Vulnerable and Stabilized States After Cerebral Ischemic Events: Implications of Kinetic Modeling in the SOCRTIES, POINT, and THALES Trials

Author(s):
James R Brorson¹; Mihai Giurcanu²; Shyam Prabhakaran¹; S. Claiborne Johnston³

Corresponding Author:
James R Brorson, jbrorson@bsd.uchicago.edu

Affiliation Information for All Authors: 1. Department of Neurology, The University of Chicago; 2. Department of Public Health Sciences, The University of Chicago; 3. CMO and Co-Founder, Harbor Health

Equal Author Contribution:

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Contributions:
James R. Brorson: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Mihai Giurcanu: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data; Additional contributions (in addition to one or more of the above criteria)
Shyam Prabhakaran: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
S. Claiborne Johnston: Major role in the acquisition of data; Analysis or interpretation of data

Figure Count:
4

Table Count:
3

Search Terms:

Acknowledgment:
The authors are grateful to James E. Siegler, MD, for providing helpful comments regarding a late draft of this manuscript. The authors would like to thank the National Institutes of Neurological Disorders and Stroke for provision of the POINT trial dataset, and the sponsors of the SOCRATES and THALES trials for approval of access to these trial datasets. This manuscript is based on research using data from data contributor AstraZeneca that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

Study Funding:
This study was supported in part by a gift from the estate of Bendt Bladel.

Disclosure:
The authors report no relevant disclosures.

Preprint DOI:

Received Date:
2023-04-26

Accepted Date:
2023-08-15

Handling Editor Statement:
Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.
Abstract

Background and Objectives: Trials of acute secondary prevention following minor stroke or TIA, such as SOCRATES, POINT, and THALES, demonstrate a high initial rate of recurrence following ischemic events that drops quickly to a lower rate, suggesting a transient vulnerable clinical state, that may call for different treatments than the subsequent stabilized state. A kinetic model incorporating vulnerable and stabilized states provides estimates of the distinct kinetic rates reflecting the temporal features of underlying stroke mechanisms. We aimed to compare these kinetic rates between treatments and across trials, asking whether these features point to common pathophysiological processes underlying stroke recurrence, and inform the targeting and timing of enhanced antiplatelet therapy in recurrent stroke prevention.

Methods: Kaplan-Meier recurrence-free survival curves in the SOCRATES, POINT, and THALES trials were estimated for each treatment group and fitted by non-linear regression to the two-state kinetic model, producing estimates of kinetic parameters, with standard errors estimated using the nonparametric bootstrap with repetitive resampling.

Results: For each trial, the two-state kinetic model fit the survival curves better than did the null (single-state) kinetic model or the Weibull model (p < 0.05). Recurrence rates in the vulnerable state \(k_1\) were 100-fold higher than in the stabilized state \(k_2\). Transition rates from the vulnerable to stabilized state \(k_0\) were still more rapid. Kinetic parameters were consistent across the trials, without significant differences between the trials. Enhanced antiplatelet regimens produced significant reductions in \(k_1\)(aspirin alone: 0.030 ± 0.004 d\(^{-1}\); active treatment: 0.016 ± 0.003 d\(^{-1}\); p < 0.01), but did not affect \(k_0\) or \(k_2\), suggesting that active treatment only affected risk in the vulnerable state. Modeling based on these kinetic parameters suggests that most of the benefit of active treatment occurred within 3 days.
Discussion: Across multiple trials of acute secondary prevention following minor stroke or TIA, recurrence of stroke is well-described by a two-state kinetic model postulating vulnerable and stabilized states, with similar kinetic parameters across trials. Enhanced antiplatelet regimens only affected the recurrence rates in the vulnerable state, over a brief period. This analysis suggests two distinct states follow acute cerebral ischemic events, subject to differential impact of immediate or delayed therapies.
Introduction

After an initial minor stroke or transient ischemic attack (TIA), the risk of recurrence of stroke is the highest initially. Trials of various antiplatelet regimens for acute secondary prevention initiated within 12 to 24 hours following the index event, such as the Clopidogrel in High-Risk Patients with Non-disabling Cerebrovascular Events (CHANCE)\textsuperscript{1}, Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES)\textsuperscript{2}, Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial (POINT)\textsuperscript{3}, and Acute Stroke or Transient Ischaemic Attack Treated with TicAgrelor and ASA for PrEvention of Stroke and Death (THALES)\textsuperscript{4}, have been consistent in showing that the early recurrences within the first week exceed those in the following months. This suggests the possibility of a shift over time between different clinical states, subject to distinct pathophysiological risks and treatment opportunities, with distinct rates of recurrence. Such temporal features can be modeled by kinetic analysis, with assumptions of state populations related by stochastic transitions determined by non-negative time-independent kinetic rates. The data from these trials that recorded the timing of outcomes starting nearly immediately following stroke or TIA provide an opportunity to precisely examine the kinetics of clinical events after an initial ischemic event, and to discover whether tested treatment regimens have distinct effects on the different clinical states.

