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Use of Ordinal Outcomes in Vascular Prevention Trials
Comparison With Binary Outcomes in Published Trials

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Background and Purpose—Vascular prevention trials mostly count "yes/no" (binary) outcome events, eg, stroke/no stroke. Analysis of ordered categorical vascular events (eg, fatal stroke/nonfatal stroke/no stroke) is clinically relevant and could be more powerful statistically. Although this is not a novel idea in the statistical community, ordinal outcomes have not been applied to stroke prevention trials in the past.

Methods—Summary data on stroke, myocardial infarction, combined vascular events, and bleeding were obtained by treatment group from published vascular prevention trials. Data were analyzed using 10 statistical approaches which allow comparison of 2 ordinal or binary treatment groups. The results for each statistical test for each trial were then compared using Friedman 2-way analysis of variance with multiple comparison procedures.

Results—Across 85 trials (335 305 subjects) the test results differed substantially so that approaches which used the ordinal nature of stroke events (fatal/nonfatal/no stroke) were more efficient than those which combined the data to form 2 groups ($P<0.0001$). The most efficient tests were bootstrapping the difference in mean rank, Mann–Whitney U test, and ordinal logistic regression; 4- and 5-level data were more efficient still. Similar findings were obtained for myocardial infarction, combined vascular outcomes, and bleeding. The findings were consistent across different types, designs and sizes of trial, and for the different types of intervention.

Conclusions—When analyzing vascular events from prevention trials, statistical tests which use ordered categorical data are more efficient and are more likely to yield reliable results than binary tests. This approach gives additional information on treatment effects by severity of event and will allow trials to be smaller. **(*Stroke*. 2008;39:000-000.)**

Key Words: stroke ■ prevention ■ randomized controlled trial ■ statistical analysis

Major advances have been made in the primary and secondary prevention of stroke with effective strategies based on lifestyle modification, antithrombotic agents, blood pressure and cholesterol lowering, and carotid endarterectomy. In parallel, the absolute risk of recurrence has fallen dramatically over time; in stroke trials, this is apparent as a decrease in the control event rate, eg, 10.8% in the Canadian American Ticlopidine Study (CATS) in 1989[2] and 3.4% in Perindopril protection against recurrent stroke study (PROGRESS) in 2001.[3] This trend is likely to continue as new and effective interventions are added. Because absolute event rates are a key component in sample size calculations for binary ("yes/no" event) outcomes, low rates equate to larger trials.[4] An additional pressure in performing trials is that their number has increased as new prophylactic strategies are tested, eg, antiplatelets (thromboxane synthase inhibitors), anticoagulants (thrombin/factor Xa inhibitors), and carotid interventions (stenting, treatment of asymptomatic stenosis). The combination of more and larger trials means it is becoming increasingly difficult to find sufficient patients to enroll into new studies.

New strategies are required to bring trial sample sizes down and to maximize the potential to demonstrate benefit. In the past, composite outcomes of vascular death, nonfatal stroke, and nonfatal myocardial infarction (MI) have been used, in part to increase the number of events. This approach can be extended to include further events in the composite such as hospitalization, silent brain infarcts (as identified by MRI), or by counting all vascular events rather than just the first one.[5] However, the use of composite outcomes has been criticized.[6] An alternative approach is to analyze vascular prevention trials in a way which does not lose clinically relevant data. Most studies compare binary (stroke/no stroke) event rates between the treatment and control group. However, stroke or MI events may be fatal or nonfatal, so trichotomous outcomes (fatal event/nonfatal event/no event) can be analyzed. This approach can be extended to 4 (fatal stroke/severe nonfatal stroke/mild stroke/no stroke) or 5 (fatal stroke/severe nonfatal stroke/mild stroke/transient ischemic attack [TIA]/no event) levels. Similar ordered categorical outcomes can be developed for MI, composite vascular

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outcomes, and bleeding, as well as other vascular events, such as heart failure. The analysis of such ordered categorical (ordinal) events is usually more efficient statistically (because data on severity are not lost) thereby offering the potential for reducing trial sample size while maximizing the potential to find small clinically relevant treatment benefits.[7] Such polytomization of events assumes that the ordering of events is meaningful, ie, that fatal vascular events are considered more severe than nonfatal ones. If so, ordinal outcomes may be more informative to patients, carers, healthcare professionals, and government than binary outcomes.

We report a comparison of the relative efficiencies of using and analyzing binary and polytomous outcomes from vascular prophylaxis trials. Although the use of ordinal statistical approaches is well defined in the methodological literature, its use for designing and analyzing vascular prevention trials is entirely novel.

Methods

Identification of Trials

We sought summary patient data from randomized controlled trials assessing primary or secondary vascular prevention, ie, preventing first or recurrent events respectively, which were either positive or negative according to the trial publication, or were included in a meta analysis showing benefit or harm; neutral trials in a neutral meta-analysis were excluded, an approach which follows our previous study in acute stroke trials.[7] We included vascular trials involving nonstroke patients and those measuring nonstroke outcomes because stroke patients suffer subsequent nonstroke vascular events, and those with other vascular conditions can go on to have a stroke. Taking this approach means the findings are generalizable across the field of vascular medicine. Published studies fulfilling these criteria were identified from electronic searches of the Cochrane Library and included studies of antithrombotic, BP or lipid lowering therapy, carotid endarterectomy, and hormone replacement therapy. Trials were excluded if they were neutral and related to a neutral intervention (as determined from a published meta-analysis) or did not include adequate ordered categorical information for at least one vascular outcome.

Trial Data

The numbers of subjects at the end of follow-up having a stroke (fatal, nonfatal, severe nonfatal, mild, TIA), MI (fatal, nonfatal), composite vascular event (fatal stroke or MI, nonfatal stroke or MI), and bleeding (major, minor, no bleeding) were obtained, where available, for each treatment group (active, control) from the primary trial publication. In factorial trials or those having more than two treatment groups,[8] data were analyzed for each active comparison versus control. Data were assessed by intention-to-treat where possible.

Statistical Tests

We compared different statistical tests for assessing treatment effect.[9–14] Some of these required the ordinal data to be combined into two groups (eg, Pearson's Chi-square test), whereas others used the raw ordered categorical data (eg, Mann–Whitney *U* test, unpooled *t* test, bootstrapping the mean rank, ordinal logistic regression [also known as the proportional odds regression]). A description of the statistical tests used is given in the supplemental Appendix I, available online at http://stroke.ahajournals.org.

Comparison and Ordering of Statistical Tests

Each data set was analyzed using each statistical test. The results were then ordered within each trial and given a rank, with the lowest rank given to the test which produced the smallest probability value within that trial. A 2-way analysis of variance test (Friedman with adjustment for ties[15]; ANOVA) was then performed to assess which statistical test produced the lowest ranks (ie, the most statistically significant values). Duncan multiple range test was used to assess the ordering of tests and determine where significant differences between tests were present. We also assessed how many statistically significant (at 5%) results each test found.

Table 1. Assessment of 10 Statistical Approaches for Analyzing Stroke as a 3-Level Event (Fatal/Nonfatal/No Stroke) in 85 Vascular Prevention Trials

Test	Mean rank	Banding
Mann-Whitney U test	3.32	
Bootstrap (difference in mean rank)	3.32	
Ordinal logistic regression	4.12	
Robust ranks test	4.51	
Cochran-Armitage trend test	4.80	
t-test	5.08	
Pearson's Chi Sq – 2x3 test	5.94	
Pearson's Chi Sq – stroke vs. no stroke	6.37	
Pearson's Chi Sq – death vs. alive	7.58	
Median test	9.97	

Analysis by 2-way ANOVA ($P<0.0001$) on the ranked data (1 to 10 with 1 "best"); comparison of tests by Duncan's multiple range test—those tests joined by the same band are not significantly different from each other at $P<0.01$.

To assess the validity and reliability of the results found, a number of supplementary analyses were carried out. First, the comparison of statistical tests was repeated within subgroups of trials sharing similar characteristics to assess whether particular types of trials suited different statistical approaches; second, the statistical assumptions of the tests were assessed; and third, the sensitivity (type 1 error) of the tests was assessed. Technical details of these supplementary analyses can be found in the supplemental Appendix II.

Analyses were carried out in SAS (version 8.2) and Stata (version 7); significance was taken at $P<0.05$ for analyses of trials and $P<0.01$ for ANOVA.

Results

Trials

Of 243 identified trials, 101 (416 020 subjects) were included, these comprising 35 primary and 66 secondary prevention studies (supplemental Table I). One hundred forty-two trials were excluded, mostly because their published data did not distinguish between fatal and nonfatal vascular events so that 3-level data could not be calculated (supplemental Table II).

