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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Short title: The win ratio for the analysis of stroke trials

Word count: 5587

Abstract

Background: Randomized trials in stroke often focus on outcomes beyond a single clinical event. Trials of stroke prevention often use composite outcomes which include multiple components (e.g. 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.

Methods: We introduce the win ratio as an alternative to conventional methods. 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 two major stroke trials: the International Carotid Stenting Study (ICSS, a trial in stroke prevention) and the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN).

Results: Potential benefits of the win ratio approach include: i) ability to emphasize clinically more important outcome (rather than just the first); ii) ability to combine components of different outcome types (e.g. a mixture of time-to-event, continuous, categorical), iii) ability to naturally and conveniently handle the competing risk of death in analyses of quantitative outcomes. The win ratio will be used in the upcoming analysis of the second European Carotid Surgery Trial (ECST-2) which has a hierarchical primary outcome of: 1) time to peri-operative death, fatal stroke or fatal MI (most important); 2) time to non-fatal stroke; 3) time to non-fatal myocardial infarction (excluding silent infarcts); 4) new silent cerebral infarct on brain imaging (least important).

Conclusions: We believe the win ratio provides a useful clinically-relevant method for analyzing trial outcomes. It has some advantages over conventional methods and recommend its wider application in future stroke trials.

Introduction

Improvements in the treatment and quality of care has resulted in a better prognosis after stroke[1]. It has therefore become increasingly difficult to run clinical trials focusing on a single outcome event (e.g. stroke, or all-cause mortality) because the frequency of outcome events in general has decreased. They are also arguably less relevant, since 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 two or more 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 first event. But limitations of this approach include that (i) all events count equally, so that a non-disabling stroke counts equally to a procedural death (i.e. both are simply counted as 'an event'), whereas in reality they vary vastly in their clinical impact; and (ii) it only captures the first event per patient, so that a fatal stroke occurring after a non-disabling 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 Institute of Health Stroke Score (NIHSS); disability as measured by Barthel index, or quality of life measures such as the the EuroQOL group 5-Demesion (EQ5D) score[2]. A challenge in the analysis of these outcomes, is how best to handle the competing risk of death. For some scales (e.g. 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 (e.g. mRS) accommodate death, they can only take into whether a death occurred and the timing is ignored. This is a limitation when assessing the longer-term impact of intervention.

In this paper, 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 prioritization of clinically more important outcomes over less important outcomes (e.g. death can be prioritized over non-disabling stroke). It also allows one to include outcomes of differing types, this can be particularly useful in the analysis of acute stroke trials, since 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. in an article in the European Heart Journal in 2012[3] and has subsequently been used in trials in cardiology[4], but it has

rarely been applied 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 paper and illustrate how it works using data from a trial in acute stroke (the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands: MR-CLEAN[5]) and a stroke prevention trial (the International Carotid Stenting Study: ICSS[6]). In addition, we propose using the win ratio as the primary analysis in the future analysis of the Second European Carotid Surgery Trial (ECST-2[7]), and give our rationale for doing so. We finish by discussing the strengths and limitations of the win ratio.

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 outcome, 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 i) fatal stroke (most severe); ii) disabling stroke; iii) non-disabling 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 non-disabling stroke that occurred in the intervention patient is not considered. But 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 non-disabling stroke, but the intervention patient had a better outcome because the non-disabling 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 done for 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 $N_i x N_c$ patients. To calculate the win ratio one adds up all the wins and all the losses, and calculates the ratio (i.e. win ratio = total wins/ total losses). Statistical software provides 95% confidence intervals and p-values[8]. The win ratio can be interpreted as the odds that for a randomly chosen pair of patients that are not tied, the better outcome occurs in the

intervention patient. In contrast to other measures of treatment effect (such as the hazard ratio or odds ratio), a win ratio >1 (rather than <1) is indicative of treatment benefit. .

The win ratio gives a relative measure of treatment effect. Trial guidelines suggest that both relative and absolute measures of treatment benefit (such as number needed to treat, or difference in the percentage of patients with an event) should be also be reported[9]. For hierarchical outcomes the win difference (also known as net benefit)[10] 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 to 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% confidence interval [CI], 1.21 to 2.30, p<0.001) in favor of thrombectomy treatment[5]. The rate of functional independence (mRS, 0 to 2) was 32.6% in the thrombectomy arm vs. 19.1% in the control arm (absolute difference 13.5%, 95% CI 5.9% to 21.2%).