We developed a two-state kinetic model of stroke recurrence, postulating an initial vulnerable state having a higher rate of stroke recurrence, rapidly transitioning to a stabilized state with a lower rate of stroke recurrence. These assumptions predict a mathematical form of the event-free survival curve that demonstrated excellent fit to the clinical data of the POINT trial\textsuperscript{5}. We hypothesized that this two-state kinetic model would better fit the survival data for each of these
recent trials of acute secondary prevention than would a model assuming only a single clinical state following the initial minor stroke or TIA.

The kinetic rates quantified in this analysis may relate to underlying pathological processes that confer risk of stroke, such as active thrombosis or ulceration in vulnerable arterial plaques. We hypothesized that if the kinetics of stroke recurrence following a minor stroke or TIA relate to fundamental underlying pathological features, the kinetic parameters determined by fitting the two-state model to clinical data ought to be similar across the control groups of acute prevention trials with similar clinical populations. Furthermore, treatments targeting distinct underlying pathophysiological processes may differentially affect the early and late phases of stroke recurrence following an index event. Awareness of such temporal changes in pathophysiology and responsiveness to enhanced antiplatelet therapy regimens over aspirin monotherapy may lead to optimized secondary prevention strategies. We hypothesized that the enhanced antiplatelet regimens tested in these trials might selectively affect the stroke recurrence rates in the vulnerable state only. Testing these hypotheses, we aimed to understand the basis for the temporal features of stroke recurrence following an initial ischemic event, providing insights into the impact of antiplatelet therapy on the pathophysiological events underlying recurrence, and into the effective timing of such treatment.
Methods

Clinical datasets

The design, methods, execution, and results of the SOCRATES, POINT, and THALES trials have been reported previously\(^2,3,4\). These trials were selected as they shared a similar focus, on acute secondary prevention in patients with TIA or minor ischemic stroke, and enrolled subjects rapidly, within 12 hours (for POINT) or 24 hours (for SOCRATES and THALES) of the index (initial) stroke event. In each of these trials, subjects in the control group were treated with aspirin alone, while those in the active treatment groups received enhanced antiplatelet regimens (ticagrelor alone in SOCRATES, aspirin plus clopidogrel in POINT, and aspirin plus ticagrelor in THALES).

The POINT trial dataset was provided by the National Institute of Neurological Disease and Stroke. Access to the datasets of the SOCRATES and THALES trials was provided through a data use agreement with AstraZeneca, Inc. and made available on a secure server through Vivli, Inc.

The shared datasets included 4,881 subjects from the POINT trial, 12,018 subjects from the SOCRATES trial, and 9,565 subjects from the THALES trial. Data were not shared for subjects who had not given or had withdrawn consent (113 subjects in SOCRATES and 20 subjects in THALES) nor for subjects from countries not allowing data re-use based on the consent wording (1,182 subjects in SOCRATES and 1,489 subjects in THALES). Survival tables were prepared from the shared datafiles using SAS Studio version 9.4. From the shared datasets, 101 subjects from the SOCRATES trial and 44 subjects from the THALES trial were not assigned to a treatment group and were excluded from the analysis. Intention-to-treat populations, definitions
of outcome events, designation of event times, and data censoring methods were defined according to the trial protocols. The present analysis utilized treatment assignments by the intention-to-treat principle, and examined ischemic stroke recurrence as the outcome event.

**Kinetic modelling of clinical events**

Kinetic modeling can be applied in the analysis of event recurrence in clinical trials by considering subjects to be in interconnected states, with transitions between states occurring stochastically with non-negative time-invariant kinetic rates\(^6\). A simple null hypothesis for stroke recurrence prevention trials would assume that all subjects are in a single vulnerable state following minor stroke or TIA, characterized by a single rate constant \(k\) for stroke recurrence, hypothesizing no difference in incidence rate of recurrent stroke across time (Figure 1). In this case, the survival function at time \(t\), denoted as \(S_u(t)\), would follow a single exponential decay:

\[
S_u(t) = e^{-kt}
\]

(1)

The two-state kinetic model postulates that patients are either in a vulnerable state \(V\), with a risk for outcome events at a rate \(k_1\), or in a stabilized state \(S\), with a lower rate \(k_2\) for outcome events, and they can transition from state \(V\) to state \(S\) with a rate \(k_0\), with the fraction of subjects initially (at time \(t = 0\)) in state \(V\) designated as \(V_0\) (Figure 1). This model can be shown\(^5\) to yield a biexponential function for event-free survival over time given by:

\[
S_u(t) = e^{-k_2t} \cdot \left[1 - \frac{k_2 \cdot V_0}{(k_0 + k_1)} \cdot (1 - e^{-(k_0 + k_1)t})\right]
\]

(2)

In this model, the survival function \(S_u(t)\) is fully determined by three parameters: \(K = k_0 + k_1, k_1' = k_1 \times V_0,\) and \(k_2\). The parameters \(k_0\) and \(k_1\) can be independently estimated from survival data only with an assumption for the value of \(V_0\). Note that the two-state model (2) can be viewed as a
mixture of two exponential distributions, with the mixing proportions determined by the event rates for each state and the transition rate between states. Moreover, the null model (1) is a particular case of model 2 obtained when \( k_2 = k \) and \( k_1 = 0 \).

