Stroke

TOPICAL REVIEW

Use of the Win Ratio for Analysis of Stroke Trials: Description, Illustration, and Planned Use in the Second European Carotid Surgery Trial (ECST-2)

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ABSTRACT: Randomized trials in stroke often focus on outcomes beyond a single clinical event. Trials of stroke prevention commonly use composite outcomes that include multiple components (eg, death, stroke, or myocardial infarction). A major limitation is that all events count equally but may differ markedly in terms of clinical severity. Trials in acute stroke often use ordinal outcomes or scale scores. Limitations include the requirement for statistical assumptions and the difficulty of handling the competing risk of death. We introduce the win ratio as an alternative method. It works by placing components of a composite into a hierarchy, whereby clinically more important outcomes take priority over less important ones. We illustrate how it works using data from 2 major stroke trials: the ICSS (International Carotid Stenting Study, a trial in stroke prevention) and the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). Potential benefits of the win ratio approach include the possibility to (1) emphasize the clinically most important outcomes, (2) combine components of different outcome types into a composite (eg, a mixture of time-to-event, continuous, and categorical), and (3) naturally handle the competing risk of death in analyses of quantitative outcomes. The win ratio will be used in the upcoming analysis of the ECST-2 (Second European Carotid Surgery Trial), which has a hierarchical primary outcome of (1) time to perioperative death, fatal stroke, or fatal myocardial infarction (most important); (2) time to nonfatal stroke; (3) time to nonfatal myocardial infarction (excluding silent infarcts); and (4) new silent cerebral infarct on brain imaging (least important). The win ratio provides a useful clinically relevant method for analyzing trial outcomes. It has some advantages over conventional methods, and we recommend its wider application in future stroke trials.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: endarterectomy, carotid ■ patient care ■ prognosis ■ quality of health care ■ stroke

Improvements in the treatment and quality of care have resulted in a better prognosis after stroke.[1] It has, therefore, become increasingly difficult to run clinical trials focusing on a single outcome event (eg, stroke or all-cause mortality) because the frequency of outcome events, in general, has decreased. They are also arguably less relevant because, as the frequency of outcome events decreases, other aspects of patient care, such as quality of life, may take on increased importance.

In trials of stroke prevention, it is common to use composite outcomes, which combine ≥2 related clinical events. For example, in trials of carotid endarterectomy, a common outcome is the time to procedural death or stroke at any time. A conventional analysis of this outcome uses the time to the first event. However, limitations of this approach include that (1) all events count equally, so that a nondisabling stroke counts equally to a procedural death (ie, both are simply counted as an event), whereas, in reality, they vary vastly in their clinical

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impact and (2) it only captures the first event per patient so that a fatal stroke occurring after a nondisabling stroke is ignored.

In trials of acute stroke, it is common to use ordinal outcomes, for example, functional impairment as measured with the modified Rankin Scale (mRS) or scale scores as in stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), disability as measured by Barthel index, or quality-of-life measures such as the EuroQOL group 5-dimension (EQ5D) score.[2] A challenge in the analysis of these outcomes is how best to handle the competing risk of death. For some scales (eg, mRS), this is done by including death as a level in the scale, but, for other outcomes such as stroke severity, it is often unclear how best to handle mortality. In addition, where ordinal scale scores (eg, mRS) accommodate death, they can only take into account whether death occurred, and the timing is ignored. This is a limitation when assessing the long-term impact of intervention.

In this article, we introduce an alternative methodology for analyzing data from stroke trials, known as the win ratio. Using the win ratio approach, component events are placed into a clinical hierarchy from most to least important. This facilitates the prioritization of clinically more important outcomes over less important outcomes (eg, death can be prioritized over nondisabling stroke). It also allows one to include outcomes of differing types; this can be particularly useful in the analysis of acute stroke trials because one can create a hierarchy consisting of death (either as a time-to-event or binary outcome) alongside ordinal or quantitative outcomes.

The win ratio approach was first proposed by Pocock et al[3] in an article in the European Heart Journal in 2012 and has subsequently been used in trials in cardiology,[4] but it has rarely been applied in stroke trials to date.[3] We propose that win ratio analyses can provide a more clinically relevant method of assessing outcomes in suitable stroke trials. We, therefore, describe the method in this article and illustrate how it works using data from a trial in acute stroke (MR CLEAN [Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands][5]) and a stroke prevention trial (the ICSS [International Carotid Stenting Study][6]). In addition, we propose using the win ratio as the primary analysis in the future analysis of the ECST-2 (Second European Carotid Surgery Trial[7]) and give our rationale for doing so. We finish by discussing the strengths and limitations of the win ratio.