Stroke

The trials variably included intracerebral hemorrhage within the outcome of stroke. The results of the statistical tests differed significantly with 3-level data (fatal stroke/nonfatal stroke/no stroke; 85 trials, 335 305 subjects; ANOVA $P<0.0001$); ordinal analyses ranked above binary approaches (Tables 1 and 2; Figure 1) with the Mann–Whitney *U* test, bootstrapping (difference in mean rank), and ordinal logistic regression significantly better than the other methods (sup-

Table 2. Ranking of Statistical Tests (1 to 10 With 1 "Best") for Measure of Stroke (3, 4, and 5-Levels), Myocardial Infarction (3-Level), Composite Vascular Outcome (3-Level), and Bleeding (3-Level)

			Ranking of Tests Relative to Each Other									
Outcome	Trials	*P* Value	MWU	BS	OLR	RRT	CAT	*t* Test	χ^2 2×3	χ^2 Event	χ^2 Dead	Median Test
Fatal stroke/nonfatal stroke/no stroke	85	<0.0001	1	2	3	4	5	6	7	8	9	10
Fatal stroke/severe nonfatal/mild/no stroke	21	<0.0001	2	1	4	3	5	6	8	7	9	10
Fatal stroke/nonfatal stroke/TIA/no stroke	29	<0.0001	2	1	5	6	3	4	7	8	9	10
Fatal stroke/severe nonfatal stroke/mild stroke/TIA/no stroke	11	<0.0001	3	4	5	6	1	2	8	7	9	10
Fatal MI/nonfatal MI/no MI	58	<0.0001	1	3	5	6	2	4	7	8	9	10
Fatal vascular event/nonfatal vascular event/no vascular event	43	<0.0001	1	2	3	4	5	6	7	8	9	10
Severe-major bleeding/minor bleeding/no bleeding	15	<0.0001	3	2	1	6	4	5	8	7	9	10

The most efficient tests are underlined and do not differ from each other statistically.
BS indicates bootstrap; CAT, Cochran–Armitage test; MWU, Mann–Whitney *U* test; OLR, ordinal logistic regression; RRT, robust ranks test.

plemental Figure I). Similar results were seen for the other stroke outcome assessments: 4-level (fatal stroke/severe nonfatal stroke/mild stroke/no stroke), 4-level including TIA (fatal stroke/nonfatal stroke/TIA/no stroke or TIA), and 5-level (fatal stroke/severe nonfatal stroke/mild stroke/TIA/no stroke or TIA; each ANOVA $P<0.0001$; Table 2). Although the absolute ordering of the tests varied for these polytomous outcomes, ordinal tests always performed better than binary ones (Table 2). Six trials gave sufficient data to compare qualitatively 3-, 4-, and 5-level stroke data; 4-level data (with TIA included as an event) and 5-level data (including TIA) appeared to be the most efficient approaches. When assessed by how many trials were statistically significant (positive or negative but not neutral), those tests which did not collapse the data into groups again out-performed other approaches; for example the Mann–Whitney *U* test gave a statistically significant result in 44% of trials in comparison with the Pearson's χ^2 2x3 test at 32% (Figure 1).

Myocardial Infarction

Fifty-eight trials (232 515 subjects) were included. The analyses differed significantly for a 3-level outcome (fatal MI/nonfatal MI/no MI; $P<0.0001$), with ordinal approaches performing better than binary (Table 2).

Composite Vascular Event

Forty-three trials (204 108 subjects) gave data for a 3-level composite vascular outcome (fatal stroke or MI/nonfatal stroke or MI/no stroke or MI). Ordinal tests performed best ($P<0.0001$) with the Mann–Whitney *U* test, bootstrapping (the difference in mean rank) and ordinal logistic regression ranking highest (Table 2).

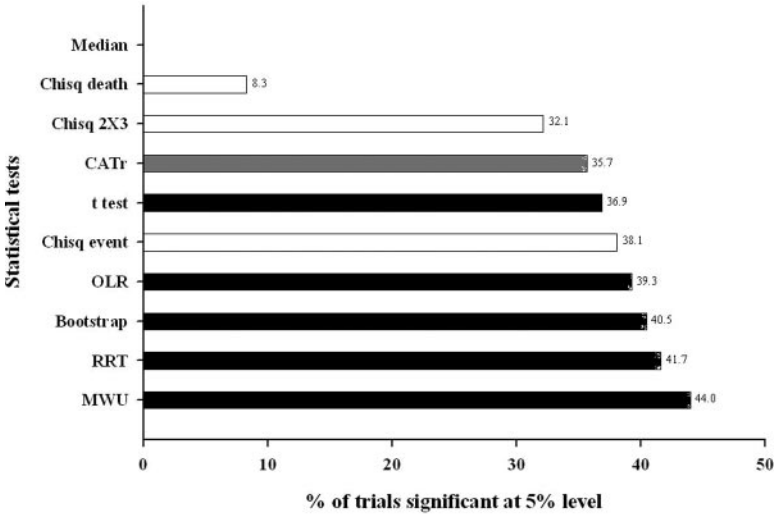

Figure 1. The number of significant trials (positive or negative but not neutral, $P<0.05$) for each statistical test for 3-level stroke (fatal, nonfatal, no stroke).

Table 3. Ranking of Statistical Tests (1 to 10 With 1 'Best') for 3-Level Stroke (Fatal, Nonfatal, No Stroke) in Subgroups of Vascular Prevention Trials

			Ranking of Tests Relative to Each Other									
Outcome	Trials	*P* Value	MWU	BS	OLR	RRT	CAT	*t* Test	χ^2 2×3	χ^2 Event	χ^2 Dead	Median Test
Prevention, primary	29	<0.0001	1	2	5	3	6	4	7	8	9	10
Prevention, secondary	56	<0.0001	2	1	3	4	5	6	7	8	9	10
Anticoagulants	12	<0.0001	2	1	7	6	4	3	5	8	9	10
Antiplatelets	33	<0.0001	1	2	3	5	4	6	7	8	9	10
Antihypertensives	23	<0.0001	2	1	3	4	5	6	7	8	9	10
Lipid lowering	10	<0.0001	2	1	3	4	5	6	8	7	9	10
Carotid endarterectomy	4	<0.0001	2	1	5	3	6	4	8	7	9	10
Hormone replacement therapy	2	0.86	…	…	…	…	…	…	…	…	…	…
Age <65 years	34	<0.0001	1	2	3	4	5	6	7	8	9	10
Age >65 years	31	<0.0001	2	1	4	3	6	5	7	8	9	10
Trial, small (n<2,520)	42	<0.0001	1	2	5	6	3	4	7	8	9	10
Trials, large (n>2,520)	42	<0.0001	2	1	3	4	5	6	8	7	9	10
Follow-up, short term (<36 months)	45	<0.0001	1	2	4	5	3	6	7	8	9	10
Follow-up, long term (>36 months)	39	<0.0001	2	1	3	4	5	6	7	8	9	10
Risk of death in control, low (<0.2% per month)	43	<0.0001	1	2	3	4	5	6	7	8	9	10
Risk of death in control, high (>0.2% per month)	41	<0.0001	2	1	3	4	5	6	7	8	9	10
Risk of stroke in control, low (<0.17% per month)	40	<0.0001	1	2	3	4	5	6	7	8	9	10
Risk of stroke in control, high (>0.17% per month)	41	<0.0001	2	1	5	6	3	4	7	8	9	10
Time from index event, short (<87 days)	22	<0.0001	1	2	3	4	5	6	8	7	9	10
Time from index event, long (>87 days)	22	<0.0001	2	1	3	6	4	5	7	8	9	10

The most efficient tests are underlined and do not differ from each other statistically.
BS indicates bootstrap; CAT, Cochran–Armitage test; MWU, Mann–Whitney *U* test; OLR, ordinal logistic regression; RRT, robust ranks test.

Bleeding

Fifteen trials (26 215 patients) were identified as including information on bleeding at three levels: major bleeding, minor bleeding, no bleeding. Definitions of bleeding differed between trials. Once again, ordinal analytic approaches ranked highest (Table 2).

Sensitivity Analysis and Test Assumptions

The ordering of statistical tests, with ordinal more efficient than binary, was maintained for all subgroups of trials irrespective of type of prevention and treatment, average age of patients, trial size and length of follow-up, risk of death or stroke, and time from index event (Table 3). When considering the 19 trials (27 datasets) with a high event rate (>10% overall), ordinal tests remained most efficient. Published hazard ratios (which take into account the time to event, as derived from the Cox proportional hazards model) for stroke were available for 36 trials; a comparison of the 11 statistical tests, including Cox results, revealed bootstrapping, Mann–Whitney *U*, and ordinal logistic regression to be as good if not slightly superior to the Cox model (Duncan multiple range test).

The statistical assumptions for ordinal logistic regression were not violated ($P>0.05$) in 79 of 85 trials with 3-level stroke data; no violations were present for 11 trials with 5-level stroke data (supplemental Appendix III). The sensitivity analysis showed that the top performing statistical tests (ordinal logistic regression, Mann–Whitney *U* test) were not

overly sensitive, and statistically significant treatment effects were only found where they are likely to be present (supplemental Appendix III). Using ordinal logistic regression, the odds ratios were similar for different strata of severity for 3-level, 4-level, and 5-level data (supplemental Table III).

Discussion

Improvements in secondary prevention are leading to falling event rates in clinical trials. This means that future vascular prevention trials will need to be longer and, with an increasing number of new interventions, the availability of subjects is becoming limited. Thus, new approaches to trial design and analysis are needed to help reduce sample size. This study has shown that it is feasible to create 3-level ordered categorical outcomes for stroke, MI, a composite vascular event (fatal stroke and MI/nonfatal stroke and MI), and bleeding. Analysis reveals that, in general, statistical approaches which use ordinal data are more efficient than conventional binary tests based on "event/no event." A further increase in efficiency comes from using 4-level or 5-level data for stroke (with or without TIA). Ordering vascular events by severity has both biological and clinical meaning. Fatal events are clearly the most extreme health state whereas a severe stroke (normally defined as a stroke resulting in dependency on others) is a disaster for the patient, their career, and society, for both clinical and economic reasons. A mild stroke leaves the patient independent, even if residual impairment remains, and those who are younger can often return to work.