An alternative comparison can be made using a more flexible parametric model that is frequently utilized in survival analyses, the Weibull model, with 2 free parameters \( \lambda \) and \( k \):

\[
S_u(t) = e^{-(t/\lambda)^k}
\]

(3)

The Weibull model is not a kinetic model and does not provide direct clinical interpretation of the parameter values.

We assessed the appropriateness of the full model (2) versus the null model (1) or the Weibull model (3) in datasets of the POINT, SOCRATES, and THALES trials, and tested for significant differences in the kinetic parameters \( k_0, k_1, \) and \( k_2 \) across the trials. For simplicity, only results under the assumption of \( V_0 = 1 \) are reported (i.e., after index event, all patients are in the vulnerable state). Similar results were obtained using values of \( V_0 = 0.5 \) or \( V_0 = 0.1 \), or using \( K \), \( k_1' \), and \( k_2 \) as free parameters.

**Statistical methods**

Using the statistical software R, version 4.2.0, Kaplan-Meier survival curves were estimated from survival data for each of the 3 studies, and compared to predictions of the simple exponential (null) model versus the two-state kinetic model, derived as described previously\(^5\). Estimates of model kinetic parameters were obtained using non-linear regression fit of survival probabilities evaluated at the event times using the nlin function, and their standard errors were estimated using the nonparametric bootstrap (with resampling)\(^7,8\). A large number (B=9999) of
simulated bootstrap samples were generated (sampling, with replacement, the pairs of survival times and censoring indicators), and for each bootstrap sample the estimated Kaplan-Meier recurrence-free survival probabilities evaluated at the event times were then fit by non-linear regression to the null and the two-state models, thus generating the bootstrap versions of the kinetic parameters, with standard errors calculated as the standard deviations of the bootstrap versions of parameter estimates. Self-starting initial values for the exponential and biexponential model were developed by the authors, with no convergence issues.

Since the null (exponential) model is nested in the full (biexponential model), the comparative goodness-of-fit of the full model was assessed using the Wald test, with the covariance matrix estimated using the nonparametric bootstrap method as described above. To test whether the two state kinetic model (biexponential model) provides a significantly better fit than the Weibull model (not nested in the full model), the estimated $R^2$ measures of goodness of fit for each model were compared using a Wald test, with the variances for the differences in $R^2$ being estimated by the bootstrap. To test for differences in the kinetic parameters between the control and active treatment groups within trials, for comparisons of the effect of active treatment on their values across the trials, and for comparisons of the values of kinetic parameters between pairs of trials, the two-sided z-tests were used, with standard errors again estimated using the nonparametric bootstrap. The significance level was set at the nominal level of 0.05 for all comparisons.

**Data harmonization for cross-trial comparisons**

For comparisons of the derived kinetic rates across trials, we sought to minimize any potential variation stemming from differences in the trial design, such as study endpoints or active treatments. The first consideration was that, for POINT, time-to-event data were recorded as fractions of days, while in SOCRATES and THALES, time-to-event data were recorded as
whole days. An adjusted POINT dataset was created using time-to-event data rounded to the nearest whole day. Re-analysis using this adjusted dataset showed only small changes in event-free survival curves and in the estimates of kinetic parameters (Supplemental Data). Secondly, in POINT, subjects were randomized within 12 hours of index event, whereas in SOCRATES and THALES the time-to-randomization (TTR) could be up to 24 hours. Finally, in SOCRATES and THALES, for the recorded event times, there was by convention a day added to the difference between the date of the event and the date of randomization. Thus, the adjusted SOCRATES and THALES datasets were constructed separating subjects with TTR of 0-12 hours from those with TTR of 12-24 hours, and with subtraction of the added day from the recorded time-to-event. Re-analysis and estimation of kinetic parameters of the two-state model using these adjusted datasets showed that qualitatively similar survival curves and model estimates were derived (eTable 1, eFigure 1).

