cannot be distinguished from a longer true duration of ischaemia. The objection is testable, and Prediction 1 in Section 8.3 is built on it; the serial-imaging study [13] and the witnessed-onset registry [34] already provide partial answers.

4.3. The Treatment Clock

For intravenous thrombolysis, the most consistent signal concerns bleeding, and most of the studies time the exposure by treatment rather than by onset. In 476 patients with non-lacunar stroke, thrombolysis started between noon and midnight was associated with less haemorrhagic transformation, defined according to the European Cooperative Acute Stroke Study (ECASS) criteria within 24 h, than thrombolysis started between midnight and 06:00 (odds ratio 0.29, 95% confidence interval 0.12–0.67 for 12:00–18:00; 0.26, 0.11–0.62 for 18:00–24:00), while major neurological improvement at 24 h was less likely with treatment between 06:00 and noon (0.35, 0.16–0.74) or noon and 18:00 (0.40, 0.20–0.81) [37]. A systematic review of six studies including 33,365 patients, which pooled analyses by onset time and by treatment time and which used varying definitions of haemorrhage, concluded that the 18:00 to midnight window carried the lowest incidence of intracranial haemorrhage and the 06:00 to noon window the highest [35]. In the largest registry analysis cited here, 21,513 patients in the Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register (SITS-ISTR) treated with alteplase during day hours (08:00–19:59) had slightly higher odds of a good functional outcome (modified Rankin Scale score 0–2 at 3 months) than those treated at night, between 20:00 and 07:59 (adjusted odds ratio 1.12, 95% confidence interval 1.04–1.21) [38]. The morning circadian peak in PAI-1 [20] is one candidate mechanism for differences in fibrinolytic response. All of the thrombolysis studies cited here report associations between time and outcome among treated patients; none tests whether the effect of thrombolysis itself differs by time.

For thrombectomy the findings are less consistent. In 438 patients grouped by onset time, the proportion with a favourable outcome (modified Rankin Scale score 0–2 at 3 months) fell from 58.6% for onset between midnight and 06:00 to 30.5% for onset between 18:00 and midnight. With onset between 18:00 and 24:00 as the reference category, the adjusted odds ratio for a favourable outcome was 4.01 (95% confidence interval 1.02–15.80) for onset between 00:00 and 06:00 and 3.24 (1.09–9.64) for onset between 06:00 and 12:00; both confidence intervals are wide. The paper also reports a single adjusted odds ratio of 0.61 (0.40–0.93) for onset time entered as one variable, but it does not state how that variable was coded, so this estimate cannot be read as a comparison between particular time blocks. Onset time was not associated with symptomatic intracranial haemorrhage, early recanalisation or mortality [39]. In 9357 patients from the German Stroke Registry, all of whom underwent thrombectomy, the primary exposure was the time of day at which flow was restored. Restoration between 05:00 and 10:59 was associated with a better 90-day modified Rankin Scale score (adjusted odds ratio 1.27, 95% confidence interval 1.08–1.47, compared with all other times of day combined, in a primary sample of 5025 patients treated in 2015–2019; 1.19, 1.01–1.41, in a replication sample of 4332 patients treated in 2020–2021), whereas the time of day of onset was not associated with outcome. Using a multiplicative interaction term, the authors also found that the association between successful recanalisation and outcome was stronger in morning-treated than in evening-treated patients (p for interaction 0.046 in the abstract and 0.049 in the results), and the association of successful recanalisation with functional independence persisted up to 24 h after onset in the morning group but was lost after 11.5 h in those treated between 17:00 and 22:59 [32]. This finding needs careful reading. Successful recanalisation was not randomised; it is a result of the procedure that depends on occlusion site, collateral status, technique and time from onset. The analysis therefore shows that the association between recanalisation and outcome differed by time of treatment among treated patients. It does not show that the benefit of thrombectomy compared with no thrombectomy varies with time of day, which only a comparison with untreated patients could establish. The authors themselves note that patients may have been selected differently for thrombectomy at different times of day and that residual confounding by time-dependent staffing cannot be excluded [32]; both apply to the interaction as much as to the main association. The interaction also rests on a single registry and on a p-value close to 0.05.

