Journal of Stroke and Cerebrovascular Diseases 34 (2025) 108132

Contents lists available at ScienceDirect

Journal of Stroke and Cerebrovascular Diseases

journal homepage: www.elsevier.com/locate/jstroke

Perception and acquaintance of stroke specialists on non-inferiority trials: An international survey

Aristeidis H. Katsanos, MD [a,*], Vasileios-Arsenios Lioutas, MD [b], Laetitia Yperzeele, MD [c], Teresa Ullberg, MD [d], Linxin Li, MD [e], Emily R. Ramage, PhD [f], Ivan A. Koltsov, MD, PhD [g], Julia Shapranova, MSc [h], George Howard, DrPH [i], Philip M. Bath, FMedSci [j], Maria Khan, MD [k], On Behalf of the World Stroke Organization Future Leaders

[a] Division of Neurology, McMaster University/ Population Health Research Institute, Hamilton, ON, Canada
[b] Beth Israel Deaconess Medical Center – Harvard Medical School, Boston, MA, United States
[c] Neurovascular Center Antwerp and Stroke Unit, Department of Neurology, Antwerp University Hospital, Antwerp, Belgium
[d] Lund University; Institution of Clinical Sciences, Neurology, Lund, Sweden
[e] Wolfson Centre for Prevention of Stoke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom
[f] Western Health and the Florey Institute, Melbourne, Australia
[g] Pirogov Russian National Research Medical University (RNRMU), Moscow, Russia
[h] World Stroke Organisation, Geneva, Switzerland
[i] University of Alabama at Birmingham, Birmingham, AL, United States
[j] Stroke Trials Unit, Mental Health & Clinical Neuroscience, University of Nottingham, Nottingham, United Kingdom
[k] Rashid Hospital, Dubai, United Arab Emirates

ARTICLE INFO

Keywords:
Stroke
Survey
Non-inferiority
Margin
Minimal clinically important difference
Acute stroke treatment
Ischemic stroke
Intracerebral hemorrhage
Stroke prevention
Trial

ABSTRACT

Introduction: The adoption of non-inferiority trial designs for assessing new interventions in stroke treatment is on the rise. We designed a survey to assess stroke specialists' understanding and familiarity with non-inferiority trials and margins.

Methods: A brief web-based questionnaire was sent to the members of the World Stroke Organization (WSO). The median acceptable non-inferiority margins in different research settings provided by responders were summarized and reported according to the acquaintance of responders with non-inferiority trials.

Results: A total of 120 WSO members from 42 countries responded to the survey. Thirty-two percent (32 %) of respondents self-identified as being very familiar with non-inferiority trials, while 6 % identified as extremely familiar. When asked about the impact of non-inferiority trials on improving stroke patient care, 42 % rated it as high and 45 % as moderate. 83 % of responders reported that the findings of non-inferiority trials affect their clinical practice. Ease of administration, relative effect of the standard treatment, clinical implications of inappropriately introducing the new treatment, availability, price, ease of storage and shipping were all considered as factors that should influence the size of the non-inferiority margin. The magnitude and variability of acceptable non-inferiority margins were seen to decrease as the acquaintance of responders with non-inferiority trials increased.

Conclusion: Although responders acknowledge the importance of non-inferiority trials, most have limited acquaintance with this research design. Educational activities are needed to enhance literacy in non-inferiority trials and the interpretation of non-inferiority margins.

Introduction

Noninferiority trials are becoming increasingly common across multiple medical disciplines, but are often poorly reported and misinterpreted.[1] Study conduct and reporting in a significant proportion of non-inferiority trials has been inconsistent and discordant with relevant recommendations.[2] Even those published in high-impact journals commonly conclude non-inferiority of the tested intervention without

* Corresponding author.
E-mail address: ar.katsanos@gmail.com (A.H. Katsanos).

https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.108132
Received 1 August 2024; Received in revised form 7 October 2024; Accepted 9 November 2024
Available online 10 November 2024

acknowledging the limitations of non-inferiority designs that may impact the interpretation and applicability of findings.[3]