Win ratio analysis of modified Rankin 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 X 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 30346/2041=1.49 (95% CI 1.16-1.90, p<0.001) . The win ratio can be interpreted as the odds that for a randomly chosen pair of patients with a different outcome, the better outcome occurs in the thrombectomy arm. The win ratio gives a relative measure of treatment effect, but it is also helpful to give an absolute measure of treatment benefit[9]. The win difference[10] can be reported for this purpose. 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 to 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. The measure of effect is the same as Agresti's generalized odds ratio, recently used in the SELECT-2 trial of endovascular thrombectomy[11]. However, unlike the win ratio Agresti's generalized odds ratio is used for ordinal outcomes and the concept does not immediately generalize to hierarchical outcomes. We also note that the p-value is very 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[11]. One benefit of the win ratio compared to ordinal logistic regression is that it avoids the need to make the proportional odds assumption. Overall, although the win ratio is a useful alternative method for anlaysing mRS, the benefits are more apparent when analyzing a hierarchical outcome as described in the following sections.

Analysis of quality of life and stroke severity

Quality of life as measured by EQ5D score at 90 day and stroke severity score as measured by National Institutes of Health Stroke Scale (NIHSS) at 5-7 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 amongst patients who die, since this scores represents a health state equivalent to death[12]. This yields a between group difference in EQ5D of 0.07 (95% CI 0.00-0.14, p=0.054). But the results from such an approach are hard to interpret: some patients report an EQ5D score less than 0 – equivalent to a health state worse than death. But imputing a better score amongst patients who died seems potentially inappropriate, since 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. But this approach also seems unsatisfactory because it means excluding over 20% of patients who died prior to 90 days.

An analysis of NIHSS score at 5-7 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 to 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 of 38) but such values would be outliers amongst 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 outcomes where death is the most important, followed by either

EQ5D or NIHSS score amongst survivors as the second level of the hierarchy. This process is illustrated in Figures 2B and 2C. For EQ5D the process yields a win ratio of 1.20 (95% CI, 0.95-1.51, p=0.11). 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[13,14]. For 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 regards 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 when compared to conventional analyses. Rather it provides a more clinically relevant, interpretable summary of treatment benefit. 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 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, i.e. death by 90 days as a binary outcome with EQ5D/NIHSS scores which 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 (i.e. also including non-disabling strokes). The main analysis of ICSS used time-to-first event analyses and Cox proportional hazards models.

In the interim analysis paper in 2010[15] 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 vs 44 events; HR 1.69, 1.16-2.45, p=0.006). The long-term outcome paper[6] reported that the number of fatal or disabling strokes (52 vs 49) and cumulative 5-year risk did not differ significantly between the stenting and endarterectomy groups (6·4% vs 6·5%; hazard ratio [HR] 1·06, 95% CI 0·72-1·57, p=0·77).

The results applying a win ratio for the to strokes in ICSS is shown in Figure 3. Excluding 3 patients that withdrew immediately following randomization, there were 853 assigned to stenting and 857 patients assigned to endarterectomy. This yields a total of 853x857=731,021 patient pairs for comparison. We analyse stroke using a 3-level hierarchy of (1) fatal stroke; (2) disabling stroke; (3) non-disabling stroke. Comparing all patients 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 2.3% (n=16300) of pairs. But in the majority of patient pairs neither patient had a fatal stroke, and hence 96.7% (n=707362) of pairs are a 'tie' based on time to fatal stroke, and so are then compared based on the time to disabling stroke. Amongst the 707362 comparisons based on disabling stroke there were 3.8% of 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 (i.e. the components of the primary outcome), we add up all the wins at the first two 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 very similar to if one inverts the hazard ratio 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), as shown in Figure 4. This is not unusual[4], and the win ratio is known to be equal to the inverse of the hazard ratio for an analysis of a single time-to-event outcome when the proportional hazards assumption holds[16].