The most efficient statistical tests were those which examined ordinal data, including ordinal logistic regression, the Mann–Whitney *U* test, and bootstrapping the mean rank. In addition to improving statistical efficiency, the use of ordered categorical outcomes gives information on the ability of an intervention to reduce the severity of an event, not just the number of events. Ordinal logistic regression allows both estimation (with confidence intervals) and inclusion of baseline prognostic covariates in analyses. However, it assumes that any treatment effect is similar across outcome levels, ie, the odds of moving a treated patient from fatal to severe nonfatal stroke are similar to those for moving from TIA to no event ("proportionality of odds"). This assumption requires justification because it is neither widely recognized nor obvious in most published vascular trial data. First, it is biologically plausible to suggest that prophylactic interventions will reduce severity as well as the total number of events. Since the development of atherosclerosis and increases in thrombosis, coagulation and inflammation are not binary events in nature, and their magnitude is a determinant of the severity of clinical vascular events, it is reasonable to expect that interventions will move patients from fatal to severe, severe to mild, and mild to no events. If this assumption (of proportional odds) is not met, an alternative ordinal model could be considered.[16]

Second, there is existing published evidence that interventions do alter severity: simvastatin reduced the risk of stroke of different severities by similar risk reductions in the Heart Protection Study (HPS),[17] hormone replacement therapy increased both stroke and its severity in the Women's Estrogen for Stroke Trial (WEST),[18] and antiplatelet agents reduced both fatal and nonfatal vascular events in the Antithrombotic Trialists' (ATT) Collaboration meta analysis.[19] The apparent failure of most vascular prevention trials to show individual effects on death or severe events is largely because they were not powered to assess these specific and, therefore, relatively uncommon events. Third, the odds reduction at each outcome level appeared to be relatively constant when individual trials were assessed (Figure 2); formal statistical assessment using the likelihood ratio test indicated that "proportionality of odds" was present in most cases (although this test is known to be conservative; Appendix 6). Last, using ordinal statistical tests was more powerful than binary approaches, the central finding of this study. Although this is not a novel idea in the statistical community,[20] ordinal outcomes have not been applied to vascular prevention trials in the past. In this context, it is worth noting that ordinal logistic regression is relatively robust to deviations in its assumptions even if they are not met in a particular trial. Another efficient ordinal test is the Mann–Whitney *U* test, which is widely available in statistical packages and can produce a point estimate (median difference between groups) with confidence intervals. The major assumption of the test is that the treatment groups should be independent, and this is met here. The final efficient statistical approach was bootstrapping the mean rank; this approach is computer intensive[13] and its application and the interpretation of results are not well appreciated by clinicians, although it is free of assumptions.

The conventional approach to analyzing vascular prevention trials is to perform time to event analyses, as visualized using Kaplan–Meier curves and analyzed with Cox regression. When the frequency of events is high, analyses based on time-to-event are more efficient than those using frequencies (as analyzed using logistic regression). However, the frequency of vascular events in most primary and secondary prevention trials running over 3 to 5 years is relatively low; recent vascular prevention trials have tended to report annualized stroke rates of 2% to 4%.[21,22] Logistic and Cox models give similar results when the overall event frequency is less than 10%.[23,24] Where the frequency of events is higher, ordinal data may be analyzed by time to event.[25,26] In the current dataset, the Cox model was slightly less efficient than bootstrapping, Mann–Whitney *U*, and ordinal logistic regression.

In this study, we have focused on assessing stroke as the primary outcome rather than using a composite vascular outcome (fatal vascular event, nonfatal stroke, and MI). Stroke was of interest since it has been used in several prevention trials, eg, the European Stroke Prevention Study-II (ESPS-II) and PROGRESS,[3,27] and 4- or 5-level data (including TIA) may be created. Nevertheless, ordered categorical outcomes may also be created for composite outcomes (fatal stroke or MI/nonfatal stroke or MI/no event) as well as other events such as MI or bleeding. Our results suggest that the use and analysis of polytomous outcomes would benefit trials assessing any of these vascular outcomes, and it is likely that the approach would work for others such as heart failure and venous thromboembolism; we are currently assessing this.

Using ordered categorical data will mean that results will need to be reported differently. The results of binary tests are

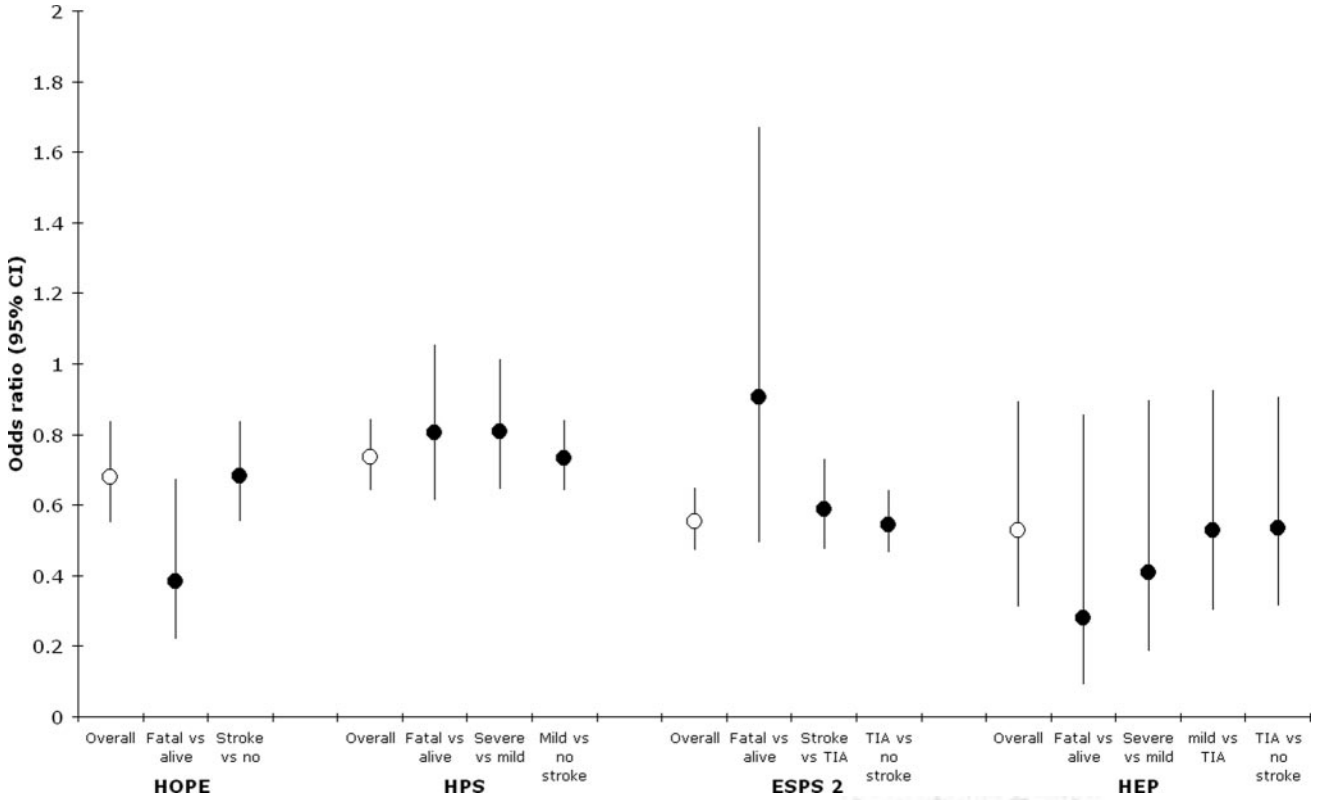

Figure 2. Odds ratios across trial (by ordinal logistic regression) and by individual outcome levels for 4 trials to illustrate the assumption of proportionality of odds.

summarized easily as the proportion of patients who benefit (or suffer) with a treatment, ie, oral anticoagulation reduced absolute stroke recurrence by 1.46% (odds ratio 0.75, $P=0.036$) in the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial.[28] In contrast, ordinal tests will need to be presented as the average absolute improvement in outcome, eg, anticoagulation reduced stroke recurrence and its severity with an odds ratio of 0.60 (or reduced the mean severity by 0.5 points, $P=0.013$) on a 5-level scale.[28] In this respect, health consumers will need to decide what odds ratio or difference in events is worthwhile, both clinically and in terms of health economics. In reality, it is reasonable to present the primary result using the odds ratio (or median change in event severity) and to give the absolute percentage change calculated from the binary outcome as a secondary measure. Further, a visual presentation of the data can be displayed as the percentage of patients within each category by treatment group (data from the North American Symptomatic Carotid Endarterectomy Trial [NASCET], Figure 3).

Just as sample size calculations exist for trials using dichotomised analyses,[4] analogous approaches exist for ordinal tests.[29] Because ordinal analyses are more powerful statistically, trial size may be reduced for a given power of say 90%; eg, sample size falls by 15% to 24% as the number of outcome categories increases from 3 to 7.[29] This reduction is worthwhile and would reduce competition between trials for patients, and lower trial costs and complexity. Taking the

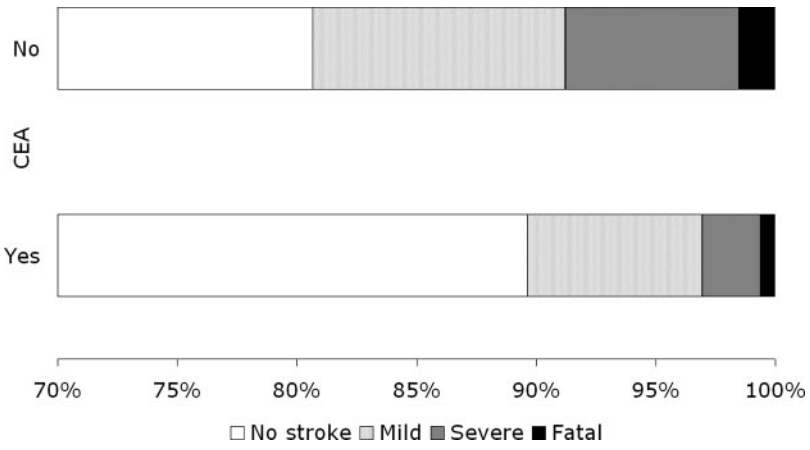

Figure 3. Example 4-level ordinal data from NASCET[1] of carotid endarterectomy (CEA).