Contrary to a superiority hypothesis, the concept of non-inferiority is more complex and interpretation of results can be more challenging. Non-inferiority trials test whether a new intervention is not unacceptably worse than the standard treatment by more than a predefined margin.[4] Selection of this margin is one of the most challenging steps because of heterogeneity between physicians regarding the magnitude of treatment differences that would affect clinical practice and lack of data regarding what non-inferiority margins are considered acceptable in different healthcare settings.[5] Over the past decade, the adoption of non-inferiority trial designs for assessing new interventions in stroke treatment is on the rise. However, there has been a lack of comprehensive reporting in these clinical trials, as shown by systematic reviews.[6]

Therefore, we designed a survey to assess the perception and acquaintance of stroke specialists on non-inferiority trials and non-inferiority margins in stroke trials.

Methods

A web-based questionnaire, consisting of 19 brief questions, was developed by members of the World Stroke Organization (WSO) Future Leaders Program, an initiative of the WSO to develop the technical and research skills of the next generation of stroke professionals (https://www.world-stroke.org/world-stroke-future-leaders). The survey questions, written in English, were kept concise to enhance response rates. We utilized SurveyMonkey, an online platform for survey creation and distribution. Initially, we conducted a pilot test with members of the WSO Future Leaders Program and WSO Executive to assess the survey's functionality and comprehensiveness. In November 2023, the WSO administrative office disseminated the survey to all WSO members, followed by two reminders in December 2023. As participation was voluntary and anonymous, ethical approval was not necessary for this study.

We performed descriptive analyses of all multiple-choice questions with the use of counts and proportions of responses. The acceptable magnitude of the non-inferiority margins in different research settings provided by responders were summarized with median values and interquartile ranges (IQRs) and were reported according to the clinical experience of the responder (years in clinical practice) or acquaintance with non-inferiority trials. Responders' acquaintance with non-inferiority was evaluated with two self-assessment questions, asking them to grade their perceived familiarity with non-inferiority trials or non-inferiority margins, and a knowledge assessment question in which we asked participants to report how many non-inferiority trials performed in stroke patients they are able to name. Because self-assessment questions provide insights into how individuals view themselves in relation to the topic but may not always align perfectly with their actual knowledge or abilities,[7] we considered the knowledge assessment question of our survey to be more reflective of the respondent's knowledge and understanding on non-inferiority trials. We did not perform any statistical tests of significance as we had neither a pre-specified a hypothesis nor performed a power calculation during the design of the survey.

Data were analyzed using Stata 13.0 (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) and graphs were generated with Microsoft Excel 2013 (Microsoft Excel 2013 [Software], Redmond, WA: Microsoft Corporation).

Results

A total of 120 out of 3200 WSO members (3.7 %) responded to the survey. Responders were from 42 countries and 6 continents (Europe: 35 %, Asia: 25 %, North America: 18 %, South America: 10 %, Oceania: 9 %, Africa: 3 %). More than 80 % of responders were practicing in an academic hospital. Most responders (76 %) were neurologists with the rest being radiologists (5 %), internists (5 %), neurosurgeons (3 %), or other specialists (10 %). Forty-one percent (41 %) of responders reported that they had more than 20 years clinical experience at the time of the survey with 12 % reporting less than 5 years of clinical experience. From the responders, 42 % and 45 % perceived that non-inferiority trials have a high or moderate impact in advancing the clinical care of stroke patients respectively, with 83 % of the total responders agreeing that the findings of a non-inferiority trial can affect their clinical practice (Table 1).

In the first self-assessment question, 4 % of the responders reported that they are not at all familiar with non-inferiority trials, while 33 % and 6 % reported that they are very or extremely familiar with non-inferiority trials. In the second self-assessment question, 10 % of the responders disagree or strongly disagree when asked if they know what a non-inferiority margin is, while 54 % and 23 % of the responders declared agreement or strong agreement of familiarity of the design. In the knowledge assessment question, 10 % of the responders were not

Table 1
Overview of responses to the survey.

