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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<sup>2</sup> and 3.4% in Perindopril protection against recurrent stroke study (PROGRESS) in 2001.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> However, the use of composite outcomes has been criticized.<sup>6</sup> 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.<sup>7</sup> 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.<sup>7</sup> 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,<sup>8</sup> 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.<sup>9–14</sup> 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, un-pooled *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

**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 <i>U</i> test              | 3.32      | [Band 1] |
| Bootstrap (difference in mean rank)     | 3.32      |          |
| Ordinal logistic regression             | 4.12      | [Band 2] |
| Robust ranks test                       | 4.51      |          |
| Cochran-Armitage trend test             | 4.80      | [Band 3] |
| <i>t</i> -test                          | 5.08      |          |
| Pearson's Chi Sq – 2x3 test             | 5.94      | [Band 4] |
| Pearson's Chi Sq – stroke vs. no stroke | 6.37      |          |
| Pearson's Chi Sq – death vs. alive      | 7.58      | [Band 5] |
| Median test                             | 9.97      | [Band 6] |

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  $P<0.01$ .

adjustment for ties<sup>15</sup>; 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.

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)**

| Outcome  | Trials | P Value | Ranking of Tests Relative to Each Other |          |          |          |          |          |              |                |               |             |
|--|--------|---------|---|----------|----------|----------|----------|----------|--------------|----------------|---------------|-------------|
|  |        |         | MWU                                     | BS       | OLR      | RRT      | CAT      | t Test   | $\chi^2$ 2x3 | $\chi^2$ Event | $\chi^2$ Dead | Median Test |
| Fatal stroke/nonfatal stroke/no stroke                         | 85     | <0.0001 | <u>1</u>                                | <u>2</u> | <u>3</u> | 4        | 5        | 6        | 7            | 8              | 9             | 10          |
| Fatal stroke/severe nonfatal/mild/no stroke                    | 21     | <0.0001 | <u>2</u>                                | <u>1</u> | 4        | 3        | 5        | 6        | 8            | 7              | 9             | 10          |
| Fatal stroke/nonfatal stroke/TIA/no stroke                     | 29     | <0.0001 | <u>2</u>                                | <u>1</u> | <u>5</u> | <u>6</u> | <u>3</u> | <u>4</u> | 7            | 8              | 9             | 10          |
| Fatal stroke/severe nonfatal stroke/mild stroke/TIA/no stroke  | 11     | <0.0001 | <u>3</u>                                | <u>4</u> | <u>5</u> | <u>6</u> | <u>1</u> | <u>2</u> | 8            | 7              | 9             | 10          |
| Fatal MI/nonfatal MI/no MI                                     | 58     | <0.0001 | <u>1</u>                                | <u>3</u> | <u>5</u> | 6        | <u>2</u> | <u>4</u> | 7            | 8              | 9             | 10          |
| Fatal vascular event/nonfatal vascular event/no vascular event | 43     | <0.0001 | <u>1</u>                                | <u>2</u> | <u>3</u> | <u>4</u> | 5        | 6        | 7            | 8              | 9             | 10          |
| Severe-major bleeding/minor bleeding/no bleeding               | 15     | <0.0001 | <u>3</u>                                | <u>2</u> | <u>1</u> | 6        | <u>4</u> | <u>5</u> | 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

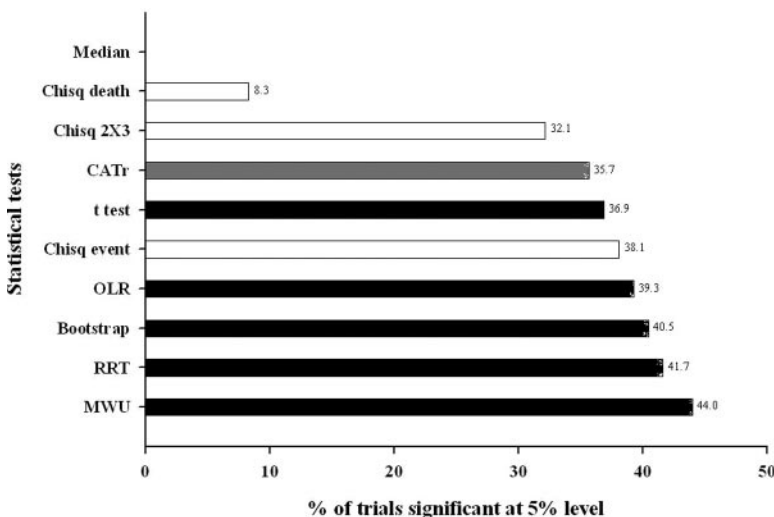
gave a statistically significant result in 44% of trials in comparison with the Pearson’s  $\chi^2$  2x3 test at 32% (Figure 1).