Model-based prediction

Model-based prediction of event-free survival, based on measured estimates of kinetic parameters, was conducted in Microsoft Excel 2016. For estimates of effects of altered timing of treatment, transitions in a kinetic parameter at times $T$ were modelled with event free survival for times $t < T$ calculated according to (1), and for times $T$ and greater, according to (1) with the altered kinetic parameters and with substitution of $V_0' = V(T) = V_0 \cdot e^{-(k_0 + k_1 + k_2)T}$ for $V_0$, and $t' = t - T$ for $t$. 
Standard Protocol Approvals, Registrations, and Patient Consents

The present study was submitted to the University of Chicago Institutional Review Board and was determined to be exempt from further review. It was not registered as a clinical trial, and a formal protocol was not prepared.

Data Availability Statement

All of the present results, including the R markdown files with reproducible analyses as well as additional details of the implementation of the methods using the R software, are available from the authors upon request.

Results

In each of the SOCRATES, POINT, and THALES trials, in both control and active treatment groups, ischemic stroke was the predominant outcome event, and the majority of events occurred within the first 7 days following trial enrollment (Table 1). Fewer events occurred over the remainder of follow-up in the trials, which extended for 90 days in POINT and SOCRATES and 30 days in THALES. This temporal course suggests a change over time of event risks that might be explained by a transition between underlying clinical states, consistent with our hypothesized two-state model.

In each treatment group and in each trial, the biexponential survivor function predicted by the two-state model fit the Kaplan-Meier stroke-free survival curves quite closely, far better than did the single-exponential survivor function predicted by the null (one-state) model and better than the Weibull model (Figure 2). Statistical comparisons showed significantly better fit to the
clinical data by the two-state model than by the one-state exponential model in both control and active treatment groups in each trial (p < 0.001 for all comparisons), and better fit than by the Weibull model (p < 0.05 for all comparisons, Table 2, eTable 2).

For comparisons of kinetic rates across trials, data harmonization was required, as described in Methods, to account for the differences in time-to-randomization in SOCRATES and THALES and for the differences in definitions of time-to-event across the trials. Generally these adjustments did not produce discernable differences in the fitted curves nor in the kinetic rates. Subtraction of an added day for time-to-event data in SOCRATES and THALES, allowing for greater resolution of the timing of very early events, produced somewhat greater values for the estimates of the transition rate parameter $k_0$ (eTable 1). Of note, in SOCRATES, there was a distinct separation in event-free survival between the control and active treatment groups only in the subset of subjects randomized within 12 hours of index event, with no suggestion of any treatment effect in those randomized at 12 to 24 hours. However, this distinction by time-to-randomization was not evident in the THALES data.

Comparisons of rates across the POINT, SOCRATES, and THALES trials, using these adjusted datasets and focusing on control groups, assigned to treatment with aspirin monotherapy in each trial, allowed for comparisons among subjects treated in similar fashion. Comparison of kinetic rates $k_0$ (the rate of transition from the vulnerable state to the stabilized state), $k_1$ (the rate of recurrence in the vulnerable state), and $k_2$ (the rate of recurrence in the stabilized state), generated under the assumption of $V_0 = 1$ (all subjects starting in the vulnerable state), showed similar values across trials, with small and non-significant differences (Figure 3). Estimated values for $k_0$ were between 0.5 d$^{-1}$ and 1 d$^{-1}$, corresponding to a predicted half-life of about 1 – 2 days for the fraction of patients remaining in the vulnerable state, while predicted values for $k_1$
were between $0.026 \text{ d}^{-1}$ and $0.037 \text{ d}^{-1}$, corresponding to half-lives of several weeks. The recurrence rates in the stabilized state, given by $k_2$, were found to be 100-fold lower, with values between $2.4 \times 10^{-4} \text{ d}^{-1}$ and $4.7 \times 10^{-4} \text{ d}^{-1}$, yielding half lives of 4 to 8 years (Table 3).

The kinetic parameters were compared between the control and active treatment groups in each trial, and for $k_0$ and $k_2$ no significant differences were found. In contrast, there were significant or near-significant decreases in the value of $k_1$ in active treatment versus control groups in each trial, and a significant decrease in the average $k_1$ across the trials (Table 3; control $k_1 = 0.030 \pm 0.004$ versus active treatment $k_1 = 0.016 \pm 0.003$, $p < 0.01$). This result points to an effect of the active treatments with enhanced antiplatelet therapy only on the rates of stroke recurrence in the patients in the vulnerable state, without a significant effect on the rates in patients in the stabilized state, nor on the rates of transition from vulnerable to stabilized states.