Questions – choices	Responses
1. Region of practice	
Africa	3 (3 %)
Asia	30 (25 %)
Europe	42 (35 %)
North America	22 (18 %)
South America	12 (10 %)
Oceania	11 (9 %)
2. Setting of practice	
Academic hospital	99 (82 %)
Non-academic hospital	18 (15 %)
Other	3 (3 %)
3. Primary specialty	
Neurology	92 (76 %)
Neurosurgery	3 (3 %)
Radiology	6 (5 %)
Internal Medicine	6 (5 %)
Geriatrics	1 (1 %)
Other	12 (10 %)
4. Years on active clinical practice	
Less than 5 years	14 (12 %)
5 to 10 years	24 (20 %)
11 to 20 years	33 (27 %)
More than 20 years	49 (41 %)
5. Impact of non-inferiority trials in advancing care of stroke patients	
High	51 (42 %)
Moderate	54 (45 %)
Low	14 (12 %)
None	1 (1 %)
6. The findings of a non-inferiority trial can affect my clinical practice	
Strongly agree	42 (35 %)
Agree	58 (48 %)
Neither agree nor disagree	16 (13 %)
Disagree	3 (3 %)
Strongly disagree	1 (1 %)
7.Familiarity with non-inferiority trials	
Extremely familiar	7 (6 %)
Very familiar	39 (33 %)
Somewhat familiar	52 (43 %)
Not so familiar	17 (14 %)
Not at all familiar	5(4 %)
8. I know what a non-inferiority margin is	
Strongly agree	24 (23 %)
Agree	55 (54 %)
Neither agree nor disagree	13 (13 %)
Disagree	9 (9 %)
Strongly disagree	1 (1 %)
9. How many non-inferiority trials in stroke patients can you name?	
None	12 (10 %)
1 to 2	19 (16 %)
3 to 5	54 (45 %)
6 to 10	25 (21 %)
More than 10	10 (8 %)

able to name any non-inferiority trials in stroke patients, while only 8 % of the responders were able to name more than 10 trials (Table 1). The responses to the knowledge assessment question stratified by the responses to the self-assessment questions on non-inferiority trials and non-inferiority margins is presented in Supplementary Figs. 1 and 2, respectively. Of those reporting that they are very or extremely familiar with non-inferiority trials, 26 % reported that they can name between 6 and 10 non-inferiority trials, while 19 % can name more than 10.

When responders were asked who should define the non-inferiority margin in a trial they ranked expert consortia first, followed by investigators, regulatory agencies, patient-caregiver groups, sponsors and hospital administration (Supplementary Fig. 3). Ninety percent of responders agreed or strongly agreed that the non-inferiority margin should be dependent on the type of intervention (Supplementary Fig. 4). The relative effect of the standard treatment, ease of administration, clinical implication of inappropriately introducing the new treatment, availability, price and ease of storage and shipping were ordered as factors that should influence the selection of the non-inferiority margin (Supplementary Fig. 5). When we stratified the ranking of the aforementioned factors by the participant's response to the knowledge assessment question, we found consistency in the ranking of administration ease, price, easy of storage and shipping. Variability was present in the ranking of availability of the new intervention and the relative effect of the standard treatment as factors to influence the selection of the non-inferiority margin, with more experienced respondents placing higher ranking on availability and less value on the relative effect of the standard treatment (Fig. 1).

The magnitude of acceptable non-inferiority margins considered acceptable by responders were highly variable. We present median values with corresponding IQRs of reported non-inferiority margins that were considered acceptable for hypothetical trial designs evaluating new medical interventions or devices in the setting of acute ischemic stroke (Supplementary Table 1), acute intracerebral hemorrhage (Supplementary Table 2), or secondary stroke prevention (Supplementary Table 3). Provided margins were stratified per clinical experience (years in clinical practice), self-assessed acquaintance (familiarity with non-inferiority trials, knowledge on non-inferiority margins) or knowledge assessment (non-inferiority trials you can name) of responders. We did not observe any specific pattern between acceptable non-inferiority margins and years of clinical experience. The acceptable non-inferiority margins for trials evaluating medical interventions or devices did not appear to differ. Acceptable non-inferiority margins appeared smaller and less variable as the knowledge of responders on non-inferiority increased (Figs. 2–4). Acceptable non-inferiority margins provided by responders with limited familiarity with non-inferiority trials were large and highly variable, making their interpretation challenging in the context of the hypothetical research settings that were provided (Supplementary Tables 1–3). The median acceptable non-