We could also extend this hierarchy to also include non-disabling stroke. The advantage of a win ratio approach over a time-to-first event approach here is that because many non-disabling occur early during follow-up (in the peri-procedural 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 more important events. Nevertheless, the results from a win ratio and time-to-first event approach are broadly similar. When comparing the remaining patients (i.e. those not already untied on the basis of fatal or disabling stroke) with regards to non-disabling stroke 2.3% (n=16675) of paired comparisons are a win for stenting, 6.7% (48808) are a loss and 81.1% (n=592993) are a tie. The win ratio was 0.61 (95% CI 0.45-0.81, p=0.0009) indicating that outcomes tended to be better in the control (endarterectomy group). The hazard ratio 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 randomised 429 patients with carotid stenosis ≥50% with a low to intermediate risk of stroke to either optimal medical therapy (OMT) alone (n=215) or carotid revascularization plus OMT (n=214)[7,17]. 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 [MI]) alone. To supplement evidence based on clinical events, we also performed brain imaging scans at both baseline and 2 years post-randomisation in order 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 primary outcome, we felt an analysis using the win ratio approach would be more appropriate than an analysis using conventional methods (e.g. Cox models with associated hazard ratios 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 OMT + revascularization arm related to the cardiovascular hazards of revascularisation, 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 a hazard ratio. 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 peri-operative death, fatal stroke or fatal MI; 2) time to non-fatal stroke; 3) time to non-fatal MI (excluding silent infarcts); 4) new silent cerebral infarct on MRI. 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-randomisation. 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 Supplementary Appendix.

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 endpoints in two large previous stroke trials, MRCLEAN 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 Graphical 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 quality of care for stroke patients continues to improve, running trials with the conventional outcomes used in major trials (e.g. stroke or death) may be increasingly difficult. Therefore, using alternative methods which capture other measures indicative of treatment benefit are helpful. This concept is already well-recognized by neurologists and outcomes capturing functional status or cognitive status (e.g. 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 on 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 benefit. For example, rather than relying solely on whether or not an event has occurred, information could be captured on the number of events (i.e. allowing inclusion of recurrent strokes) or on the severity of events. We also illustrated how use of the win ratio is a convenient way to handle the competing risk of death in the analysis of quantitative outcomes.

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 (e.g. it is the inverse of an odds ratios for a binary outcome) should help in providing intuition to 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. An additional limitation is that although adjustment for baseline covariates is theoretically possible with the win ratio, it is not implemented in existing statistical software[8,18]. Adjustment for important prognostic factors (i.e. those that are predictive of outcomes) is known to improve statistical power[19] or equivalently reduce the number of patients required in a trial. This may make the win ratio a less attractive option in

scenarios where there are strong predictors of the primary outcome. Finally, sample size calculations are more complex when a win ratio approach is used for the primary analysis.[20]

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.

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Acknowledgements:

We would like to acknowledge the principal investigators of MR CLEAN for providing data: Robert van Oostenbrugge, Wim van Zwam, Yvo Roos, Charles Majoie and Aad van der Lugt

Graphical Abstract: Comparison of the win ratio compared to conventional statistical analyses for some outcomes commonly used in stroke trials

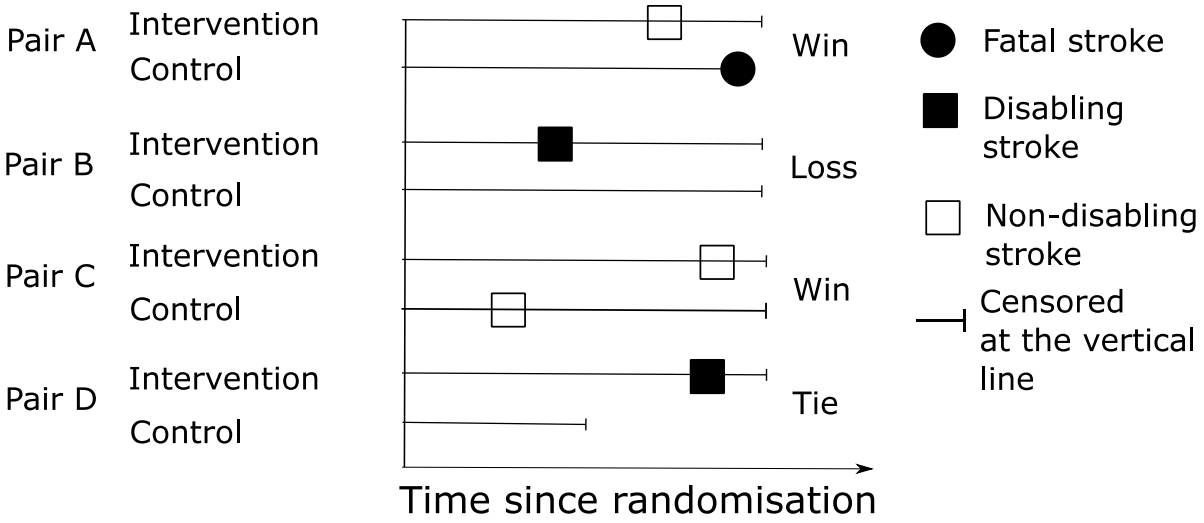
<table>
<tr><th>Outcome

(typical conventional analysis)</th><th>Advantage of a win ratio approach</th><th>Disadvantages</th></tr>
<tr><td>Composite outcomes, e.g. death, or stroke (time-to-first of composite)</td><td>Can prioritize most important outcomes (e.g. death→ disabling stroke→non-disabling stroke)