Hypertension in Elderly Patients (HEP) trial[30] as an example (and assuming significance=0.05 and power=0.9), the sample size is reduced by 48% from 1556 for a binary outcome of stroke/no stroke to 810 for a 3-level stroke outcome as calculated using the method of Whitehead;[29] this is further reduced to 772 with a 5 level stroke outcome.

A number of caveats must be made about this study. First, a majority of identified trials could not be included because they did not publish adequate information on vascular events. As data were missing for a variety of trial types (primary, secondary prevention), sizes, and outcome measures (stroke/MI/vascular/bleeding) it is unlikely that a systematic bias was introduced into the findings; however, the precision of the results will have been attenuated by the missing data. Future trial publications should give this information, including vital status for the main vascular outcomes, so that ordered outcome categories can be calculated. Second, we did not use all possible statistical tests relevant to the problem of analyzing ordered categorical data; instead, we focused on those approaches which are readily available in statistical textbooks[11] and computer packages.

In summary, we suggest that vascular prevention trials should consider using statistical approaches, which use the inherent ordered categorical data present within vascular outcome events. The resulting trials could be smaller (with savings in patient numbers, numbers of centers, and study cost and complexity) and would allow appreciation of the effect of interventions on severity, as well as absolute number of events, to be highlighted. Appropriate tests include ordinal logistic regression, the Mann–Whitney *U* test, and bootstrapping the mean rank.

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Disclosures

P.W.B. participated in some of the included trials.

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Supplemental Appendix I: Statistical Tests Compared

Included Tests

Univariate statistical approaches for analyzing dichotomous and ordinal data comprised tests based on Pearson's Chi-square, ordinal, and bootstrap approaches.[1,2] Ten statistical approaches were assessed:

(1) Pearson's Chi-square 2×2 test—stroke versus no stroke; (2) Pearson Chi-square 2×2 test—death versus alive; (3) Pearson's Chi-square 2×3 test (unordered data)—fatal stroke versus non fatal stroke versus no stroke; (4) Cochran-Armitage trend test; (5) ordinal logistic regression; (6) median test; (7) Wilcoxon/Mann–Whitney *U* test (adjusted for ties); (8) robust ranks test (RRT)[3]; (9) *t* test; (10) bootstrap of difference in mean rank (with 3×3000 cycles).[4,5] Pearson Chi-square tests were performed without continuity correction because most trials enrolled more than 100 patients.

Statistical Detail for Nonstandard Tests

Robust Rank Test

The Robust rank test[3] is an alternative to the Wilcoxon test; it tests whether the median of one group is equal to another, but unlike the Wilcoxon test it does not assume that the distributions of the two groups are equal, ie, it makes no assumptions about the variance of the two groups.

Bootstrapping

Bootstrapping is a computationally intensive method which involves resampling data from a given sample. The main advantage of bootstrapping over more traditional methods is that it does not make assumptions about the distribution of the data. In this report we bootstrap the difference in mean rank; the procedure for doing this is outlined below:

1. Take a dataset, which contains n observations.
2. Draw a sample with replacement of size n (using replacement means that some of the original observations may appear in the new sample more than once and some not at all).
3. Estimate the parameter of interest (here the difference in mean rank) and store the result.
4. Repeat 2 and 3 many times; here we use 3 sets of 3,000 as used in the ECASS II trial.[5]
5. Compare the distribution of the stored results to the actual point estimate from the original dataset.

Ordinal Logistic Regression

Ordinal logistic regression (also called proportional odds regression)[6] can be used when the dependent variable is ordered categorical. It is similar to logistic regression but it simultaneously estimates multiple end points instead of just one. The number of end points it estimates is equivalent to the number of ordered categories minus one. For example if the mRS was the dependent variable of interest it would compare the following j categories:

0 versus 1, 2, 3, 4, 5, 6
0, 1 versus 2, 3, 4, 5, 6
0, 1, 2 versus 3, 4, 5, 6
0, 1, 2, 3 versus 4, 5, 6
0, 1, 2, 3, 4 versus 5, 6
0, 1, 2, 3, 4, 5 versus 6

Ordinal logistic regression provides one overall estimate for each covariate in the model and not one for each cut point. This assumes that the overall odds ratio is constant no matter which cut is taken. So, for example the odds ratio for the treatment effect would be interpreted as the odds of being in category *j* or above for all choices of j comparing treatment 1 to treatment 0.

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Supplemental Appendix II: Supplementary Analyses

Subgroup Analysis

Subgroup analyses were performed by assessing the efficiency of the different tests for differing trial characteristics: type of prevention (primary, secondary); type of treatment (anticoagulants, antiplatelets, antihypertensives, lipid lowering, carotid endarterectomy, hormone replacement therapy); patient age (≤65, >65 years); trial size (<2520, ≥2250 participants); length of follow up (≤36 months, >36 months); baseline severity (control group death rate adjusted for length of follow up, ≤median [0.2], >median [0.2]); time from index event (≤87 days, >87 days).

Statistical Assumptions

The principal statistical assumptions underlying the tests which performed well were assessed to ensure that their use was appropriate for stroke trial data. Assumptions included: ordinal logistic regression—proportionality of odds across response categories (ie, the magnitude of improvement or hazard, with a treatment, would be similar irrespective of baseline severity, age etc); Mann–Whitney *U*—independence of groups.

Type 1 Error

While assessing the statistical power of a particular test it is also important to ensure that the test maintains an acceptable proportion of type 1 errors (false-positive). A type I error occurs when a statistical test produces a significant result when in truth no treatment difference exists. If a test is maintaining adherence to the nominal proportion of type I errors then, under repeated sampling from a population in which the null-hypothesis of no treatment effect is true, we would expect to see a significant result ($P<0.05$) on 5% of occasions at the 5% significance level.

We assessed the proportion of type I errors for the three most efficient statistical tests, using data from five representative trials. From these we generated 1000 data sets, using random sampling with replacement, in which any treatment difference could have occurred only by chance. Tests maintaining an acceptable proportion of type I errors would expect to see a significant result in around 50 of the 1000 data sets.

Supplemental Appendix III: Results

Type 1 Error

Analysis of 1000 resampled random datasets from 5 representative trials did not find any evidence of an increased proportion of type I errors for ordinal logistic regression (SPAF-2, positive data sets n=54/1000, $P=0.30$[1]; ESPS-2, n=56, $P=0.21$[2]; HOPE, n=56, $P=0.21$[3]; HPS, n=46, $P=0.74$[4]; NASCET, n=47, $P=0.69$)[5]; Mann–Whitney *U* test (SPAF-2, n=21, $P>0.99$; ESPS-2, n=30, $P=0.99$; HOPE, n=17, $P>0.99$; HPS, n=26, $P>0.99$; NASCET, n=18, $P>0.99$).

Test Assumptions

When assessing ordinal logistic regression, the assumption of proportionality of odds (likelihood ratio test comparing the multinomial logistic model to the ordinal logistic regression model) was not met ($P<0.05$) in 6 of the 85 data sets (ASPECT $P=0.04$,[6] TPT-I $P=0.0002$,[7] TPT-II $P=0.03$, HOPE $P=0.02$,[3] ANBP2 $P=0.04$,[8] WEST $P=0.05$[9]). The same analysis was repeated on the 5-way stroke data, and the assumption of proportionality of odds was met for all 11 trials included in this part. In contrast, the assumption of the Mann–Whitney *U* test was met in all cases while the bootstrap approach is assumption free.

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Table I. Appendix 3: Included Trials