These results are difficult to reconcile. One cohort finds onset between 18:00 and 06:00 harmful [34]; another finds that onset between midnight and 06:00 carries the best thrombectomy outcomes [39]; a third places the advantage on the time at which flow was restored rather than the time of onset, which in that registry was not associated with outcome [32]. Some studies time the onset, others the treatment, and the windows and populations differ. The inconsistency is itself informative: either the true effects are small and unstable, or the studies are measuring different things under the same label.

Clinical practice has already solved one circadian problem by setting the clock aside altogether. For patients with stroke of unknown onset, a diffusion-weighted lesion without a corresponding fluid-attenuated inversion recovery (FLAIR) hyperintensity identified 503 patients in whom alteplase increased the proportion with a modified Rankin Scale score of 0 or 1 (53.3% vs. 41.8%; adjusted odds ratio 1.61) [52], and perfusion imaging extended thrombolysis to selected patients treated 4.5 to 9 h after onset or on waking with stroke [53]. Tissue time replaced clock time. The Three-Clock Model asks the next question: whether circadian phase changes what a given imaging profile means for the patient being assessed.

5. Why Human Time-of-Day Data Are Hard to Interpret

The human studies in Table 1 are exposed, to differing degrees, to five sources of confounding, summarised in Table 2. Any one of them could produce a time-of-day effect where none exists, or conceal one that does.

Table 2. Five sources of confounding in human time-of-day studies of stroke.

Confounder	How It Operates	Possible Direction of Bias	Mitigation
Onset misclassification	Wake-up and other unwitnessed onsets; timing conventions differ (last known well, discovery, midpoint of sleep)	Night onsets may appear to have larger cores and faster single-scan growth	Record onset certainty; primary analysis in witnessed onsets; serial-imaging designs
Out-of-hours care	If staffing, imaging access, transfer or operator experience differ by hour, care may differ by hour	Night or evening treatment may appear less effective	Record process times and service model; compare across centres
Selection	Who presents, who is transported and who is enrolled may vary across the day	Unpredictable; can flatten or exaggerate peaks	Population-based denominators; report screening logs
Clock time versus circadian phase	Shift work and stroke itself can displace or disrupt internal rhythms; almost no study measures phase	Attenuates true circadian effects	Record shift work and usual sleep timing; treat phase statements as inference
Definitional heterogeneity	Blocks of 6 or 12 h; onset time versus treatment time; any HT versus sICH	Inconsistent results; misleading pooling	Analyse time as continuous (cosinor or spline); pre-specify windows; use consensus time segmentations [14]

HT, haemorrhagic transformation; sICH, symptomatic intracranial haemorrhage.

Onset misclassification comes first and is probably the most damaging. Wake-up strokes are unwitnessed by definition and accounted for one in seven ischaemic strokes in a population-based study [41], and the conventions for timing them vary; the EXTEND trial of perfusion-imaging-selected thrombolysis, for example, timed them from the midpoint of sleep [53]. Each convention places the recorded onset at a different point in time. Out-of-hours care is the second. Treatment follows onset within hours, so onset time and treatment time move together; if staffing, imaging access, transfer arrangements or operator experience differ by hour, treatment given at different hours may also differ in quality. Unless process times and service models are recorded, a time-of-day difference in outcome cannot be separated from a difference in care. The third is selection. Patients who present at different hours may differ from one another, and those enrolled in trials and registries differ again; the flatter onset distribution in a prehospital trial population is a reminder of this [36]. The fourth is the gap between clock time and internal circadian phase discussed in Section 3.1. The fifth is mundane but pervasive: several studies in Table 1 divide the day into blocks of six or twelve hours, and some analyse onset time while others analyse treatment time. Pooling such studies, as a systematic review does, mixes exposures that are not the same thing.

6. The Rodent Problem and Translational Failure

The Esposito experiments merit careful reading, because their implications run in two directions [9]. A rodent studied by day is in its inactive phase, which corresponds to night in humans, when strokes are least common [1]. If neuroprotectants work best against inactive-phase physiology, the human patients most likely to benefit would be those with night-time onset, a group that includes strokes discovered on waking, whose onset times are the least certain of all [41]. Clinical trial populations, in which most strokes occur during the active phase [9], would then be enriched for precisely the physiology in which the treatments failed in rodents.