Can include events after first (e.g. deaths after non-fatal stroke)</td><td rowspan="3">Lack of familiarity

Estimates translate less readily into clinical practice</td></tr>
<tr><td>Ordinal outcomes, e.g. modified Rankin score (proportional odds model)</td><td>Avoid statistical assumptions</td></tr>
<tr><td>Quantitative outcomes (linear regression of outcome amongst survivors)</td><td>Analyse outcome after allowing for competing risk of death</td></tr>
<tr><td colspan="3">The win ratio is a method that compares pairs of patients (one from intervention and one from control) and evaluates which patient had a better outcome based on a hierarchy of clinical priorities</td></tr>
</table>

Figure 1: Schematic showing how the win ratio works for with a hierarchical outcome of (1) time to fatal stroke (2) time to disabling stroke (3) time to non-disabling stroke



The schematic shows how pairs of patients are analysed with respect to a clinical hierarchical of (1) time to fatal stroke, (2) time to disabling stroke, (3) time to non-disabling 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 non-disabling stroke that occurs in the intervention arm is not considered. But 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 non-disabling stroke, but the non-disabling 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.

Figure 2: Analysis using the win ratio in MR CLEAN for: A) the primary outcome of modified Rankin score at 90 days; B) a hierarchical composite of all-cause mortality then EQ5D quality of life score at 90 days; C) a hierarchical composite of all-cause mortality and NIHSS score at discharge (or 1 week)