Intervention	Trial	Year	Subjects-Prevention Stage	Active Group	Control Group	Subjects (Active/Control)	Age (Years)
Anticoagulation	AFASAK[1]	1989	Chronic nonrheumatic AF:1	Warfarin	Placebo	335/336	74
	BAATAF[2]	1990	Non rheumatic AF:1	Warfarin	Control	212/208	68
	SPAF 1[3]	1991	Non rheumatic AF:1	Warfarin	Placebo	210/211	67
	VASPNAFI[4]	1992	Non rheumatic AF:1	Warfarin	Placebo	260/265	67
	VASPNAFI[4]	1992	Previous ischaemic stroke:2	Warfarin	Placebo	21/25	67
	ASPECT[5]	1994	Post MI:2	Anticoagulant	Placebo	1700/1704	61
	SPAF 2[6]	1994	Non rheumatic AF:1	Warfarin	Aspirin	555/545	...
	SPAF3[7]	1998	Nonvalvular AF:1	W+Asp	Adjusted dose W	521/523	72
	TPT[8]	1998	At risk of IHD:1	W+Asp	Placebo	1277/1272	57
	TPT[8]	1998	At risk of IHD:1	Warfarin	Placebo	1268/1272	57
	NASPEAF-IM risk[9]	2004	Patients with MS without prior embolism:1	Combined (A+triflusal)	Anticoagulant	222/232	...
	NASPEAF-H risk[9]	2004	Non valvular AF with prior embolism:2	Combined (A+triflusal)	Anticoagulant	223/247	...
Antiplatelets	Acheson[10]	1969	Post stroke:2	Dipiridamole	Placebo	69/70	58
	Canadian Co-op[11]	1978	Recent cerebral or retinal ischaemic attack:2	Sulphinpyrazone	Placebo	156/139	...
	Breddin[12]	1980	Post MI:2	Aspirin	Placebo	317/309	...
	Breddin[12]	1980	Post MI:2	Aspirin	Phenprocoumon	317/320	...
	Herskovits[13]	1981	Post TIA:2	Pentoxifylline	Antiaggregant	30/36	61
	ARIS[14]	1982	Post MI	Sulphinpyrazone	Placebo	365/362	...
	AICLA[15]	1983	Atherothrombotic cerebral or retinal ischaemic event	Aspirin	Placebo	198/204	63
	ACCSG[16]	1985	Recent carotid territory TIAs:2	Dip+Asp	Aspirin	448/442	63
	Matius-Guiu[17]	1987	Post stroke:2	Asp+Dip	Dipiridamole	115/71	56
	Swedish Co-op[18]	1987	Post minor or major stroke	Aspirin	Placebo	253/252	68
	TASS[19]	1989	Post TIA/stroke:2	Ticlopidine	Aspirin	1529/1540	63
	STIMS[20]	1990	PAD	Ticlopidine	Placebo	346/341	60
	UKTIA high dose[21]	1991	Post stroke-TIA:2	Asp high dose	Placebo	815/814	...
	UKTIA low dose[21]	1991	Post stroke-TIA:2	Asp low dose	Placebo	806/814	...
	SALT[22]	1991	Post stroke, TIA	Aspirin	Placebo	676/684	67
	SPAF 1[3]	1991	Non rheumatic AF:1	Aspirin	Placebo	552/568	67
	Fornaro[23]	1993	Chronic non valvular AF:1	Indobufen	Placebo	98/98	62
	CAPRIE[24]	1996	Atherosclerotic vascular disease:2	Clopidogrel	Aspirin	9599/9586	62
	ESPS 2[25]	1997	Post stroke-TIA:2	Aspirin	Placebo	1649/1649	67
	TISS[26]	1997	Post TIA, minor stroke, amaurosis fugax	Ticlopidine	Indobufen	821/811	65
	TPT[8]	1998	At risk of IHD:1	Aspirin	Placebo	1268/1272	57
	Taylor[27]	1999	Carotid stenosis:2	LD Aspirin	HD Aspirin	1395/1409	69
	TACIP[28]	2001	Post TIA or non disabling stroke:2	Triflusal	Aspirin	1058/1055	65
	AAASPS[29]	2003	Post stroke:2	Ticlopidine	Aspirin	902/907	61
	Ridker (WHS)[30]	2005	Healthy women 45 years or older:1	Aspirin	Placebo	19 934/19 942	55
BP control	VACS1970[31]	1970	Hypertension	Active treatment	Placebo	186/194	49
	Mild HT Oslo[32]	1980	Mild hypertension:1	Active treatment	Control	406/379	45
	IPPSH[33]	1985	Essential Hypertension:1	BB	Non BB	3185/3172	52
	MRC mild[34]	1985	Mild hypertension	Active treatment	Placebo	8700/8654	...

(*Continued*)

Table I. Continued

Male (%)	Time From Event (Weeks)	Follow-Up (Months)	Control Stroke Rate (%)	Control MI Rate (%)	Primary Outcome	ICH as Part	Trial Result
54	...	24	4.8	...	Thromboembolic complications	...	+
72	...	26	6.25	...	Ischaemic stroke	...	+
71	...	15	8.1	0.9	Ischaemic stroke+systemic embolism	...	+
...	...	21	7.2	...	Ischaemic stroke	...	+
...	...	20	16.0	...	Ischaemic stroke	...	0
80	...	37	3.3	9.6	Death from any cause	+	+
...	...	28	6.8	3.5	Ischaemic stroke+systemic embolism	+	0
61	...	13	2.7	0.9	Ischaemic stroke+systemic embolism	...	...
100	...	...	2.0	8.4	Coronary death+fatal and non fatal MI	+	+
100	...	...	2.0	8.4	Coronary death+fatal and non fatal MI	+	+
...	...	32	2.6	...	Vascular death+TIA+nonfatal stroke or systemic embolism	...	+
...	...	36	4.8	...	Vascular death+TIA+nonfatal stroke or systemic embolism	...	+
69	52	25	5.7		Stroke		0
...	1	26	14.4	...	TIA+stroke+death	...	0
79	...	24	...	8.1	Total mortality+coronary death+non fatal MI	...	0
79	...	24	...	5.0	Coronary death+non fatal MI	...	0
76	...	12	2.8	...	TIA+stroke	...	+
...	...	19	1.6	9.4	Fatal+non fatal MI+other thromboembolic episodes+sudden death+other cardiac death	...	+
70	...	36	16.1	4.4	Fatal+non fatal cerebral infarction	+	0
67	3	25	19.0	...	Stroke+retinal infarction+death		0
77	1	40	12.7	...	Stroke	...	0
62	...	24	12.7	3.6	Recurrent stroke or death	+	0
65	...	28	13.8	...	Stroke	...	+
76	...	60	6.5	19.9	Stroke+TIA+MI	+	0
73	...	48	14.6	...	Stroke+myocardial infarction+vascular death	...	+
73	...	48	14.6	...	Stroke+myocardial infarction+vascular death	...	+
66	8	32	16.2	9.9	Stroke+all death		+
71	...	15	7.4	2.1	Ischaemic stroke+systemic embolism		+
51	...	36	5.1	...	Ischaemic stroke+TIA+systemic embolism+pulmonary embolism+fatal MI	...	+
72	...	23	1.9	3.9	Ischaemic stroke+myocardial infarction or vascular death	+	+
58	...	24	15.1	2.7	Stroke	...	+
63	...	12	3.6	0.6	Non fatal stroke+non fatal MI+vascular death from any other cause	...	+
100	...	...	2.0	8.4	Coronary death+fatal and non fatal MI	+	+
70	...	3	6.0	2.5	Stroke+MI+death	+	+
66		30	10.6	...	Vascular death+non fatal ischaemic stroke+non fatal MI	+	0
...	...	24	9.48	0.9	Recurrent stroke+MI or vascular death	...	0
0	...	121	1.3	0.9	Non fatal MI+non fatal stroke+death from cardiovascular caues	...	0
100	...	36	...	2.6	Death	...	+
100	...	66	...	2.1	...	...	0
50	...	60	1.5	2.3	Sudden cardiac death+fatal MI+Non fatal MI+CVA	...	0
...	...	60	1.3	2.7	Stroke	...	+

(*Continued*)

Table I. Continued

Intervention	Trial	Year	Subjects-Prevention Stage	Active Group	Control Group	Subjects (Active/Control)	Age (Years)
	HEP[35]	1986	Hypertension (old)	Atenalol/ Bendrofluazide	Control	348/377	69
	SHEP[36]	1991	hypertension:2 (systolic)	Active treatment	Placebo	2365/2371	72
	MRC old[37]	1992	Hypertension (old)	Diuretic	Placebo	1081/2213	70
	MRC old[37]	1992	Hypertension (old)	Beta blocker	Placebo	1102/2213	70
	PATS[38]	1995	Hypertension+post stroke/TIA:2	Indapamide	Placebo	2841/2824	60
	Syst China[39]	1998	Hypertension (systolic)	Active treatment	Placebo	1253/1141	67
	UKPDS 38[40]	1998	Diabetes	Tight	Less tight	758/390	56
	ABCD[41]	1998	Hypertension	Nisoldipine	Enalapril	235/235	58
	UKPDS-39[42]	1998	Type 2 diabetes	Captopril	Atenolol	400/358	56
	CAPPP[43]	1999	Hypertension:2	Captopril	Conventional treatment	5492/5493	52
	NICH-EH[44]	1999	Elderly hypertension:1	Nicardipine	Trichlormethiazide	204/210	70
	Syst-Eur[45]	1999	Hypertension (systolic)	Active treatment	Placebo	2398/2297	70
	STOP-HT[46]	1999	Hypertension:2	ACE inhibitors	Conventional drugs	2205/2213	76
	STOP-HT[46]	1999	Hypertension:2	Calcium antagonists	Conventional drugs	2196/2213	76
	HOPE[47]	2000	Having cardiovascular risk factors:2	Ramipril	Placebo	4645/4652	66
	INSIGHT[48]	2000	Hypertension	Nifedipine	Co-amilozide	3157/3164	65
	NORDIL[49]	2000	Hypertension	Diltiazem	Diuretics+beta blocker	5410/5471	60
	MacMahon[50]	2000	Post MI, TIA, PVD	Ramipril	Placebo	308/309	61
	PROGRESS[51]	2001	Hypertension, post stroke/TIA:2	Perindopril+ Indapamide	Placebo	3051/3054	64
	OPTIMAL[52]	2002	Post MI:2	Losartan	Captopril	2744/2733	67
	ANBP2[53]	2003	Hypertension (old)	Enalapril	Hydrochlorothiazide	3044/3039	80
	DIABHYCAR[54]	2004	Type 2 diabetes	Ramipril	Placebo	2443/2469	65
	SCOPE[55]	2004	Hypertension (old, systolic)	Candesartan	Control	754/764	77
Statins	4S[56]	1994	Patients with coronary heart disease;2	Simvastatin	Placebo	2221/2223	...
	KAPS[57]	1995	Atherosclerosis:1	Pravastatin	Placebo	212/212	57
	REGRESS[58]	1995	Coronary atherosclerosis:2	Pravastatin	Placebo	450/434	56
	WOSCOPS[59]	1995	Coronary heart disease:2	Pravastatin	Placebo	3302/3293	55
	CARE[60]	1996	Post MI:2	Pravastatin	Placebo	2081/2078	59
	Post CABG[61]	1997	Coronary heart disease:2	Aggressive treatment	Moderate treatment	676/675	62
	LIPID[62]	1998	Coronary heart disease:2	Pravastatin	Placebo	4512/4502	62
	BIP[63]	2000	Coronary heart disease:2	Bezafibrate	Placebo	1548/1542	60
	GISSIP-P[64]	2000	Coronary heart disease:2	Pravastatin	Control	2138/2133	...
	SCAT[65]	2000	Coronary heart disease:2	Simvastatin	Placebo	230/230	61
	MIRACL[66]	2001	Coronary heart disease:2	Atorvastatin	Placebo	1538/1548	65
	HPS[67]	2002	CHD (stroke):2	Simvastatin	Placebo	10 269/10 267	64
	PROSPER[68]	2002	Elderly with risk factors for cardiovascular disease	Pravastatin	Placebo	2891/2913	75
	ALLHAT-LLT[69]	2002	Coronary heart disease:2	Pravastatin	Control	5170/5185	66
	ALERT[70]	2003	Renal transplant	Fluvastatin	Placebo	1050/1052	50
	CARDS[71]	2004	Type 2 diabetes:1	Atorvastatin	Placebo	1428/1410	...