DATA AVAILABILITY STATEMENT

MR CLEAN data are available upon reasonable request through the CONTRAST-CONSORIUM website (www.contrast-consortium.nl). For ICSS, deidentified patient-level data will be made available upon request to the chief investigator and the receipt of an appropriate research proposal.

HOW THE WIN RATIO WORKS

The win ratio works by comparing pairs of patients: one from the intervention arm and one from the control arm. Within each pair, one compares their outcomes to determine if we know which patient had a better outcome. For a single quantitative ordinal or binary outcome, determining which patient had the better outcome is straightforward: the patient with a better outcome is the one with either a higher or lower value, depending on the context. If the patient with the better outcome is in the intervention arm, we classify that patient pair as a win. If the control patient has a better outcome, it is a loss, and if the value is the same, it is a tie. However, the win ratio has mainly been used in the context of hierarchical outcomes. Figure 1 illustrates how the process of determining wins, losses, and ties works for a hierarchical outcome containing information on time to stroke. The first step is to specify the clinical priorities as a hierarchy of outcomes. We consider here a hierarchy of (1) fatal stroke (most severe), (2) disabling stroke, and (3) nondisabling stroke (least severe). One begins by comparing patients based on the highest priority outcome: fatal stroke. For example, in pair A, the intervention patient survives, and the control patient has a fatal stroke, so this is a win because the better outcome is in the intervention arm. When a win or loss has been decided, lower levels of the hierarchy are not considered. Therefore, the nondisabling stroke that occurred in the intervention patient is not considered. However, when patients are tied at one level of the hierarchy, a decision can be made at the next level, as illustrated in pair B. Both patients survive until the end of follow-up, and so we next consider what happens with regard to disabling stroke. The intervention patient had a disabling stroke and the control patient did not, so this is considered a loss. Pair C illustrates that the timing of an event can be taken into account. Both patients had a nondisabling stroke, but the intervention patient had a better outcome because the nondisabling stroke occurred later, and so this is a win. Pair D illustrates that we only compare patients based on what we know. The intervention patient had a disabling stroke, but the control patient was lost to follow-up and so was censored before it occurred. Therefore, we do not know for sure that the intervention patient had a stroke before the control patient, and this pair is considered a tie.

This process of comparing pairs of patients is usually done by comparing all possible pairs of patients so that if there are N_i intervention patients and N_c control patients, then the comparison is made for all $N_i \times N_c$ patients. To calculate the win ratio, one adds up all the wins and all the losses and calculates the ratio (ie, win ratio=total

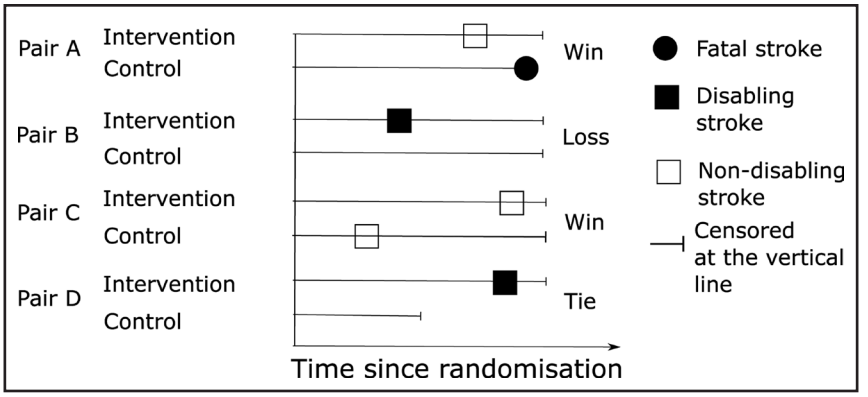

Figure 1. Schematic showing how the win ratio works with a hierarchical outcome of (1) time to fatal stroke, (2) time to disabling stroke, and (3) time to nondisabling stroke.