This model provides for prediction of the effects of delays in the initiation of treatment or of changes in the duration of treatments that may alter one kinetic parameter or another. For example, if enhanced antiplatelet therapy indeed only affects $k_1$, decreasing its value from about $0.03 \text{ d}^{-1}$ to $0.016 \text{ d}^{-1}$, with $k_0$ and $k_2$ estimated as $0.6 \text{ d}^{-1}$ and $0.0003 \text{ d}^{-1}$, as suggested by the present results, effects of the active antiplatelet therapy are quite transient. Using these estimated values and effect sizes, and under the assumption that all the patients start in the vulnerable state (i.e., $V_0 = 1$), immediate and continuous enhanced antiplatelet treatment improves fractional event-free survival at 90 days from 0.927 to 0.948. Delaying the initiation by 1, 2, or 3 days diminishes this to approximately 53%, 28%, and 15%, respectively, of the full treatment benefit (Figure 4). On the other hand, limiting the duration of antiplatelet treatment to 1, 3, or 7 days provides about 46%, 84%, and 98%, respectively, of the effects of treatment for the full 90 days.
Discussion

Recent trials of acute secondary prevention with anti-platelet agents, including SOCRATES, POINT, and THALES, by virtue of rapid randomization of subjects following index events, have illuminated the very high early rate of stroke recurrence following initial minor stroke or TIA. The clinical reasons for the enhanced early risk have not been fully explained but can be ascribed to features such as unstable intravascular thrombus, inflamed activated plaque, or critical arterial stenosis\(^9\). These cited trials share similarities in the study design and show striking similarities in qualitative temporal features of event-free survival curves, with rapid early rates of recurring events slowing to a much lower long-term rate. Our current study demonstrates that in each trial, these features support a model consisting of a short-lived vulnerable state rapidly transitioning to a stabilized state, with kinetic rates characterizing these transitions that are quantitatively similar across trials. The two-state kinetic model produces excellent fits of clinical survival data for each trial, superior to the fits produced by either the null kinetic (exponential) model with a single underlying state or the Weibull model. The Weibull model, while more flexible than the one-state model, does not allow for a physiological interpretation of the parameters, and does not provide as adequate a fit as does the two-state model. The rejection of the null model provides strong evidence against the assumption of one clinical state following index stroke or TIA that is uniform over time. An early transient vulnerable state during the first week following ischemic stroke has previously been inferred from other observations, such as by detection of recurrent ischemic lesions by diffusion weighted imaging\(^9\). Heightened awareness of this transient vulnerable state can inform future randomized clinical trial design in secondary stroke prevention, when planning exposure duration and timing of outcome assessments. Further, it may guide treatment optimization in the clinical setting.
The kinetic parameters were similar in the aspirin-treated control groups across trials after differences in trial designs were corrected suggesting that common underlying pathophysiological states were represented in the different trial populations. Although availability of data did not allow for the CHANCE\(^1\) and CHANCE 2\(^10\) trials to be analyzed in parallel, inspection of published survival curves in these trials suggests that they also follow a temporal course suggestive of two clinical states, with qualitatively similar kinetics.

As hypothesized, the kinetic rates of stroke recurrence for the vulnerable state ($k_1$) in the active treatment groups with enhanced antiplatelet regimens were significantly lower than the rates in the control groups, while the kinetic rates $k_0$ and $k_2$ were not found to be significantly different between the active treatment and control groups. This finding suggests that the intensity of antiplatelet therapy primarily affects the recurrence rate in the vulnerable state and does not affect the recurrence rates in the stabilized state nor the rates of transition from the vulnerable to stabilized states. There are likely to be other mechanisms that also affect these rates, including the type of stroke, age, and comorbidities, and this model may be refined to test the effects of these risk factors on the kinetic parameters. It is intriguing that in SOCRATES, although the overall effect of treatment on the primary trial endpoint did not achieve significance, the present analysis suggests that treatment assignment to the rapidly-acting antiplatelet agent ticagrelor had a potentially significant effect only in the subset of subjects randomized within 12 hours of the index stroke or TIA, supporting an effect of the active treatment when administered quickly, within 12 hours from the index event.

A clinical implication of the present analysis is that the mechanisms underlying short-term recurrence of stroke, reflected by $k_1$, are not necessarily the same as those for longer-term recurrence, reflected by $k_2$, and therapeutic strategies effectively targeting acute secondary
prevention in the days following minor stroke or TIA may not be the same as those that will be optimal in long-term secondary prevention. Already many centers, when applying the CHANCE or POINT trial results to practice, follow implications of results of previous time-course analyses\textsuperscript{11, 12}, and recommend aspirin and clopidogrel for only 1-3 weeks following minor stroke or TIA rather than for the 90 day period used in the POINT protocol. Even protective effects of aspirin monotherapy in comparison to control, in a large analysis of pooled data from multiple trials, predominately occurred in the initial 6 weeks following minor stroke or TIA\textsuperscript{13}. Different antithrombotic regimens may be more appropriate for long-term secondary stroke recurrence prevention. Trials comparing dual antiplatelet strategies against antiplatelet monotherapy for long-term secondary prevention have generally failed to demonstrate convincing benefit\textsuperscript{14, 15}, suggesting counterbalancing risks from the combination of clopidogrel and aspirin as compared to monotherapy\textsuperscript{16, 17}. Positive trial results favoring dual antiplatelet therapy over the long-term are largely restricted to support for addition of cilostazol to aspirin or clopidogrel\textsuperscript{18}. Further trials, incorporating an arm with antiplatelet monotherapy, are needed to identify the best antiplatelet strategies to reduce the long-term risks following a minor stroke event, reflected in the $k_2$ rate.