(*Continued*)

Table I. Continued

Male (%)	Time From Event (Weeks)	Follow-Up (Months)	Control Stroke Rate (%)	Control MI Rate (%)	Primary Outcome	ICH as Part	Trial Result
31	...	53	10.3	10.1	MI+stroke+TIA	...	+
43	...	54	6.9	4.2	Non fatal stroke+fatal stroke	...	+
42	...	70	6.1	7.2	Stroke+coronary events+death from all causes	...	+
42	...	70	6.1	7.2	Stroke+coronary events+death from all causes	...	0
72	...	24	7.7	...	Fatal stroke+non fatal stroke	...	+
64	...	36	5.3	0.6	Fatal stroke+non fatal stroke	...	+
55	...	101	9.5	18.2	Diabetes death or complications	...	+
67	...	67	3.0	2.1	MI	...	...
54	...	...	4.7	12.6	Fatal and non fatal related to diabetes+diabetes death+all cause mortality	...	0
53	...	73	2.7	2.9	Fatal MI+non fatal MI+stroke+other cardiovascular deaths	...	0
33	...	60	3.8	1.0	...	+	0
...	...	24	3.5	...	Stroke	...	+
33	...	...	10.7	6.9	Fatal stroke+fatal MI+other fatal cardiovascular disease	...	0
33	...	...	10.7	6.9	Fatal stroke+fatal MI+other fatal cardiovascular disease	...	0
73	...	60	4.8	12.2	MI+stroke+death from cardiovascular causes	...	+
46	...	51	2.3	1.9	Cardiovascular death+MI+heart failure+stroke	...	0
51	...	54	3.6	2.9	Fatal and non fatal stroke+MI+other cardiovascular death	...	0
82	...	56	...	10.7	Carotid atherosclerosis+left ventricular mass	...	0
70	...	47	14.0	...	Total stroke (fatal or non fatal)	+	+
71	...	32	4.8	13.8	All cause mortality	...	0
49	...	49	3.6	2.7	All cardiovascular events+death from any cause	...	+
70	...	48	4.7	3.2	Cardiovascular death+non fatal acute MI+Stroke+heart failure+end stage renal failure	...	0
36	...	43	4.6	3.5	Cardiovascular death+non fatal MI+nonfatal stroke	...	+
81	...	65	2.5	19.9	Total mortality	+	+
100	...	36	1.9	3.8	Rate of carotid atherosclerotic progression	...	+
100	...	24	...	2.9	Change in average MSD+MOD per patient	...	+
...	...	59	...	7.8	Non fatal MI+death from CHD	...	+
86	...	60	...	9.9	Fatal coronary event+non fatal MI	...	+
92	...	52	2.2	5.9	Rate of progression of atherosclerosis in the graft	...	+
83	...	73	4.5	10.2	Mortality from coronary heart disease	...	+
91	...	74	4.9	12.3	Fatal or non fatal MI+sudden death	...	0
86	...	24	0.9	2.4	Total mortality+non fatal MI+stroke	...	+
89	...	48	3.0	4.3	Death+MI+stroke+revascularisation	...	
65	...	16	1.6	...	Death+non fatal MI	...	+
75	...	...	6.0	12.5	Death	+	+
48	...	38	4.6	12.9	Death from coronary heart disease+non fatal MI+fatal or non fatal stroke	...	+
51	...	58	4.5	8.1	All cause mortality	...	...
66	...	61	5.9	11.4	Cardiac death+non fatal MI+coronary intervention	...	0
...	...	47	2.5	4.3	Acute coronary heart disease+coronary revascularisation+stroke	...	+

(*Continued*)

Table I. Continued

Intervention	Trial	Year	Subjects-Prevention Stage	Active Group	Control Group	Subjects (Active/Control)	Age (Years)
	SPARCL[72]	2006	Post TIA/stroke:2	Atorvastatin	Placebo	2365/2366	63
Surgery	NASCET[73]	1991	Post stroke:2	CEA	Medical	328/331	66
	VACS[74]	1993	Asymptomatic carotid stenosis	Surgical treatment	Medical treatment	211/233	64
	ACAS[75]	1995	Asymptomatic carotid stenosis	Immediate surgery	Deferred surgery	825/834	67
	ACST[76]	2004	Asymptomatic carotid stenosis	Immediate surgery	Deferred surgery	1560/1560	68
HRT	ERA[77]	2000	Coronary heart disease:2	HRT	Placebo	204/105	66
	WEST[78]	2001	Post stroke, TIA:2	Estradiol	Placebo	337/327	71
	Clarke[79]	2002	Coronary heart disease:2	HRT	Control	134/121	67
	WHI-EP[80]	2003	Post menopausal women:1	Estrogen+Progestin	Placebo	8506/8102	63

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Table I. Continued

Male (%)	Time From Event (Weeks)	Follow-Up (Months)	Control Stroke Rate (%)	Control MI Rate (%)	Primary Outcome	ICH as Part	Trial Result
...	...	59	13.5	...	Fatal stroke+non fatal stroke	+	+
69	4	33	19.3	...	Ipsilateral stroke		+
100	4	48	9.4	...	TIA+transient monoccular blindness stroke+death	...	+
66	...	32	10.3	...	Ipsilataral stroke+perioprative stroke or death	+	+
66	...	40	8.4	...	Stroke	+	+
0	...	38	...	7.6	Mean minimal coronary artery diameter	...	0
0	...	34	17.1	5.2	Death+non fatal stroke+TIA+non fatal MI	+	...
0	...	31	...	4.1	Unstable angina+MI+cardiac death	...	0
0	...	67	1.3	...	Stroke	+	...

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Table II. Excluded Trials

Trial		Year	Patient Group	n	Reason for Exclusion
BP lowering	VACSG[1]	1967	Male hypertensive patients	143	Relevant outcome data not available
	Co-op RCT[2]	1973	Patients with diastolic BP 100–120	58	Relevant outcome data not available
	Sprackling[3]	1981	Elderly hypertensive patients	123	Relevant outcome data not available
	EWPHE[4]	1985	Elderly hypertensive patients	840	Relevant data not available
	Wikstrand[5]	1986	Elderly hypertensive patients	562	Relevant data not given
	BBB[6]	1988	Hypertension	2127	Neutral
	TOMHS[7]	1993	Patients with hypertension aged 45 to 69 years	902	Neutral
	ASIST[8]	1994	Patients with coronary artery disease	306	Relevant outcome data not available
	CIBIS[9]	1994	Patients with chronic heart failure	641	Relevant outcome data not available
	HYCAR[10]	1995	Patients with hypertension and LVH	115	Relevant outcome data not available
	GLANT[11]	1995	Patients with mild to moderate essential hypertension	1936	Neutral
	STONE[12]	1996	Patients with hypertension	1632	Relevant data not given
	MIDAS[13]	1996	Patients with hypertension	883	Relevant data not given
	ACCT[14]	1996	Patients with essential hypertension	1084	Relevant outcome data not available
	ELITE[15]	1997	Patients aged 65 or more with heart failure	722	Relevant outcome data not available
	VHAS[16]	1997	Patients with hypertension	1414	Relevant outcome data not available
	LOA[17]	1997	Patients with hypertension	898	Relevant outcome data not available
	AIREX[18]	1997	Patients with heart failure after MI	603	Relevant outcome data not available
	VHAS[19]	1998	Patients with hypertension	456	Relevant outcome data not available
	FACET[20]	1999	Patients with hypertension and NIDDM	380	Relevant data not given
	HOT[21]	1998	Patients with hypertension	18 790	Neutral
	Tuomilehto[22]	1999	Older patients with diabetes and systolic hypertension	4695	Relevant outcome data not available
	ALLHAT[23]	2000	Patients with hypertension 55 years or older	33 357	Relevant outcome data not available
	PREVENT[24]	2000	Patients with coronary atherosclerosis	825	Relevant outcome data not available
	ATIME[25]	2000	Patients with hypertension	2935	Relevant outcome data not available
	CALM[26]	2000	Patients with type 2 diabetes having hypertension and microalbuminurea	197	Relevant data not given
	ELITE-2[27]	2001	Patients with symptomatic heart failure	3152	Relevant outcome data not available
	CONVINCE[28]	2001	Patients with hypertension	16 602	Relevant outcome data not available
	CAPRICON[29]	2001	Patients had MI	1959	Relevant data not available
	CASTLE[30]	2001	Patients with mild hypertension	251	Relevant data not available
	AASK[31]	2002	Patients 18–70 years with hypertensive renal disease.	1094	Relevant outcome data not available
	LIFE[32]	2002	Patients with essential HT and LVH ascertained by ECG	9193	Relevant outcome data not available
	ELSA[33]	2002	Patients with hypertension	2334	Relevant outcome data not available
	EUROPA[34]	2003	Patients with previous MI, coronary revascularisation, angiographic evidence of CAD or positive stress test	18 328	Relevant outcome data not available
	CHARM-preserved[35]	2003	Patients had NYHA class 11-1V CHF and LVEF >40%	3023	Relevant outcome data not available
	CHARM-alternative[36]	2003	Patients with symptomatic heart failure(NYHA class 11-1V), LVEF 40% or less and intolerance to ACEIs	2028	Relevant outcome data not available
	CHARM-added[37]	2003	Patients had NYHA class 11-1V, LVEF 40% or less and being treated with ACEIs	2548	Relevant outcome data not available
	NICOLE[38]	2003	Patients who has undergone successful coronary angioplasty	826	Relevant data not given
	E-COST[39]	2003	Patients with essential hypertension	2048	Relevant outcome data not available
	SHELL[40]	2003	Elderly patients with isolated systolic hypertension	1882	Neutral
	Berl[41]	2003	Patients with diabetic nephropathy and hypertension	1715	Relevant outcome data not available
	CAMELOT[42]	2004	Patients with coronary artery disease and normal blood pressure	1991	Relevant outcome data not available
	JMIC-B[43]	2004	Patients with hypertension and coronary artery disease	1650	Relevant outcome data not available
	PEACE[44]	2004	Patients with stable coronary artery disease having normal or reduced LV function	8290	Relevant outcome data not available