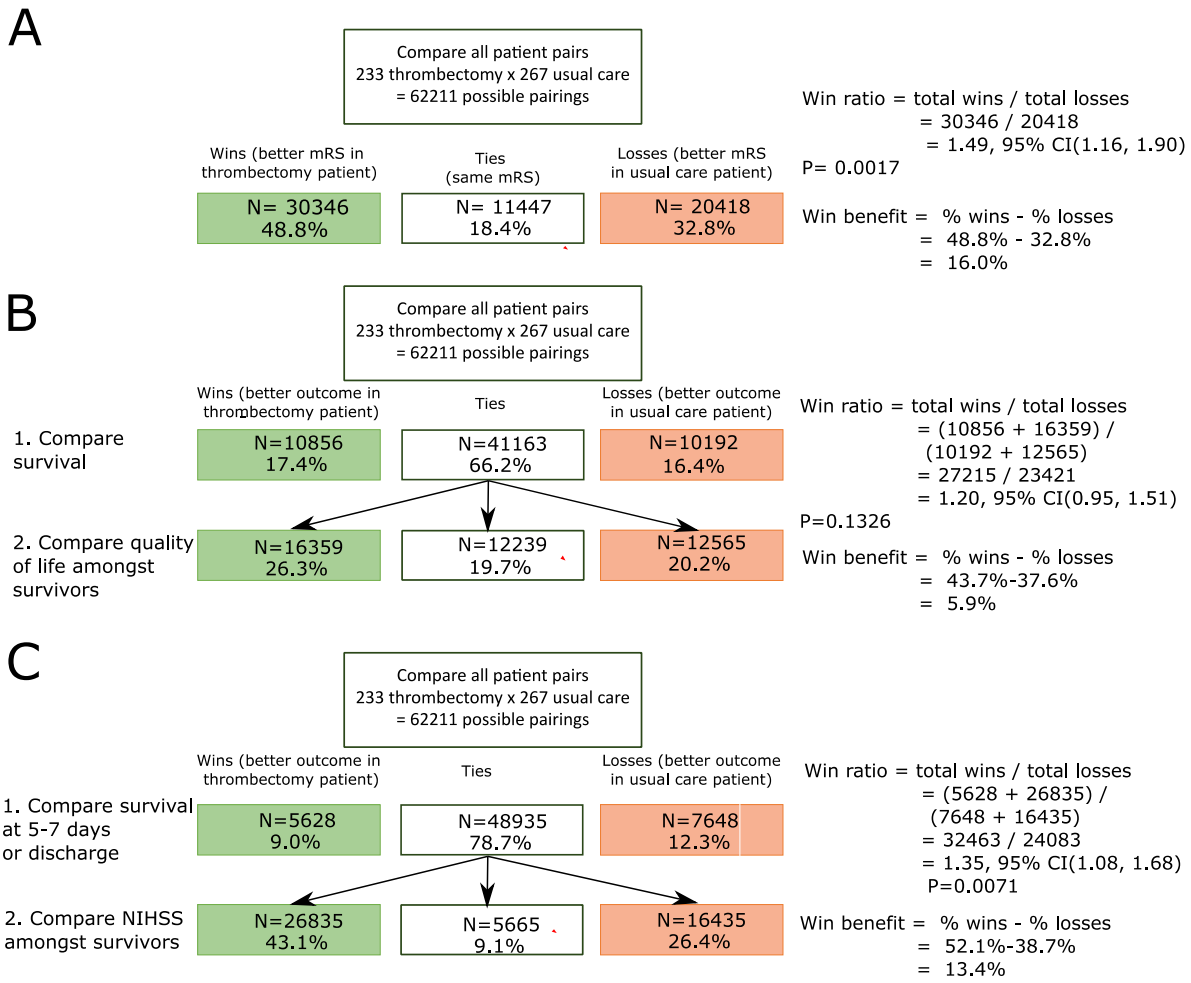
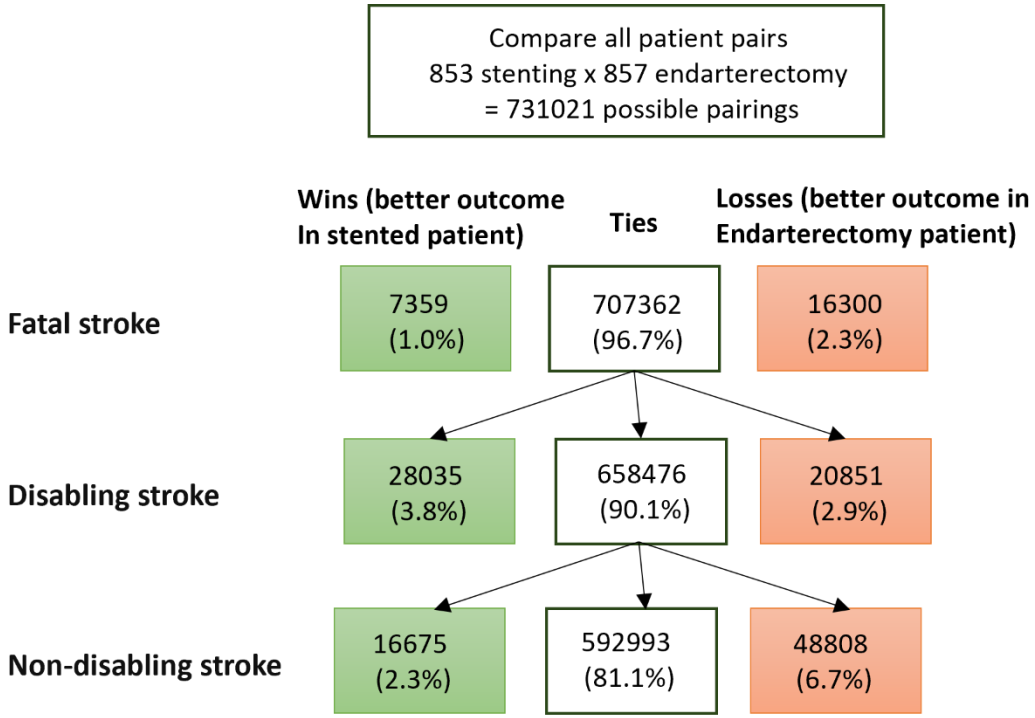


Figure 3: An analysis of stroke in ICSS using a hierarchy of either (1) fatal stroke (2) disabling stroke; or (1) fatal stroke (2) disabling stroke (3) non-disabling stroke



Win ratio based on fatal /disabling stroke (ignoring non-disabling stroke)

= (7359 + 28035) / (16300+ 20851)
= 35216 / 37155
= 0.95, 95% CI(0.63, 1.42)
P=0.79

Win ratio based on fatal /disabling / non-disabling stroke

= 7359 + 28035 + 16675) /
(16300+ 20851 + 48808)
= 52069 / 85959
= 0.61, 95% CI(0.45, 0.81)
P=0.0009

Figure 4: Conventional Kaplan Meier and Cox proportional hazards models applied to ICSS for (A) fatal or disabling stroke (B) any stroke