The hypothesized vulnerable state producing similar rates of early stroke recurrence across trials may result in some cases from active inflammation or ulcerated plaques in supplying vessels, perhaps with superimposed platelet-rich thrombus, in patients with underlying large-artery atherosclerosis. There is suggestion that enhanced antiplatelet therapies in these trials have the greatest efficacy in this subgroup\textsuperscript{19}. The very short half-life of this vulnerable state implies a surprisingly rapid resolution of this vulnerability. Treatments aiming to further shorten the duration of the vulnerable state by suppression of plaque inflammation or promotion of
endothelial recovery would need to be delivered immediately and to act very rapidly in order to effectively reduce the duration of vulnerability.

A significant limitation of the present quantitative analysis is the inability to simultaneously determine $V_0$, $k_0$, and $k_1$ from the survival data alone. If some alternative means could provide an independent estimate of $V_0$ (the fraction of subjects initially in the vulnerable state), definitive estimates of $k_0$, $k_1$, and $k_2$ would be possible. Still, even without direct estimation of $V_0$, the model allows for unambiguous determination of the recurrence rate in the stabilized state $k_2$ and of the ratio of $k_1$ between the active and control groups, and shows that active treatment significantly decreases $k_1$. Another limitation is the shorter duration of clinical observation in the THALES trial, limiting the precision in the estimation of $k_2$ for THALES, and possibly indirectly affecting the estimations of the other rates.

In conclusion, kinetic analysis of acute secondary stroke prevention trials shows that after minor stroke or TIA, patients experience a vulnerable state that transitions rapidly to a more stabilized state, with distinct pathobiologies and treatment responses likely associated with these distinct states. More intensive antiplatelet therapy regimens primarily protect against recurrence of stroke in the vulnerable state and are quite transient in effect. In the stabilized state, there is no detectable benefit of enhanced anti-platelet therapy and risks of bleeding likely outweigh any potential benefit. The results support a practice of very rapid introduction of enhanced antiplatelet therapy following initial minor stroke or TIA, and also support limiting its duration to the short term. Other treatment strategies may be needed to alter risks of recurrence over the long-term, in the stabilized state. Awareness of the kinetic features of this temporal shift may inform design of future randomized clinical trials when determining the duration of interventions and the timing of outcome assessments.
Author contributions:

J.B. conceived the kinetic model and the study concept, obtained access to and tabulated the data, drafted and revised the manuscript, and prepared the figures. M.G. devised and implemented the statistical approaches, conducted data analysis using the statistical software R, and revised the manuscript. S.P. advised on design of the study and provided editorial suggestions. S.C.J. assisted with obtaining access to the trial datasets and advised on interpretation of results.

WNL-2023-001687_efig1 -- http://links.lww.com/WNL/D183
WNL-2023-001687_etab1 -- http://links.lww.com/WNL/D184
WNL-2023-001687_etab2 -- http://links.lww.com/WNL/D185
References


Table 1. Characteristics of the SOCRATES, POINT, and THALES trial datasets

Sample sizes for shared subject data, entry time window, trial duration, and outcome events stratified by treatment are shown. Primary outcomes included ischemic strokes (IS) in each trial, hemorrhagic stroke (HS) in SOCRATES and THALES, and myocardial infarction (MI) in SOCRATES and POINT. Early (less than 7 days) and total outcomes are shown.