In pair A, the intervention patient survives, and the control patient has a fatal stroke, so this is a win because the better outcome is in the intervention arm. When a win or loss has been decided, lower levels of the hierarchy are not considered. Therefore, the nondisabling stroke that occurs in the intervention arm is not considered. However, when patients are tied at one level of the hierarchy, a decision can be made at the next level, as illustrated in pair B. Both patients survive until the end of follow-up, and so we next consider what happens with regard to disabling stroke. The intervention patient had a disabling stroke, and the control patient did not, so this is considered a loss. Pair C illustrates that the timing of events can be taken into account. Both patients had a nondisabling stroke, but the nondisabling stroke occurred later in the intervention arm, so this is a win. Pair D illustrates that we only compare patients based on what we know. The intervention patient had a disabling stroke, but the control patient was lost to follow-up and so was censored before it occurred. Therefore, we do not know for sure that the intervention patient had a stroke before the control patient, and this pair is considered a tie.

wins/total losses). Statistical software provides 95% CIs and *P* values.[8] The win ratio can be interpreted as the odds that for a randomly chosen pair of patients who are not tied, the better outcome occurs in the intervention patient. In contrast to other measures of treatment effect (such as the hazard ratio [HR] or odds ratio), a win ratio >1 (rather than <1) is indicative of treatment benefit. There is no requirement for 1:1 randomization so that the concept can also be applied in scenarios with unequal randomization, as has been done in the past.[9]

The win ratio gives a relative measure of the treatment effect. Trial guidelines suggest that both relative and absolute measures of treatment benefit (such as the number needed to treat or the difference in the percentage of patients with an event) should also be reported.[10] For hierarchical outcomes, the win difference (also known as net benefit)[11] can be reported, which is calculated as the percentage of comparisons that are wins minus the percentage of comparisons that are losses. For a randomly chosen pair of patients, the win difference is the percentage difference in the chance of a favorable outcome on intervention compared with control.

We used individual patient data from MR CLEAN and ICSS and to show how the win ratio works in trials of acute stroke and stroke prevention, respectively.

WIN RATIO IN MR CLEAN

In MR CLEAN, patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion were randomized to either endovascular thrombectomy plus usual care (n=233) or usual care alone (n=267). The primary outcome was the score on the mRS at 90 days.

The primary analysis used a proportional odds model and gave an adjusted common odds ratio of 1.67 (95% CI, 1.21–2.30; *P*<0.001) in favor of thrombectomy treatment.[5] The rate of functional independence (mRS, 0–2) was 32.6% in the thrombectomy arm versus 19.1% in the control arm (absolute difference, 13.5% [95% CI, 5.9%–21.2%]).

Win Ratio Analysis of mRS Score at 90 Days

To apply the win ratio to the primary outcome, we compare every patient in the thrombectomy arm to every patient in the usual care arm to form 233×267=62 211 pairs of patients (Figure 2A). Within each pair, if a better mRS occurs in the thrombectomy arm, it is a win; if it occurs in the usual care arm, it is a loss; or if the mRS is the same, it is a tie. In total, there are 30 346 wins and 20 418 losses, and the win ratio is calculated as 30 346/2041=1.49 (95% CI, 1.16–1.90; *P*=0.0017). The win difference can also be reported in MR CLEAN, this is 16.0% and can be interpreted as follows: for a randomly chosen pair of patients, the percentage chance of a favorable outcome is 16.0% higher on thrombectomy treatment compared with usual care. We note the similarity between the win ratio approach and statistical methods already used in stroke trials. The *P* value is calculated using the well-known Mann-Whitney *U* test. For the mRS, the measure of effect is the same as the Agresti generalized odds ratio, recently used in the SELECT-2 trial (Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke) of endovascular thrombectomy.[12] However, unlike the win ratio, the Agresti generalized odds