(*Continued*)

Table II. Continued

Trial		Year	Patient Group	n	Reason for Exclusion
	VALUE[45]	2006	Patients with hypertension and high cardiovascular risk	15 245	Relevant outcome data not available
	ACTION[46]	2004	Patients with treated stable symptomatic coronary disease	3825	Relevant outcome data not available
	ASCOT-BPLA[47]	2005	Hypertension	19 257	Relevant data not given
	ADVANCE[48]	2005	Hypertension	11 140	Relevant data not given
	MOSES[49]	2005	Hypertensive stroke patients	1405	Relevant data not given
	Gradman[50]	2005	Patients with hypertension	652	Relevant data not given
	Hermida[51]	2005	Patients with essential hypertension	200	Relevant data not given
	Stokes[52]	2005	Patients with systolic hypertension	16	Relevant outcome data not available
	Ernst[53]	2006	Untreated hypertensive patients	30	Relevant data not given
	Kushiro[54]	2006	Patients with hypertension		Relevant data not given
HRT	Marmorston[55]	1962	Previous cerebrovascular disease	200	Relevant outcome data not available
	VACS[56]	1966	Males with atherosclerotic myocardial infarction and cerebral infarction	582	Relevant data not given
	McDowell[57]	1967	Post-menopausal women with non embolic cerebral infarction	176	Relevant data not given
	Nachtigall[58]	1979	Post-menopausal women 2 or more years after menopause	329	Relevant data not given
	Hall[59]	1994	Post menopausal women with rheumatoid arthritis	200	Relevant data not given
	PEPI[60]	1995	Post-menopausal women age 45 to 64	875	Relevant data not given
	Hall[61]	1998	Post-menopausal women with coronary heart disease	60	Relevant data not given
	Hulley[62]	1998	Post menopausal women with established coronary heart disease	2763	Relevant outcome data not available
	Mijatovic[63]	1998	Post menopausal women	52	Relevant data not given
	HERS[64]	1998	Post-menopausal women with established coronary heart disease	2763	Relevant outcome data not available
	Ravn[65]	1999	Post menopausal women 45 to 59 years of age	1609	Relevant outcome data not given
	Recker[66]	1999	Women older than 65 years and having low bone mass	128	Relevant outcome data not available
	Komulainen[67]	1999	Non osteoprotic early post menopausal women	464	Relevant outcome data not available
	MORE[68]	1999	Osteoporotic post-menopausal women	7705	Relevant outcome data not available
	Mulnard[69]	2000	Women with mild to moderate AD, MMSE 12–28 and had a hysterectomy	120	Relevant outcome data not available
	EWA[70]	2000	Post-menopausal women with angiographically verified coronary heart disease	118	Relevant data not given
	EVTET[71]	2000	Post-menopausal women who suffered previous DVT or PE	140	Relevant data not given
	Mosekilde[72]	2000	Post menopausal women	2016	Relevant outcome data not available
	Gallagher[73]	2001	Post menopausal women with normal bone density	489	Relevant outcome data not available
	PHOREA[74]	2001	Post-menopausal women	264	Relevant outcome data not available
	Binder[75]	2001	Post-menopausal women 75 years of age or older	59	Relevant data not given
	EPAT[76]	2001	Post menopausal women without pre-existing cardiovascular disease	222	Relevant outcome data not available
	WAVE[77]	2002	Post-menopausal women with coronary stenosis	423	Relevant outcome data not available
	ESPRIT[78]	2002	Post-menopausal women survived first MI	1017	Relevant outcome data not available
	Giske[79]	2002	Apparently healthy peri and post menopausal women	166	Relevant outcome data not given
	Arrenbrecht[80]	2002	Non osteoporotic post menopausal volunteers	160	Relevant outcome data not given
	Haines[81]	2003	Post menopausal Chinese women	152	Relevant outcome data not available
	HABITS[82]	2004	Female patients with previous breast cancer	434	Relevant outcome data not available
Anticoagulants	Olsson[83]	1980	Patients who had TIA or RIND	156	Neutral
	CAFA[84]	1991	Patients with chronic atrial fibrillation	378	Relevant outcome data not available
	EAFT[85]	1995	Patients with non rheumatic AF and recent minor IS	214	Relevant outcome data not available
	SPRIT[86]	1997	Patients after cerebral ischaemia of presumed arterial origin	1316	Relevant outcome data not available
	CARS[87]	1997	Patients who had MI	8803	Neutral
	Hellemons[88]	1999	Atrial fibrillation	729	Neutral

(*Continued*)

Table II. Continued

Trial		Year	Patient Group	n	Reason for Exclusion
	AFASAK 2[89]	1999	Patients with non valvular chronic atrial fibrillation	677	Neutral
	HEAST[90]	2000	Atrial fibrillation	449	Relevant outcome data not available
	Yamaguchi[91]	2000	Atrial fibrillation		Relevant outcome data not available
	WARSS[92]	2001	Patients had noncardioembolic IS within previous 30 days	2206	Relevant outcome data not available
	ASPECT 2[93]	2002	Patients with ischaemic heart disease	661	Relevant outcome data not available
	SPINAF[94]	2005	Patients with non rheumatic atrial fibrillation	525	Relevant data not given
	WASID[95]	2005	Patients had TIA or stroke	569	Neutral
	SPORTIF[96]	2005	Patients with nonvalvular atrial fibrillation	3922	Neutral
Antiplatelets	Elwood[97]	1974	Male patients who had recent MI	1239	Relevant outcome data not available
	AITIA[98]	1977	Patients who had carotid TIAs	178	Relevant outcome data not available
	Vogel[99]	1979	Patients with previous MI	1340	Relevant outcome data not available
	Elwood[100]	1979	Patients had confirmed MI	1682	Relevant data not given
	ART[101]	1980	Patients with previous MI	1558	Relevant outcome data not available
	CDPA[102]	1980	Patients with previous MI	2915	Relevant outcome data not available
	PARIS-1[103]	1980	Patients with previous MI	2026	Relevant outcome data not available
	PARIS-2[104]	1986	Patients recovered from MI 4wks to 4 month previously	3128	Relevant outcome data not available
	Boysen[105]	1988	Patients after carotid endarterctomy	301	Neutral
	Hass[106]	1989	Patients had previous TIA, amaurosis fugax, RIND or minor stroke	3069	Relevant outcome data not available
	CATS[107]	1989	Patients with previous thromboembolic stroke	1072	Relevant outcome data not available
	Dutch TIA[108]	1991	Patients had TIA or minor ischaemic stoke	3131	Relevant outcome data not available
	PACE pilot[109]	1994	Elderly patients without a pre-existing clinical history of cardiovascular disease	400	No outcome data available
	EPIC[110]	1995	Patients with coronary artery disease	2099	Relevant outcome data not available
	Kereiakes[111]	1998			
	ESPS 1[112]	1998	Patients with recent stroke, TIA or RIND	1306	Relevant outcome data not available
	EXCITE[113]	2000	Patients with angiographic evidence of clinically significant coronary artery disease	7232	Neutral
	APLAUD[114]	2000	Patients with recent cardiovascular or cerebrovascular event	451	Relevant outcome data not available
	TACIP[115]	2003	Patients who suffered from TIA or non disabling stroke	2113	Neutral
	ESPRIT[116]	2003	Patients with recent cerebral ischaemia of arterial origin	591	Relevant outcome data not available
	TAPIRSS[117]	2004	Patients with previous cerebrovascular event	431	Neutral
	MATCH[118]	2004	Patients with recent ischaemic stroke or TIA	7599	Neutral
	PLUTO-Stroke[119]	2005	Patients after ischaemic stroke	70	Relevant outcome data not available
	CARESS[120]	2005	Patients with symptomatic carotid stenosis	107	Relevant outcome data not available
	CHARISMA[121]	2006	Patients with clinically evident cardiovascular disease	15 603	Neutral
Statins	ACAPS[122]	1994	Patients with moderately elevated cholesterol levels and free of symptomatic cardiovascular disease	1953	Relevant outcome data not available
	CCAIT[123]	1994	Patients with diffuse coronary atherosclerosis	331	Relevant data not given
	Weintraub[124]	1994	Patients with coronary artery disease	404	Relevant outcome data not available
	Shepherd[125]	1995	Male patients with hypercholestrolemia	6595	Relevant outcome data not available
	CCAIT[126]	1996	Patients with coronary atherosclerosis	331	Relevant outcome data not available
	PLAC 1[127]	1995	Patients with coronary artery disease	408	Relevant outcome data not available
	CIS[128]	1997	Male patients with coronary artery disease and hypercholesterolemia	254	Relevant outcome data not available
	AFCAPS/TexCAPS[129]	1998	Patients with average TC and LDL-C and below average HDL-C	6605	Relevant outcome data not available
	Riegger[130]	1999	Patients with symptomatic coronary heart disease and hyperlipidaemia	365	Relevant outcome data not available
	Brown[131]	2001	Patients with coronary artery disease and low HDL cholesterol levels	160	Relevant outcome data not available