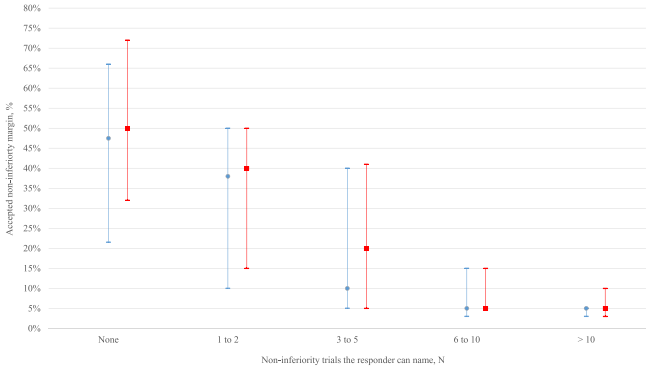

Fig. 2. Median values with corresponding interquartile ranges of accepted non-inferiority margins for new interventions in the treatment of acute ischemic stroke, stratified by the knowledge of responders on non-inferiority trials. Blue lines represent responses on medical treatments; Red lines represent responses on medical devices.

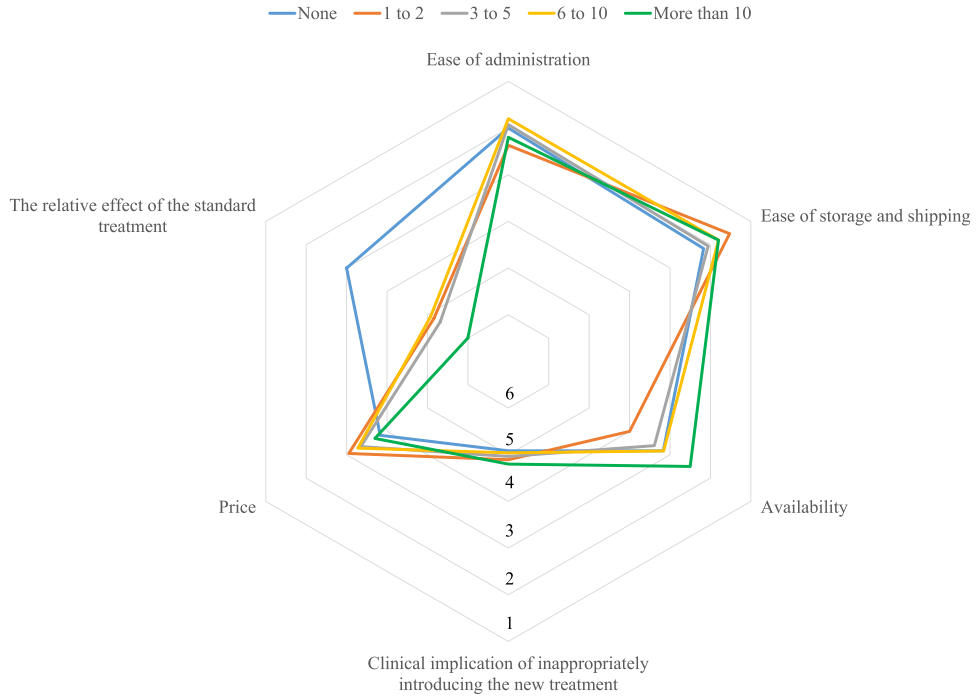

Fig. 1. Radar chart on the ranking of factors that can influence the non-inferiority margin in a trial testing a new therapeutic intervention stratified by the acquaintance of responders with non-inferiority trials. Each of the six ranks (1 to 6, with lower scores reflecting a greater perceived importance) is plotted on a separate axis delineated by the hexagon vertices. Hexagons mark 1-point increments, increasing from the 6th rank at the center of the chart to the 1st rank at the outermost hexagon. The acquaintance of responders with non-inferiority trials was assessed with the number of the non-inferiority trials they can name and is represented by plot color: blue, none; red, 1 to 2 trials; grey, 3 to 5 trials; yellow, 6 to 10 trials; green, more than 10 trials.