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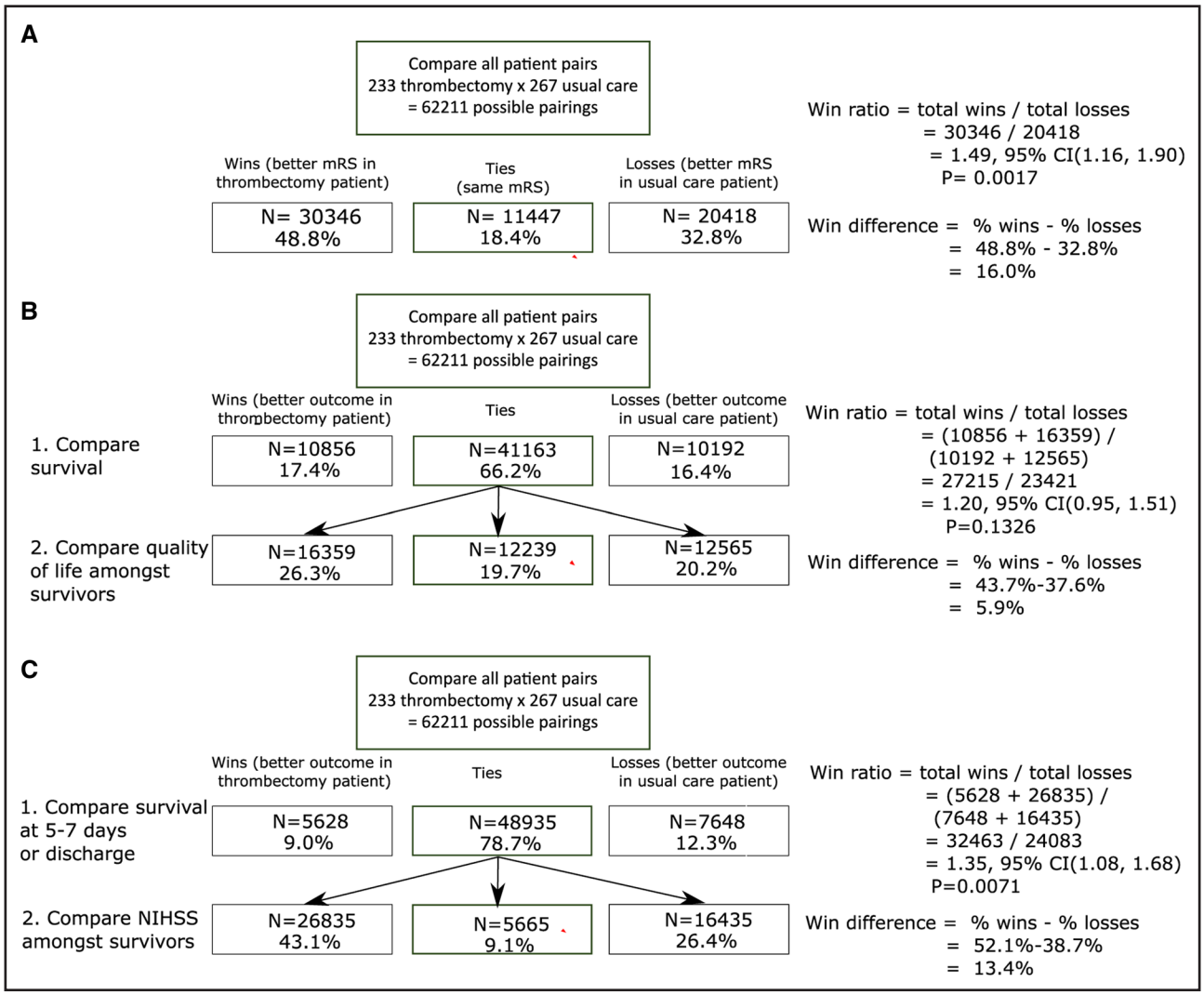

Figure 2. Analysis using the win ratio in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands).

Analyses shown are for (**A**) the primary outcome of modified Rankin Scale (mRS) at 90 days, (**B**) a hierarchical composite of all-cause mortality then EuroQOL group 5-dimension quality-of-life score at 90 days, and (**C**) a hierarchical composite of all-cause mortality and National Institutes of Health Stroke Scale (NIHSS) at discharge (or 1 week).

ratio is used for ordinal outcomes, and the concept does not immediately generalize to hierarchical outcomes. We also note that the *P* value is similar to when an unadjusted ordinal logistic regression model is used: common odds ratio, 1.66 (95% CI, 1.21–2.28; *P*=0.002).[12] One benefit of the win ratio compared with ordinal logistic regression is that it avoids the need to make the proportional odds assumption. However, overall, the potential benefits of using the win to analyze mRS are small: benefits are more apparent when a hierarchical outcome is used, as described in the following sections.

Analysis of Quality of Life and Stroke Severity

Quality of life as measured by EQ5D score at 90 days and stroke severity score as measured by NIHSS at 5 to 7 days or discharge were important secondary outcomes in MR CLEAN. However, the analysis of these outcomes is complicated by high mortality rates.