(*Continued*)

Table II. Continued

Trial		Year	Patient Group	n	Reason for Exclusion
	DIAS[132]	1996	Patients with type 2 diabetes and atherosclerosis	731	Relevant outcome data not available
	LIPIS[133]	2002	Patients underwent their first PCI	1677	Relevant outcome data not available
	ASCOT-LLA[134]	2003	Patients with hypertension	10 305	Relevant outcome data not available
Surgery	Eikelboom[135]	1988	Patients undergoing CEA	129	Relevant data not available
	Clagett[136]	1989	Patients undergoing CEA	152	Relevant data not available
	Lord[137]	1989	Patients undergoing CEA	140	Relevant outcome data not available
	CASANOVA[138]	1991	Patients with carotid stenosis	410	Neutral
	Shah[139]	1994	Patients undergoing CEA	873	Relevant data not available
	Katz[140]	1994	Patients undergoing CEA	100	Relevant data not available
	Myers[141]	1994	Patients undergoing CEA	136	Relevant data not available
	Rockman[142]	1996	Patients undergoing CEA	3975	Relevant data not available
	AbuRahama[143]	1997	Patients undergoing CEA	399	Relevant outcome data not available
	Fiorani[144]	1997	Patients with carotid stenosis	1020	Relevant data not available
	ECST[145]	1998	Patients with carotid stenosis	3018	Relevant outcome data not available
	Stoughton[146]	1998	Patients with carotid stenosis	208	Relevant outcome data not available
	Sbarigia[147]	1999	Patients with carotid stenosis	107	Relevant outcome data not available
	McCarthy[148]	2002	Patients with carotid stenosis	240	Neutral
	CAVATAS[149]	2001	Patients with carotid stenosis	504	Neutral
	Yadav[150]	2004	Patients undergoing CEA	334	Relevant outcome data not available

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Table III. Odds Ratios for Example Trials for Different Outcome Levels

A. Stroke, 3 Levels: Fatal Stroke/Nonfatal Stroke/No Stroke

	Odds Ratio (95% Confidence Intervals)		
Trial	Overall	Fatal Versus Alive	Stroke Versus No Stroke
HPS	0.736 (0.651–0.833)	0.805 (0.614–1.054)	0.736 (0.650–0.832)
ESPS 2	0.740 (0.594–0.921)	0.999 (0.536–1.864)	0.737 (0.591–0.918)
PROGRESS	0.710 (0.608–0.828)	0.839 (0.555–1.268)	0.708 (0.606–0.826)
HOPE	0.678 (0.551–0.835)	0.385 (0.219–0.674)	0.681 (0.553–0.838)
MRC mild	0.545 (0.397–0.747)	0.662 (0.365–1.204)	0.544 (0.397–0.747)

B. Stroke, 4 Levels: Fatal Stroke/Nonfatal Severe Stroke/Mild Stroke/No Stroke

	Odds Ratio (95% Confidence Intervals)			
Trial	Overall	Fatal Versus Alive	Severe Versus Mild	Mild Versus No Stroke
HPS	0.735 (0.642–0.842)	0.804 (0.614–1.053)	0.808 (0.645–1.013)	0.734 (0.641–0.841)
SPAF 1	0.550 (0.326–0.927)	1.546 (0.257–9.291)	0.737 (0.358–1.519)	0.545 (0.323–0.918)
SALT	0.798 (0.591–1.077)	1.425 (0.629–3.232)	0.814 (0.514–1.289)	0.793 (0.587–1.071)
HEP	0.521 (0.298–0.912)	0.281 (0.092–0.854)	0.409 (0.186–0.896)	0.528 (0.302–0.925)
NASCET	0.473 (0.302–0.789)	0.400 (0.077–2.077)	0.327 (0.157–0.683)	0.482 (0.308–0.755)

C. Stroke, 4 Levels: Fatal/Nonfatal/TIA/No Stroke

	Odds Ratio (95% Confidence Intervals)			
Trial	Overall	Fatal Versus alive	Stroke Versus TIA	TIA Versus No stroke
SPARCL	0.764 (0.663–0.881)	0.581 (0.350–0.965)	0.824 (0.694–0.980)	0.759 (0.658–0.875)
SPAF 1	0.539 (0.340–0.854)	1.546 (0.257–9.291)	0.545 (0.323–0.918)	0.536 (0.338–0.850)
ESPS 2	0.553 (0.472–0.647)	0.907 (0.493–1.669)	0.588 (0.476–0.728)	0.545 (0.465–0.640)
Ridker	0.804 (0.705–0.918)	1.046 (0.583–1.877)	0.829 (0.693–0.992)	0.804 (0.704–0.917)
HEP	0.529 (0.312–0.895)	0.281 (0.092–0.854)	0.528 (0.302–0.925)	0.536 (0.316–0.907)

D. Stroke 5-level: fatal stroke/severe/mild/TIA/no stroke

	Odds Ratio (95% Confidence Intervals)				
Trial	Overall	Fatal Versus Alive	Severe Versus Mild	Mild Versus TIA	TIA Versus No Stroke
ASPECT	0.598 (0.397–0.899)	1.381 (0.554–3.441)	0.665 (0.365–1.211)	0.625 (0.410–0.954)	0.596 (0.396–0.896)
SPAF 3	2.676 (1.705–4.201)	5.058 (0.589–43.444)	2.790 (1.163–6.694)	3.605 (1.959–6.633)	2.644 (1.684–4.152)
HEP	0.528 (0.312–0.894)	0.281 (0.092–0.854)	0.409 (0.186–0.896)	0.528 (0.302–0.925)	0.536 (0.316–0.907)

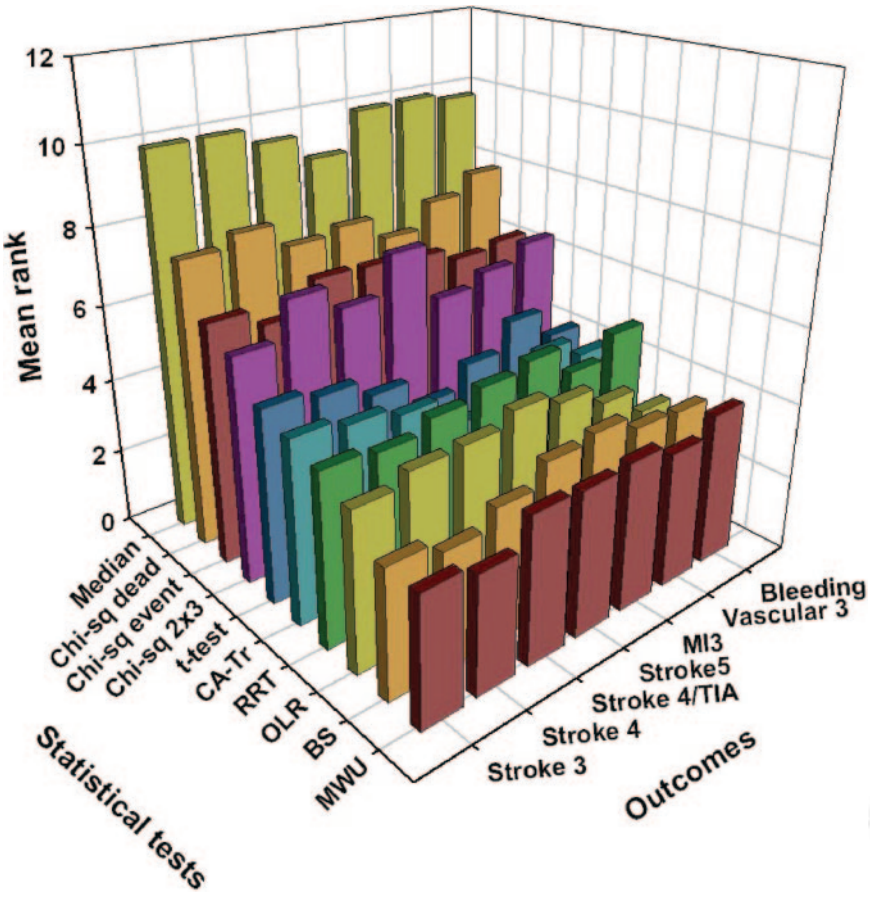

Figure I. Ordering of statistical tests for stroke (3, 4 and 5-level), myocardial infarction (3-level), vascular events (3-level) and bleeding (3-level). Ordinal tests (Mann–Whitney *U* test, ordinal logistic regression) were superior (lower rank) to dichotomous tests.