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Entry Time window</th>
<th>Trial duration</th>
<th>Primary outcome</th>
<th>Treatment groups</th>
<th>N</th>
<th>Primary outcome Events - total</th>
<th>Primary outcome Events – 7 days</th>
<th>IS outcome Events - total</th>
<th>IS outcome events - 7 days</th>
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</thead>
<tbody>
<tr>
<td>SOCRATES</td>
<td>11917</td>
<td>24 hours</td>
<td>90 days</td>
<td>Stroke (IS or HS), MI, or death</td>
<td>Control: aspirin 100 mg daily</td>
<td>5960</td>
<td>408</td>
<td>246</td>
<td>360</td>
<td>239</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Active: ticagrelor 90 mg bid</td>
<td>5957</td>
<td>376</td>
<td>215</td>
<td>325</td>
<td>198</td>
</tr>
<tr>
<td>POINT</td>
<td>4881</td>
<td>12 hours</td>
<td>90 days</td>
<td>IS, MI, or vascular death</td>
<td>Control: aspirin 81 mg daily</td>
<td>2449</td>
<td>160</td>
<td>111</td>
<td>155</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Active: aspirin 81 mg plus clopidogrel 75 mg daily</td>
<td>2432</td>
<td>121</td>
<td>70</td>
<td>112</td>
<td>67</td>
</tr>
<tr>
<td>THALES</td>
<td>9521</td>
<td>24 hours</td>
<td>30 days</td>
<td>Stroke (IS or HS)</td>
<td>Control: aspirin 75 to 100 mg daily</td>
<td>4749</td>
<td>258</td>
<td>197</td>
<td>243</td>
<td>194</td>
</tr>
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<td></td>
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<td></td>
<td>Active: aspirin plus ticagrelor 90 mg bid</td>
<td>4772</td>
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</tbody>
</table>
Table 2. Kinetic parameter estimates of the null model \( (k_{\text{Null}}) \) and of the two-state kinetic model \( (k_0, k_1, \text{and } k_2) \), including nonparametric bootstrap estimates of their standard errors \( \text{(estimate} \pm \text{SE)} \) for SOCRATES, POINT, and THALES, with p-values for the full (two-state) model compared to the null (one-state) kinetic model and to the Weibull model.

<table>
<thead>
<tr>
<th>Model:</th>
<th>One-state kinetic model</th>
<th>Two-state kinetic model</th>
<th>Two-state model vs. one-state model</th>
<th>Two-state model vs. Weibull model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( k_{\text{Null}} ) ( (\text{d}^{-1}) )</td>
<td>( k_0 ) ( (\text{d}^{-1}) )</td>
<td>( k_1 ) ( (\text{d}^{-1}) )</td>
<td>( k_2 ) ( (\text{d}^{-1}) )</td>
</tr>
<tr>
<td>SOCRATES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control ((n=5960))</td>
<td>9.6 ( \cdot 10^{-4} )</td>
<td>0.28 ( \pm ) 0.02</td>
<td>0.013 ( \pm ) 0.001</td>
<td>2.0 ( \cdot 10^{-4} ) ( \pm ) 0.2 ( \cdot 10^{-4} )</td>
</tr>
<tr>
<td>Active ((n=5957))</td>
<td>8.8 ( \cdot 10^{-4} )</td>
<td>0.26 ( \pm ) 0.02</td>
<td>0.010 ( \pm ) 0.001</td>
<td>2.1 ( \cdot 10^{-4} ) ( \pm ) 0.2 ( \cdot 10^{-4} )</td>
</tr>
<tr>
<td>POINT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control ((n=2449))</td>
<td>1.3 ( \cdot 10^{-3} )</td>
<td>0.62 ( \pm ) 0.10</td>
<td>0.030 ( \pm ) 0.005</td>
<td>2.9 ( \cdot 10^{-3} ) ( \pm ) 0.5 ( \cdot 10^{-3} )</td>
</tr>
<tr>
<td>Active ((n=2432))</td>
<td>7.7 ( \cdot 10^{-4} )</td>
<td>0.48 ( \pm ) 0.10</td>
<td>0.015 ( \pm ) 0.003</td>
<td>2.1 ( \cdot 10^{-4} ) ( \pm ) 0.4 ( \cdot 10^{-4} )</td>
</tr>
<tr>
<td>THALES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control ((n=4749))</td>
<td>2.2 ( \cdot 10^{-3} )</td>
<td>0.31 ( \pm ) 0.02</td>
<td>0.014 ( \pm ) 0.001</td>
<td>2.7 ( \cdot 10^{-3} ) ( \pm ) 0.7 ( \cdot 10^{-4} )</td>
</tr>
<tr>
<td>Active ((n=4772))</td>
<td>2.0 ( \cdot 10^{-3} )</td>
<td>0.30 ( \pm ) 0.03</td>
<td>0.010 ( \pm ) 0.001</td>
<td>2.1 ( \cdot 10^{-3} ) ( \pm ) 0.7 ( \cdot 10^{-4} )</td>
</tr>
</tbody>
</table>
Table 3. Cross-trial statistical comparisons of kinetic rates for ischemic stroke outcomes, using adjusted datasets with event times rounded to the nearest day for the POINT trial, and including only subjects with time-to-randomization < 12 hours, and counting day of randomization as day 0 for event times for the SOCRATES and THALES trials

Estimates and bootstrap estimates of standard errors (SE) are shown for each trial.