For an analysis of EQ5D at 90 days, a common approach to this problem is to set the EQ5D score to 0 among patients who die because this score represents a health state equivalent to death.[13] This yields a between-group difference in EQ5D of 0.07 (95% CI, 0.00–0.14; *P*=0.054) in favor of thrombectomy. However, the results from such an approach are hard to interpret: some patients report an EQ5D score <0, equivalent to a health state worse than death. Imputing a better score among patients who died seems potentially inappropriate because we would expect an effective treatment to prolong survival. An alternative approach is to simply exclude patients who died from the analysis. This yields an (unadjusted) between-group difference EQ5D of 0.08 (95% CI, 0.00–0.15; *P*=0.038) in favor of

thrombectomy treatment. However, this approach also seems unsatisfactory because it means excluding over 20% of patients who died before 90 days.

An analysis of the NIHSS score at 5 to 7 days has similar problems. An unadjusted analysis including only survivors yields a reduction in stroke severity with thrombectomy from 16 to 13 (difference, 3.2 [95% CI, 1.7–4.7]) but ignores death. If we wish to include patients who die in the analysis, there are difficulties. One could impute the worst possible value (NIHSS score, 38), but such values would be outliers among the distribution of NIHSS. Therefore, a chance between-group difference in mortality could drive spurious findings in relation to stroke severity (or mask real between-group differences). The win ratio provides a solution. One considers a hierarchical outcome where death is the most important, followed by either EQ5D or NIHSS score among survivors as the second level of the hierarchy. This process is illustrated in Figure 2B and 2C, respectively. For EQ5D, the process yields a win ratio of 1.20 (95% CI, 0.95–1.51; *P*=0.133). Overall, there is little evidence for a benefit with respect to the composite hierarchical outcome of death or EQ5D at 90 days although the data are consistent with anything from no effect to a moderate benefit in favor of thrombectomy treatment. We note that such an approach to analyzing quality-of-life outcomes has been used in recent trials both in stroke and in cardiology.[14,15] For the NIHSS score, the process yields a win ratio of 1.35 (95% CI, 1.08–1.68; *P*=0.007), giving strong evidence that patients tend to have a better outcome with regard to death or stroke severity with thrombectomy treatment.

We note that in MR CLEAN, an analysis using the win ratio approach does not gain statistical power, which can be seen by the win ratio resulting in similar or larger *P* values compared with conventional analyses. Rather it provides a more clinically relevant and interpretable summary of treatment benefits. The lack of gain in terms of statistical power is expected in MR CLEAN because mortality is given the highest priority and was similar between treatment arms. Therefore, any treatment signal with respect to EQ5D or NIHSS will be diluted by a lack of impact on mortality. In instances where a mortality benefit is anticipated, the win ratio may instead improve statistical power. We finish this section by noting the flexibility of the win ratio in that by comparing pairs of patients in a hierarchy, it was possible to combine outcomes of different types, that is, death by 90 days as a binary outcome with EQ5D/NIHSS scores that are continuous quantitative measures.

WIN RATIO IN ICSS

In ICSS, patients with symptomatic carotid stenosis were randomized to either stenting (n=855) or endarterectomy (n=858). Patients were followed up for a median duration of 4.2 years, and the primary outcome was fatal or disabling stroke in any territory; an important secondary outcome was any stroke (ie, also including nondisabling strokes). The main analysis of ICSS used time-to-first event analyses and Cox proportional hazards models.

In the interim analysis article in 2010,[16] the investigators reported that the incidence of stroke, death, or myocardial infarction by 120 days was 8.5% in the stenting group compared with 5.2% in the endarterectomy group (72 versus 44 events; HR, 1.69 [95% CI, 1.16–2.45]; *P*=0.006). The long-term outcome paper[6] reported that the number of fatal or disabling strokes (52 versus 49) and cumulative 5-year risk did not differ significantly between the stenting and endarterectomy groups (6·4% versus 6·5%; HR, 1.06 [95% CI, 0.72–1.57]; *P*=0·77).