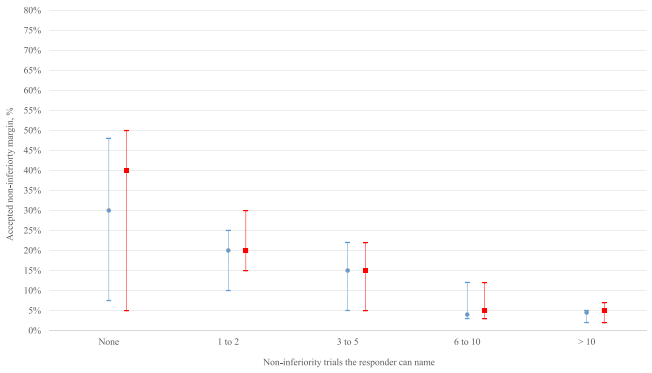

Fig. 3. Median values with corresponding interquartile ranges of accepted non-inferiority margins for new interventions in the treatment of acute intracerebral hemorrhage, stratified by the knowledge of responders on non-inferiority trials. Blue lines represent responses on medical treatments; Red lines represent responses on medical devices.

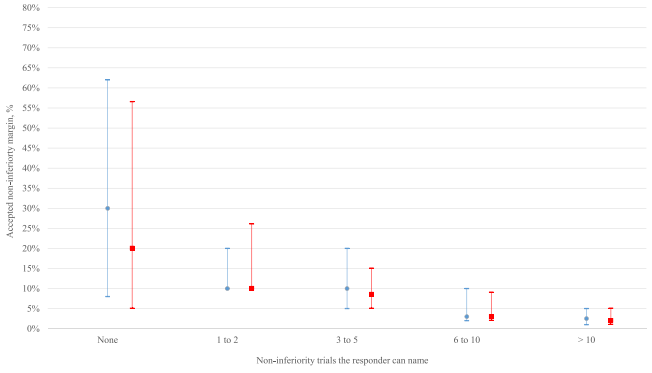

Fig. 4. Median values with corresponding interquartile ranges of accepted non-inferiority margins for new interventions in secondary stroke prevention, stratified by the knowledge of responders on non-inferiority trials. Blue lines represent responses on medical treatments; Red lines represent responses on medical devices.

inferiority margins reported by responders deemed knowledgeable (those who could name more than 10 non-inferiority trials in stroke) were 5 % for good functional recovery outcomes (modified Rankin Scale score of 0–2) in cases of acute ischemic stroke (Supplementary Table 1) or acute intracerebral hemorrhage (Supplementary Table 2), and 2 % for the annual risk of stroke recurrence in the context of secondary stroke prevention (Supplementary Table 3).

Discussion

More than 80 % of the 120 stroke specialists responding to our survey report that non-inferiority trials can have a major impact in their clinical practice and care of stroke patients. However, considerable variability exists in familiarity with non-inferiority trials and understanding of non-inferiority margins. Nine out of ten responders agree that the non-inferiority margin should be dependent on the type of intervention, but their perception on the importance of other factors that should influence non-inferiority margins varies. We also found high variability on margins that are considered acceptable by responders, which was inversely correlated with the degree of acquaintance with non-inferiority trials.