Several caveats constrain this hypothesis. The original work tested three strategies (normobaric hyperoxia, the free-radical scavenger α-phenyl-*N*-tert-butylnitrone and the *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801) [9]. Experimental studies disagree about which phase carries the greater injury (Section 4.2). The DNase-I experiments showed the same pattern of protection confined to the inactive phase [31], which strengthens the observation without explaining it. Boltze and colleagues suggested that taking chronotype into account may complement the many other factors that influence the efficacy of experimental stroke therapies [10]. One practical step follows directly: preclinical stroke studies should report the zeitgeber time of both the insult and the treatment, and confirmatory studies should test candidate agents in both phases. The argument in this section concerns adjunctive and neuroprotective agents; mechanical reperfusion was not studied in these experiments, and we do not extend the hypothesis to it.

7. Chronotherapy So Far: What the Large Trials Have Shown

If the trigger clock is real, timing preventive treatment to cover the vulnerable morning hours might help. Table 3 summarises what the trials have found.

Table 3. Randomised chronotherapy studies relevant to the trigger clock.

Study	Design and Population	Result	Comment
Hygia 2020 [54]	19,084 hypertensive adults, Spain; bedtime vs. morning intake of usual antihypertensive medication; median 6.3 years	Primary cardiovascular outcome HR 0.55 (0.50–0.61)	Expression of Concern (April 2020) [55]; investigation found no grounds for ethical or factual concern (Editor's Note, 2020) [56]; source data not verified and methodological critique published [57]
TIME 2022 [58]	21,104 hypertensive adults, UK; evening vs. morning intake of usual antihypertensive medication	Primary outcome 3.4% vs. 3.7%; HR 0.95 (0.83–1.10)	Pragmatic, decentralised
BedMed 2025 [59]	3357 hypertensive adults, Canada; bedtime vs. morning intake of usual antihypertensive medication; median 4.6 years	2.3 vs. 2.4 events per 100 patient-years; HR 0.96 (0.77–1.19)	No difference in falls, fractures, glaucoma or cognitive decline
Bonten 2015 [60]	290 adults on low-dose aspirin for secondary prevention randomised to a crossover of bedtime vs. on-waking aspirin (two 3-month periods); 263 analysed for 24 h ambulatory BP and 133 for platelet reactivity	No difference in 24 h BP; morning platelet reactivity 22 ARU lower with bedtime intake (VerifyNow Aspirin assay)	Biomarker study; no clinical outcomes

ARU, aspirin reaction units; BP, blood pressure; HR, hazard ratio (95% confidence interval).

The Hygia Chronotherapy Trial reported a 45% reduction in cardiovascular events when hypertensive patients took their usual antihypertensive medication at bedtime rather than on waking [54]. Its publication history should be stated completely. The *European Heart Journal* issued an Expression of Concern in April 2020, advising caution in interpreting the results while the content and conduct of the trial were investigated [55]. Later in 2020 the journal published an Editor's Note reporting that its investigation had found no grounds for an ethical or factual concern [56]. A subsequent commentary in *Hypertension* reported that the European Society of Cardiology Journals Ethics Committee had found no evidence of fraud but could not verify the source data, criticised the absence of any account of randomisation and the baseline differences between groups, and noted that lack of source-data verification had been the key reason for retracting other articles in the field [57]. No misconduct has been found, but the methodological questions about the trial have not been resolved, and its effect size is far outside the range of the two pragmatic trials that followed. The pragmatic, decentralised TIME study in 21,104 patients in the United Kingdom [58] and the BedMed trial in 3357 patients in Canada [59] each found no difference in cardiovascular outcomes between evening or bedtime and morning dosing of usual antihypertensive medication. Decades earlier, the morning peak in myocardial infarction had not been detectable among patients already taking beta-blockers [2], an observation consistent with the idea that a drug acting on the sympathetic surge can flatten the trigger window.

These neutral trials should be read narrowly. TIME and BedMed asked when patients should take their usual antihypertensive tablets, and they answered that question clearly. They were not designed to test whether selectively blunting the morning prothrombotic window prevents stroke. That is what makes the aspirin data interesting. In a randomised crossover trial, 290 patients taking low-dose aspirin for secondary prevention were allocated to intake on waking or at bedtime for two 3-month periods; among the 133 patients with valid platelet measurements, bedtime intake lowered morning platelet reactivity, measured with the VerifyNow Aspirin assay, by a mean of 22 aspirin reaction units, whereas 24 h ambulatory blood pressure in 263 patients did not change [60]. Whether that shift in a biomarker translates into fewer strokes is unknown, and settling it would take a large outcome trial (Prediction 5).