The results applying a win ratio to stroke outcomes in ICSS are shown in Figure 3. Excluding 3 patients who withdrew immediately following randomization, there were 853 assigned to stenting and 857 patients assigned to endarterectomy. This yields a total of 853×857=731 021 patient pairs for comparison. We will now use the win ratio to analyze the stroke outcomes using a 3-level hierarchy of (1) fatal stroke, (2) disabling stroke, and (3) nondisabling stroke. Comparing all patient pairs with regard to time to fatal stroke, the outcome was better in the stenting (intervention) group in 1.0% (n=7359) of pairs and better in the endarterectomy (control) group in 2.2% (n=16 300) of pairs. However, in the majority of patient pairs, neither patient had a fatal stroke, and hence, 96.7% (n=707 362) of pairs are a tie based on time to fatal stroke and so are then compared based on the time to disabling stroke. Among the 707 362 comparisons based on disabling stroke, there were 3.8% wins and 2.9% losses, with a further 90.1% of pairs tied on both outcomes. If we were to stop at this point, thereby only considering fatal and disabling stroke (ie, the components of the primary outcome), we add up all the wins at the first 2 levels of the hierarchy and divide it by the losses to yield a win ratio of 0.95 (95% CI, 0.63–1.42; *P*=0.79). The result is similar to if one inverts the HR for time to fatal or disabling stroke from a Cox proportional hazards model (HR, 1.06 [95% CI, 0.72–1.57]; *P*=0.77). This is not unusual,[4] and the win ratio is known to be equal to the inverse of the HR for an analysis of a single time-to-event outcome when the proportional hazards assumption holds.[17]

We could also extend this hierarchy to also include nondisabling stroke. The advantage of a win ratio approach over a time-to-first event approach here is that because many nondisabling strokes occur early during follow-up (in the periprocedural period), a time-to-first event approach tends to place most emphasis on these events, ignoring subsequent, potentially clinically more important events. The win ratio avoids this, instead placing items in a deliberate hierarchy, whereby greater emphasis is always placed on the clinically

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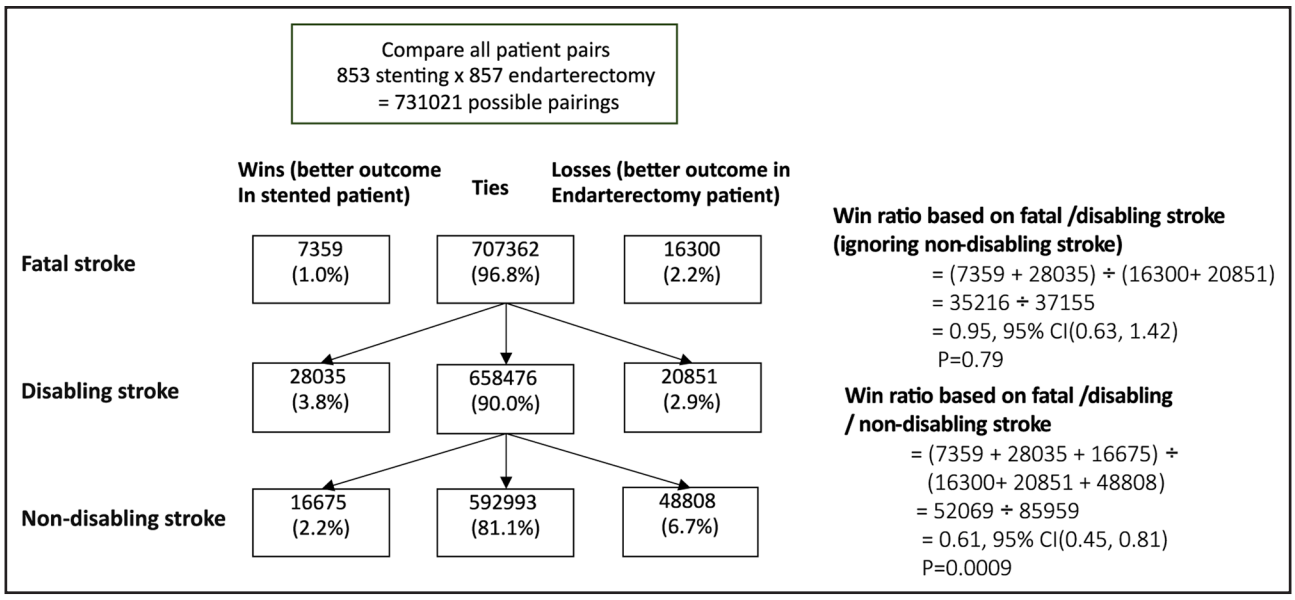

Figure 3. An analysis of stroke in ICSS (International Carotid Stenting Study) using a hierarchy of either (1) fatal stroke and (2) disabling stroke or (1) fatal stroke, (2) disabling stroke, and (3) nondisabling stroke.