The number of published non-inferiority trials is rapidly increasing and almost a fifth are performed in cardiovascular medicine.[8] Due to the advances in healthcare delivery and standard of care over the past decade, the incremental benefits of newly developed treatments may only be marginal over existing treatments and thus further emphasis on the use of non-inferiority trial designs in cardiovascular medicine is expected.[9] Non-inferiority trials are particularly attractive where the new treatment offers advantages over standard treatment in certain important aspects. For example, easier administration, lower cost, or less side-effects could be sufficient reasons to justify testing the non-inferiority of a new thrombolytic agent in place of an existing one for the treatment of acute ischemic stroke patients, provided that the clinical efficacy is preserved within an acceptable margin.[10]

Although it is recommended by all guidelines that non-inferiority margins should be based on clinical grounds,[11] we found substantial variability in the perception of responders on the factors that should influence the selection of a non-inferiority margin and the magnitude of a non-inferiority margin that is considered acceptable for a given setting. Concerns over the selection of non-inferiority margins have been raised in previous publications, suggesting that in two third of non-inferiority trials selected margins that were too wide, resulting to inappropriate recommendations.[12] Non-inferiority margins that have been used in stroke thrombectomy trials have regularly exceeded the acceptable range as previously determined by stroke experts.[11] In a previous web-based, structured survey, academic neurologists/neurointerventionalists were provided a scenario for a hypothetical non-inferiority trial comparing intravenous thrombolysis plus endovascular thrombectomy (standard treatment) versus endovascular thrombectomy alone (experimental treatment). The median chosen acceptable non-inferiority margin in the rate of functional independence at 90 days (modified Ranking Scale score 0–2) was 3 % (IQR 1–5 %),[13] which is close to the 5 % margin provided by the responders to our survey. Our findings highlight the observation that these estimations are largely based on intuition and “common sense”, rather than an evidence-based, methodical approach. This reality underscores the need for thorough guidelines on non-inferiority margin selection and the creation of shared spaces with all stakeholders during the design of non-inferiority trials.[14]

The present study has significant limitations. First, our response rate was low, with limited representation from Africa (3 %) and South America (10 %), a problem seen in another survey recently distributed to WSO members.[14] Low engagement due to the lack of any direct or indirect benefit from survey completion, together with email overload and survey fatigue could explain the low response rate.[15] Monetary and non-monetary incentives, contacting participants before sending questionnaires and using personalized reminders are strategies that were found to increase response rates to postal and electronic questionnaires.[16] As in previous WSO surveys,[17,18] neurologists were over-represented and thus we did not test for differences between specialties. Moreover, we cannot assess the impact of non-inferiority margins used in recently published trials on survey responses,[19–22] and in particular for the responders having acquaintance with non-inferiority trials in stroke. We need to acknowledge that in our questions on acceptable non-inferiority margins for different research settings (Supplementary Tables 1–3) we did not specify the effect estimate to be reported (absolute vs. relative risk reduction). It seems from the numbers provided that responders having acquaintance with non-inferiority trials reported acceptable non-inferiority margins with the use of absolute risk differences. In addition, the research scenarios provided in our survey are overly simplified and we were unable to address for nuances that may be important for selecting a non-inferiority margin.

Conclusions

Although responders acknowledge the importance of non-inferiority trials, there is limited acquaintance with this research design. Educational activities, including knowledge dissemination, learning promotion, and engagement in interactive sessions, are needed to enhance the literacy of stroke specialists in non-inferiority trials and non-inferiority margins.

Funding

None.

CRediT authorship contribution statement

Aristeidis H. Katsanos: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Vasileios-Arsenios Lioutas:** Writing – review & editing, Methodology, Conceptualization. **Laetitia Yperzeele:** Writing – review & editing, Methodology. **Teresa Ullberg:** Writing – review & editing, Methodology. **Linxin Li:** Writing – review & editing, Methodology. **Emily R. Ramage:** Writing – review & editing, Methodology. **Ivan A. Koltsov:** Writing – review & editing, Methodology. **Julia Shapranova:** Writing – review & editing, Project administration. **George Howard:** Writing – review & editing, Supervision, Methodology. **Philip M. Bath:** Writing – review & editing, Methodology. **Maria Khan:** Writing – review & editing, Methodology.

Declaration of competing interest

None.

Acknowledgment

Dr. Katsanos is supported by a New Investigator Award from the Heart and Stroke Foundation Canada. PMB is Stroke Association Professor of Stroke Medicine and an emeritus NIHR Senior Investigator; he has consulted for CoMind, DiaMedica, Phagenesis and Roche on topics not related to this publication

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2024.108132.