<table>
<thead>
<tr>
<th></th>
<th>k₀ (d⁻¹)</th>
<th>k₁ (d⁻¹)</th>
<th>k₂ (d⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOCRATES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (5960)</td>
<td>0.50 ± 0.09</td>
<td>0.026 ± 0.005</td>
<td>2.5·10⁻⁴ ± 0.4·10⁻⁴</td>
</tr>
<tr>
<td>Active (5957)</td>
<td>0.36 ± 0.08</td>
<td>0.014 ± 0.003</td>
<td>2.4·10⁻⁴ ± 0.5·10⁻⁴</td>
</tr>
<tr>
<td>p = 0.22</td>
<td>p = 0.027</td>
<td>p = 0.93</td>
<td></td>
</tr>
<tr>
<td><strong>POINT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (2449)</td>
<td>0.53 ± 0.11</td>
<td>0.026 ± 0.006</td>
<td>2.4·10⁻⁴ ± 0.4·10⁻⁴</td>
</tr>
<tr>
<td>Active (2432)</td>
<td>0.48 ± 0.12</td>
<td>0.015 ± 0.004</td>
<td>2.0·10⁻⁴ ± 0.3·10⁻⁴</td>
</tr>
<tr>
<td>p = 0.78</td>
<td>p = 0.12</td>
<td>p = 0.37</td>
<td></td>
</tr>
<tr>
<td><strong>THALES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (4749)</td>
<td>0.98 ± 0.24</td>
<td>0.037 ± 0.010</td>
<td>4.7·10⁻⁴ ± 1.10·10⁻⁴</td>
</tr>
<tr>
<td>Active (4772)</td>
<td>0.78 ± 0.19</td>
<td>0.019 ± 0.006</td>
<td>4.3·10⁻⁴ ± 1.4·10⁻⁴</td>
</tr>
<tr>
<td>p = 0.37</td>
<td>p = 0.11</td>
<td>p = 0.81</td>
<td></td>
</tr>
<tr>
<td><strong>Mean values across trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.67 ± 0.09</td>
<td>0.030 ± 0.004</td>
<td>3.2·10⁻⁴ ± 0.4·10⁻⁴</td>
</tr>
<tr>
<td>Active</td>
<td>0.51 ± 0.08</td>
<td>0.016 ± 0.002</td>
<td>2.9·10⁻⁴ ± 0.5·10⁻⁴</td>
</tr>
<tr>
<td>p = 0.28</td>
<td>p = 0.004</td>
<td>p = 0.45</td>
<td></td>
</tr>
<tr>
<td><strong>Comparison between treatment groups across all trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POINT vs. SOCRATES</td>
<td>p = 0.84</td>
<td>p = 0.99</td>
<td>p = 0.94</td>
</tr>
<tr>
<td>POINT vs. THALES</td>
<td>p = 0.09</td>
<td>p = 0.34</td>
<td>p = 0.05</td>
</tr>
<tr>
<td>SOCRATES vs. THALES</td>
<td>p = 0.06</td>
<td>p = 0.31</td>
<td>p = 0.06</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1. Kinetic models of stroke recurrence

Stroke recurrence following initial stroke or TIA may be conceived as (A) a simple kinetic model with a single state and a single kinetic rate characterizing event occurrences (null model), or as (B) a two-state model, in which subjects are initially in a vulnerable state V, susceptible to stroke outcomes by a rapid process with rate $k_1$ but also can transition at rate $k_0$ to a stabilized state S, no longer vulnerable to the rapid rate of stroke outcomes. In both states, events can occur by a slower process with rate $k_2$. The Weibull model is not shown because it is not a kinetic model that can be represented by a kinetic diagram.
Figure 2. Fits of event-free survival data by different models.

Kaplan-Meier estimates of event-free survival functions for occurrence of ischemic stroke in control (red) and active treatment (green) groups in POINT, SOCRATES and THALES trials, with fitted survival functions provided by the null (one-state) model, the Weibull model, and the full (two-state) model.
Figure 3. Estimates of kinetic parameters across trials.

Comparisons of estimates (with bootstrap standard errors) of $k_0$, $k_1$, and $k_2$ (estimates ± SE), assuming $V_0 = 1$, in control and active treatment groups across the three trials. Rates are plotted on a logarithmic scale for comparison. *Across trials, $k_1$ was significantly less in active treatment groups than in control groups (p < 0.05).
Figure 4. Model-based predictions of effects of treatment timing.

Predicted effects of delayed start of enhanced antiplatelet therapy (A) or of limited duration of enhanced antiplatelet therapy (B), using estimates for kinetic parameters taken from the present results ($k_0 = 0.6 \text{ d}^{-1}$, $k_I = 0.03 \text{ d}^{-1}$ in control group and $0.016 \text{ d}^{-1}$ in active treatment group, and $k_2 = 0.0003 \text{ d}^{-1}$, with $V_0 = 1$).
Vulnerable and Stabilized States After Cerebral Ischemic Events: Implications of Kinetic Modeling in the SOCRATES, POINT, and THALES Trials

James R Brorson, Mihai Giurcanu, Shyam Prabhakaran, et al.

Neurology published online October 19, 2023
DOI 10.1212/WNL.0000000000207904

This information is current as of October 19, 2023