more important events. Nevertheless, the results from a win ratio and time-to-first event approach are broadly similar. When comparing the remaining patients (ie, those not already untied on the basis of fatal or disabling stroke) with regard to nondisabling stroke, 2.3% (n=16 675) of paired comparisons are a win for stenting, 6.7% (48 808) are a loss, and 81.1% (n=592 993) are a tie. The win ratio comparing all 3 stroke outcomes in the hierarchy was then 0.61 (95% CI, 0.45–0.81; *P*=0.0009), indicating that outcomes tended to be better in the control (endarterectomy group). The HR from Cox proportional hazards models was 1.71 (95% CI, 1.28–2.30; *P*=0.0003), indicating higher rates of stroke in the intervention (stenting) group.

PLANNED USE OF THE WIN RATIO IN ECST-2

The ECST-2 trial randomized 429 patients with carotid stenosis ≥50% with a low to intermediate risk of stroke to either optimal medical therapy alone (n=215) or carotid revascularization plus optimal medical therapy (n=214).[7,18] Both symptomatic and asymptomatic patients were included. The sample size of 429 patients was not designed to provide an accurate comparison of treatment groups based on clinical events (procedural death, stroke, or myocardial infarction) alone. To supplement evidence based on clinical events, we also performed brain imaging scans at both baseline and 2 years post-randomization to identify new silent brain infarcts and included these as part of the primary outcome. These were expected to occur at roughly twice the rate of clinically manifest stroke.

Given our choice of the primary outcome, we felt that an analysis using the win ratio approach would be more appropriate than an analysis using conventional methods (eg, Cox models with associated HR and *P* value) for several reasons. First, the range in the severity of the outcomes is huge (from fatal to silent), and therefore, a greater emphasis should be placed on the more severe outcomes, as occurs as a feature of using the win ratio. Second, we anticipate an early surplus of events in the optimal medical therapy plus revascularization arm related to the procedure-related hazards of revascularization, which may be offset by a protective effect on stroke events later in follow-up. Therefore, the proportional hazards assumption from the Cox model is unlikely to hold, complicating the interpretation of an HR. No such assumption is required when using the win ratio. Third, the timing of clinical events is known, but the timing of silent brain infarcts is not, so how best to combine these outcomes in a time-to-event analysis is unclear.

In our analysis of ECST-2, we will use the following hierarchy of outcomes: (1) time to perioperative death, fatal stroke, or fatal myocardial infarction; (2) time to nonfatal stroke; (3) time to nonfatal myocardial infarction (excluding silent infarcts); and (4) new silent cerebral infarct on magnetic resonance imaging. The initial analysis will focus on clinical events occurring up until 2 years. A subsequent analysis will include additional follow-up data up until 5 years post-randomization. We will report the win ratio as a measure of relative treatment effect and the win difference as a measure of absolute treatment benefit. In addition to presenting results using the win ratio, we will also conduct a range of conventional statistical analyses. For example, for clinical events, we will present cumulative incidence curves and Kaplan-Meier

estimates of the proportion with the event at 2 years. For brain imaging scans, we will provide the proportion of patients with and without new silent infarcts.

The full statistical analysis plan is provided in the Appendix in the Supplemental Material.

DISCUSSION

This article illustrates the win ratio method and how it could be applied to future trials in stroke. We demonstrated potential additional value in reporting end points in 2 large previous stroke trials, MR CLEAN and ICSS, and proposed how the win ratio approach will be used in the upcoming analysis of ECST-2. We summarize our findings in the Graphic Abstract. In most circumstances, an analysis using the win ratio gave results that were similar to analyses using conventional statistical methods. However, we illustrate how the flexibility of the method can be used to prioritize clinically more important outcomes and, thereby, provide a more clinically relevant statistical analysis. As the quality of care for patients with stroke continues to improve, running trials with the conventional outcomes used in major trials (eg, stroke or death) may be increasingly difficult. Therefore, using alternative methods that capture additional measures indicative of treatment benefit is helpful. This concept is already well-recognized by neurologists, and outcomes capturing functional status or cognitive status (eg, mRS and other scale scores) are commonplace. The win ratio approach could be used to extend these concepts by allowing even greater flexibility. In ECST-2, we plan to use this flexibility to include data on both time to clinical events and data on the presence of silent infarcts on imaging at a fixed time point. The win ratio could also be used to capture more detailed information on clinical events that may be indicative of treatment benefits. For example, rather than relying solely on whether or not an event has occurred, information could be captured on the number of events (ie, allowing the inclusion of recurrent strokes) or on the severity of events. We also illustrated how the use of the win ratio is a convenient way to handle the competing risk of death in the analysis of quantitative outcomes.