8. Proposals

8.1. The CHRONO-STROKE Minimum Dataset

Much of the confounding described in Section 5 could be reduced, though not removed, if studies recorded a small number of additional items. Table 4 sets out a ten-item minimum dataset, CHRONO-STROKE, intended for registries, cohort studies and the secondary analysis of acute stroke trials. It is an author-proposed framework. It has not been validated, piloted or endorsed by any consortium, and it is intended to supplement, not replace, the standard clinical variables collected in stroke research and the more comprehensive common data elements published by the Leducq CIRCA consortium, which define 48 data elements, 14 time segmentations and 7 validated scales for circadian stroke research [14]. Our dataset is deliberately short, so that it can be added to existing registries at low cost; the CIRCA elements should be preferred wherever a study can accommodate them. Items 1 and 2 (onset misclassification), 3 and 5 (out-of-hours care), 6 (clock time versus circadian phase) and 10 (definitional heterogeneity) correspond to four of the five confounders in Table 2; the fifth, selection, depends on study design, such as population-based denominators and screening logs, rather than on recorded variables.

Two aspects of the dataset require specification. First, the onset-certainty categories in item 1 are defined to be mutually exclusive: (a) witnessed onset, with the time of

symptom onset observed and recorded; (b) unwitnessed onset while awake, where the patient was awake but the onset was not observed, so that only the last-known-well time and the time of discovery are available; (c) wake-up stroke, where symptoms were first noticed on waking from sleep; and (d) unknown, where no last-known-well time can be established. Whenever they are available, the relevant times are recorded separately: for category (b), the last-known-well time and the time symptoms were discovered; for category (c), these two times together with the time of sleep onset and the time of awakening. The last-known-well time is not assumed to equal bedtime or sleep onset. A patient may have been seen or heard to be normal after going to bed, for example during a nocturnal awakening, and that later time is then the last-known-well time; conversely, sleep onset may follow the last observation of normal function by some time. A last-known-well time is recorded in categories (b) and (c) but defines neither; the category is determined by whether the patient was asleep or awake during the unobserved interval. Second, missing or uncertain timing is handled by rule rather than by imputation. The primary analysis of onset time does not impute onset: it is restricted to category (a), in which onset was observed. Patients in categories (b), (c) and (d) are analysed separately, with the last-known-well time as the lower bound of possible onset and the time symptoms were discovered (on awakening, for wake-up stroke) as the upper bound, where both exist. A sensitivity analysis that assigns onset to the midpoint of that interval, as EXTEND did for wake-up stroke [53], may be reported, but it is a distinct, labelled analysis that imputes onset time and does not replace the primary analysis. Analyses of treatment time can include all patients, because the treatment timestamp is recorded directly. They are not free of onset uncertainty, however: adjustment for the interval from onset to treatment, and the interpretation of any difference between treatment-time blocks, still depend on when the stroke began. Analyses that adjust for onset-to-treatment time should therefore use the timing anchors in item 2 and state how uncertain onset was handled.

Table 4. The CHRONO-STROKE minimum dataset for studies of time of day in acute stroke. The dataset is author-proposed and unvalidated. It is intended to supplement standard clinical variables and the Leducq CIRCA consensus data elements [14], not to replace them.

No.	Item	Specification
1	Onset-certainty category	One of four mutually exclusive categories: (a) witnessed onset; (b) unwitnessed onset while awake; (c) wake-up stroke (symptoms first noticed on waking from sleep); (d) unknown. See Section 8.1 for definitions
2	Timing anchors	Recorded separately, in local clock time, whenever available: witnessed onset time (category a); last-known-well time and time of symptom discovery (category b); last-known-well time, time of sleep onset, time of awakening and time of symptom discovery (category c). Last known well is not set equal to bedtime or sleep onset by default
3	Process times	Arrival, imaging, needle and groin puncture, each timestamped; for transferred patients, imaging time at each centre
4	Calendar context	Day of week; public holiday; daylight saving status
5	Staffing model	In-hours or out-of-hours; on-site or remote decision-maker
6	Usual sleep–wake timing	Habitual bedtime and waking time; shift work in the past year
7	Sleep-disordered breathing	Known obstructive sleep apnoea or screening result, if available (see Section 4.1)