References

1. Mauri L, D'Agostino Sr RB. Challenges in the design and interpretation of noninferiority trials. *N Engl J Med*. 2017;377:1357–1367.
2. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*. 2012;308:2594–2604.
3. Bikdeli B, Welsh JW, Akram Y, et al. Noninferiority designed cardiovascular trials in highest-impact journals. *Circulation*. 2019;140:379–389.
4. Leung JT, Barnes SL, Lo ST, Leung DY. Non-inferiority trials in cardiology: what clinicians need to know. *Heart*. 2020;106:99–104.
5. Pong S, Fowler RA, Mitsakakis N, et al. Noninferiority margin size and acceptance of trial results: contingent valuation survey of clinician preferences for noninferior mortality. *Med Decis Mak*. 2022;42:832–836.
6. Saver JL, Mistry E. Time to recognize three classes of non-inferiority trial margins. *J Neurointerv Surg*. 2023;15:2–4.
7. Dunning D, Heath C, Suls JM. Flawed self-assessment: implications for health, education, and the workplace. *Psychol Sci Public Interest*. 2004;5:69–106.
8. Murthy VL, Desai NR, Vora A, Bhatt DL. Increasing proportion of clinical trials using noninferiority end points. *Clin Cardiol*. 2012;35:522–523.
9. Leung JT, Barnes SL, Lo ST, Leung DY. Non-inferiority trials in cardiology: what clinicians need to know. *Heart*. 2020;106:99–104.
10. Tsivgoulis G, Katsanos AH, Sandset EC, et al. Thrombolysis for acute ischaemic stroke: current status and future perspectives. *Lancet Neurol*. 2023;22:418–429.
11. Rehal S, Morris TP, Fielding K, et al. Non-inferiority trials: are they inferior? A systematic review of reporting in major medical journals. *BMJ Open*. 2016;6, e012594.
12. Tsui M, Rehal S, Jairath V, Kahan BC. Most noninferiority trials were not designed to preserve active comparator treatment effects. *J Clin Epidemiol*. 2019 Jun;110:82–89.
13. Lin CJ, Saver JL. Noninferiority margins in trials of thrombectomy devices for acute ischemic stroke: is the bar being set too low? *Stroke*. 2019;50:3519–3526.
14. Kaesmacher J, Mujanovic A, Treurniet K, et al. Perceived acceptable uncertainty regarding comparability of endovascular treatment alone versus intravenous thrombolysis plus endovascular treatment. *J Neurointerv Surg*. 2023;15:227–232.
15. Cho YI, Johnson TP, Vangeest JB. Enhancing surveys of health care professionals: a meta-analysis of techniques to improve response. *Eval Health Prof*. 2013;36:382–407.
16. Edwards PJ, Roberts I, Clarke MJ, DiGuiseppi C, Woolf B, Perkins C. Methods to increase response to postal and electronic questionnaires. *Cochrane Database Syst Rev*. 2023;11, MR000008.
17. Attard N, Totton N, Gillies K, Goulao B. How do we know a treatment is good enough? A survey of non-inferiority trials. *Trials*. 2022;23:1021.
18. Rudd AG, Zhao J, Ford G, et al. Results of an international survey on the status of prehospital care. *Int J Stroke*. 2023;18:1084–1091.
19. Meretoja A, Acciarresi M, Akinyemi RO, et al. Stroke doctors: who are we? A World Stroke Organization survey. *Int J Stroke*. 2017;12:858–868.
20. Chen HS, Cui Y, Zhou ZH, et al. Dual antiplatelet therapy vs alteplase for patients with minor nondisabling acute ischemic stroke: the ARAMIS randomized clinical trial. *JAMA*. 2023;329:2135–2144.
21. Pan Y, Meng X, Yuan B, et al. Indobufen versus aspirin in patients with acute ischaemic stroke in China (INSURE): a randomised, double-blind, double-dummy, active control, non-inferiority trial. *Lancet Neurol*. 2023;22:485–493.
22. Menon BK, Buck BH, Singh N, et al. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. *Lancet*. 2022;400:161–169.