It is worth considering the use of the win ratio in other medical fields to inform where it can be helpful. The main uses of the win ratio in major trials to date have been in cardiology,[4] particularly in heart failure, although there are examples in other disease areas (eg, COVID-19[19]). A major reason to use the win ratio appears to be to enable the use of hierarchical outcomes that include both clinical events (typically cardiovascular death or heart failure) and quantitative outcomes (such as data on quality of life or biomarkers).[20,21] Within the context of cardiology, the win ratio appears to have been embraced by regulatory agencies including the US Food and Drug Administration, which has approved the use of new pharmaceuticals, extended their use, and approved medical devices on the basis of studies using the win ratio for their primary analysis.[9,20,21]

We note some limitations of the win ratio approach. Because the method is new, there is a lack of familiarity. This may improve over time if the method is used more often. The close relationship between the win ratio and other measures of treatment benefit (eg, it is the inverse of an odds ratio for a binary outcome) should help in providing intuition for its interpretation. Nevertheless, the interpretation of the win ratio is more complex than for some conventional measures of treatment benefit. The win ratio is often applied to composite outcomes, and the same limitations of conventional analyses of composite outcomes apply and should be considered. For example, one should assess the direction and size of treatment benefit for each component of the composite as a means of assessing which components are driving the overall result. As for other composite outcomes, it is possible to have a signal for treatment benefit (win ratio >1) that is driven by a benefit on less important components, despite the intervention having no effect (or a harmful effect) on higher priority components. However, we note that because outcomes are prioritized, the win ratio is less prone to this issue than for an equivalent conventional composite outcome. The ordering of components within the hierarchical outcome is also an important consideration when using the win ratio. It requires clinical judgment and may depend on the specific trial and the granularity of data available. A general principle should be that a majority of patients and physicians would agree with the rankings for the typical case. The ranking is unlikely to be perfect in every case, for example, death is usually ranked as more important than nonfatal stroke, but some patients might consider severely disabling strokes to be worse than death. However, considering hierarchical outcomes is likely to be more representative of preferences than counting all events equally as is done in a conventional analysis.

An additional limitation is that although adjustment for baseline covariates is theoretically possible with the win ratio, it is not yet implemented in existing statistical software.[8,22] Adjustment for important prognostic factors (ie, those that are predictive of outcomes) is known to improve statistical power[23] or equivalently reduce the number of patients required in a trial. This may make the win ratio a (temporarily) less attractive option in scenarios where there are strong predictors of the primary outcome, for example, the volume of intracranial hemorrhage, or NIHSS at baseline for stroke trials. It also may make the win ratio less attractive for smaller trials, which may be more prone to baseline imbalances in important prognostic factors. In this context, randomization techniques that minimize these differences such as stratification or minimization could be helpful. Sample size calculations for the win ratio are more complex than

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for many conventional outcome types and have typically been performed using simulation studies, whereby one mimics the expected trial data (and its variability) under the alternative hypothesis.[24] However, more recently statistical software and Web applications have become available where one can input the expected distribution of each component of the hierarchical outcome under intervention and control and immediately generate the approximate sample size for a given statistical power.[25,26] Intuitively, a win ratio approach should enhance statistical power compared with using a conventional composite outcome when an intervention most strongly influences higher priority components. It should reduce statistical power if the intervention mainly influences lower priority components, which are downplayed by the win ratio. For an analysis of an ordinal variable, statistical power is expected to be similar to analyses using proportional odds.[27]

From a statistical perspective, we present the win ratio within a frequentist paradigm. However, the concepts extend naturally to trials using a Bayesian approach, and the win ratio has been used in this setting.[21] The win ratio has also been used as part of an adaptive design,[21] whereby the sample size was reestimated based on an unblinded review of interim trial data. However, such an approach could be complex in trials with long-term outcomes.[28]

In conclusion, the win ratio approach is a flexible method for analyzing composite outcomes and, in suitable studies, provides a more clinically relevant analysis than traditional methods used in stroke trials. We will use the win ratio as the primary analysis in ECST-2 and recommend its wider application in future stroke trials.

ARTICLE INFORMATION

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Supplemental Material

Statistical Analysis Plan for ECST-2 Trial

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