8	Imaging tissue status	Core and penumbral volumes with interval from the relevant timing anchor to imaging; where paired imaging exists, both volumes and the scan interval
9	Timestamped outcomes	Early neurological deterioration; haemorrhage on 24 h imaging, classified as any HT and as sICH; 90-day mRS
10	Analysis plan and handling of missing timing	Time of day as a continuous variable (cosinor or spline), pre-specified. Primary onset-time analysis restricted to category (a), without imputation; categories (b)–(d) analysed separately using interval bounds; any midpoint assignment reported only as a labelled sensitivity analysis. Treatment-time analyses include all patients, with adjustment for onset-to-treatment time based on the recorded timing anchors and a statement of how uncertain onset was handled

HT, haemorrhagic transformation; mRS, modified Rankin Scale; sICH, symptomatic intracranial haemorrhage.

8.2. A Clock-Time-Stratified Design for Trials of Adjunctive Therapy

For clinical trials of neuroprotective or other adjunctive agents, the following changes would allow the treatment clock to be examined without placing trials beyond practical reach. Randomisation should be stratified by the local clock-time block in which randomisation takes place, which is known for every patient whatever the certainty of onset, for example four 6 h blocks, so that the arms are balanced across the day; this is stratification by clock time, not by circadian phase, which cannot be measured at the bedside. A treatment-by-time-block interaction should be pre-specified as a secondary analysis, in the expectation that it will be underpowered on its own but available for pooling across trials that use the same blocks. The time of treatment administration should be recorded and analysed separately from the time of onset, because the two can be separated by many hours and may carry different information. And the primary analysis by onset time should be restricted to patients with witnessed onset, without imputation of onset time, with unwitnessed and wake-up onsets analysed separately as described in Section 8.1. The same elements can be applied to secondary analyses of randomised reperfusion trials. Because patients in the control arm receive no reperfusion treatment, the time-of-day exposure in such analyses must be one that exists in both arms, such as the time of randomisation or, in patients with witnessed onset, the time of onset. Only in such trials, which include an untreated control group, can a treatment-by-time interaction show whether the benefit of reperfusion itself differs by time of day. Registry analyses of treated patients, such as the German Stroke Registry study [32], can describe how outcomes, and the association between recanalisation and outcome, vary with time, but they cannot answer that question. For preclinical confirmatory work the corresponding requirements are to report zeitgeber time and to test in both the active and the inactive phase, since that comparison is the one on which the original observation rests [9].

8.3. Five Testable Predictions

The model makes claims that could turn out to be wrong. Five of them are set out here in a form that existing datasets, or modest new studies, could test. In each case we state what a result would and would not establish, because none of these tests can on its own distinguish an endogenous circadian mechanism from the alternatives.

- Prediction 1 (tissue clock versus onset error). In cohorts restricted to witnessed onset with precisely recorded times, the association between night onset and larger admission core, or faster single-scan core growth, will be attenuated compared with analyses that include all onsets. We do not specify the degree of attenuation, because no data exist on which to base one. If the association persists in witnessed-onset

cohorts and in serial-imaging studies that do not depend on onset time [13], onset misclassification can be excluded as the explanation; that would support a tissue clock but would not establish that it is endogenous, since night-time physiology also includes sleep, posture and reduced blood pressure. If the association largely disappears, onset misclassification is the most economical explanation.

- Prediction 2 (treatment clock versus organisation of care). In centres that provide thrombectomy around the clock with comparable process times across the day, the association between morning treatment and better outcome will persist after adjustment for door-to-groin time and other process measures. Persistence would make a purely organisational explanation less likely but would not establish a biological one, because unmeasured differences in case mix across the day could remain. Disappearance after adjustment would favour an organisational explanation but would not exclude a biological effect that is correlated with, and therefore adjusted away with, process time.
- Prediction 3 (preclinical phase interaction). A multicentre preclinical trial testing a single candidate neuroprotectant in both the active and the inactive phase will reproduce a phase-by-treatment interaction of the kind reported by Esposito and colleagues [9]. Reproduction would substantially strengthen the circadian explanation of translational failure. Failure to reproduce it would weaken that explanation for the agent tested, but a null interaction in an underpowered study would not refute the broader hypothesis, and other agents might behave differently.
- Prediction 4 (thrombolysis and haemorrhage**).** In large thrombolysis registries, the lower rate of haemorrhagic transformation with evening treatment will remain detectable after adjustment for age, stroke severity, glucose, blood pressure and process times. If it does not, the signal in the smaller series is most likely chance or confounding. If it does, the result would still be an association between treatment time and bleeding, and a test of whether the effect of thrombolysis differs by time would require a design that compares treated with untreated patients across the day.
- Prediction 5 (aspirin timing). A randomised trial of bedtime versus morning aspirin in secondary prevention will confirm lower morning platelet reactivity [60] but, we predict, will not show a clinically important reduction in recurrent ischaemic stroke, because the behavioural component of the morning window is left untouched. The clinical effect of aspirin timing is at present unknown in either direction; a clear reduction in events would be strong support for treating the trigger clock pharmacologically, and the prediction is offered as a hypothesis to be tested rather than as a conclusion.

9. Where This Argument Could Be Wrong

The Three-Clock Model is a way of organising evidence, and it has limits. The three clocks may share more biology than the model implies; PAI-1, for instance, matters both to the morning prothrombotic window and, as the inhibitor of tissue plasminogen activator [26], to the response to thrombolysis. The separation is offered as a tool for asking cleaner questions, not as a claim that the underlying mechanisms are distinct.

The effects may also be too small to matter at the bedside. Time since onset and tissue status on imaging underpin reperfusion selection, as in [52,53], and nothing in this review suggests that circadian considerations should delay or alter such a decision today. A tissue-clock effect of the size reported so far, a difference of 6.4 mL in median admission core volume [33] or of about 3 mL/h in median growth during transfer [13], would be scientifically interesting and of uncertain clinical weight.

As a narrative review, this work carries the risk of selective citation, and the published time-of-day analyses may themselves be enriched for positive findings if null

analyses of onset time go unreported. The fact that two relevant publications were identified only during peer review (Section 2) shows that our search was not exhaustive. Much of the mechanistic evidence comes from animals and from small studies of healthy volunteers [9,20,21,27]; whether it holds in older patients with vascular comorbidities has not been tested in the studies reviewed here. Finally, almost every human study cited here measured clock time, so every statement about circadian phase in human stroke is an inference.

10. Conclusions and Future Directions

The morning excess of stroke onset is well documented, and plausible prothrombotic correlates have been identified. Whether the hour also governs how fast the brain is lost and how it responds to treatment is a younger and far less secure proposition. The human evidence is suggestive but inconsistent, and it is exposed to confounders that could produce the observed patterns without any circadian biology at all; the one serial-imaging study that avoids onset misclassification [13] and the one registry that found the recanalisation–outcome association to differ by time of treatment [32] are the most informative, and both need replication; neither shows that the benefit of a reperfusion treatment varies with the hour. The experimental evidence is better controlled but disagrees on direction, and it carries an uncomfortable message for research into adjunctive therapy.

Progress now depends less on new biology than on better measurement. Recording onset certainty, staffing context and usual sleep timing, analysing time of day as a continuous variable, and stratifying trials by clock-time block would allow the next generation of studies to determine which clock is responsible. If the predictions set out here fail, circadian biology will have earned a modest footnote in acute stroke care. If they hold, the time on the clock will join the time since onset as something a stroke physician needs to know.

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Abbreviations

The following abbreviations are used in this manuscript:

aOR	adjusted odds ratio
ARU	aspirin reaction units
BMAL1	brain and muscle ARNT-like 1
BP	blood pressure
CI	confidence interval
CLOCK	circadian locomotor output cycles kaput
CT	computed tomography
DNase-I	deoxyribonuclease I
DWI	diffusion-weighted imaging
ECASS	European Cooperative Acute Stroke Study
END	early neurological deterioration
EVT	endovascular thrombectomy
FAST-MAG	Field Administration of Stroke Therapy–Magnesium
FLAIR	fluid-attenuated inversion recovery
HR	hazard ratio
HT	haemorrhagic transformation
ICH	intracerebral haemorrhage
IVT	intravenous thrombolysis
LVO	large vessel occlusion
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NMDA	N-methyl-D-aspartate
OR	odds ratio
PAI-1	plasminogen activator inhibitor-1
RR	relative risk
sICH	symptomatic intracranial haemorrhage
SITS-ISTR	Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register
TOAST	Trial of Org 10172 in Acute Stroke Treatment

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