**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**

| Outcome  | Trials | P Value | Ranking of Tests Relative to Each Other |          |          |          |          |          |              |                |               |             |
|--|--------|---------|---|----------|----------|----------|----------|----------|--------------|----------------|---------------|-------------|
|  |        |         | MWU                                     | BS       | OLR      | RRT      | CAT      | t Test   | $\chi^2$ 2×3 | $\chi^2$ Event | $\chi^2$ Dead | Median Test |
| Prevention, primary                                | 29     | <0.0001 | <u>1</u>                                | <u>2</u> | 5        | <u>3</u> | 6        | 4        | 7            | 8              | 9             | 10          |
| Prevention, secondary                              | 56     | <0.0001 | <u>2</u>                                | <u>1</u> | <u>3</u> | 4        | 5        | 6        | 7            | 8              | 9             | 10          |
| Anticoagulants                                     | 12     | <0.0001 | <u>2</u>                                | <u>1</u> | <u>7</u> | <u>6</u> | <u>4</u> | <u>3</u> | <u>5</u>     | 8              | 9             | 10          |
| Antiplatelets                                      | 33     | <0.0001 | <u>1</u>                                | <u>2</u> | <u>3</u> | 5        | <u>4</u> | 6        | 7            | 8              | 9             | 10          |
| Antihypertensives                                  | 23     | <0.0001 | <u>2</u>                                | <u>1</u> | <u>3</u> | 4        | 5        | 6        | 7            | 8              | 9             | 10          |
| Lipid lowering                                     | 10     | <0.0001 | <u>2</u>                                | <u>1</u> | <u>3</u> | <u>4</u> | <u>5</u> | 6        | 8            | 7              | 9             | 10          |
| Carotid endarterectomy                             | 4      | <0.0001 | <u>2</u>                                | <u>1</u> | <u>5</u> | <u>3</u> | 6        | <u>4</u> | 8            | 7              | 9             | 10          |
| Hormone replacement therapy                        | 2      | 0.86    | ...                                     | ...      | ...      | ...      | ...      | ...      | ...          | ...            | ...           | ...         |
| Age <65 years                                      | 34     | <0.0001 | <u>1</u>                                | <u>2</u> | <u>3</u> | 4        | 5        | 6        | 7            | 8              | 9             | 10          |
| Age >65 years                                      | 31     | <0.0001 | <u>2</u>                                | <u>1</u> | 4        | 3        | 6        | 5        | 7            | 8              | 9             | 10          |
| Trial, small (n<2,520)                             | 42     | <0.0001 | <u>1</u>                                | <u>2</u> | 5        | 6        | <u>3</u> | <u>4</u> | 7            | 8              | 9             | 10          |
| Trials, large (n>2,520)                            | 42     | <0.0001 | <u>2</u>                                | <u>1</u> | <u>3</u> | <u>4</u> | 5        | 6        | 8            | 7              | 9             | 10          |
| Follow-up, short term (<36 months)                 | 45     | <0.0001 | <u>1</u>                                | <u>2</u> | 4        | 5        | 3        | 6        | 7            | 8              | 9             | 10          |
| Follow-up, long term (>36 months)                  | 39     | <0.0001 | <u>2</u>                                | <u>1</u> | <u>3</u> | <u>4</u> | 5        | 6        | 7            | 8              | 9             | 10          |
| Risk of death in control, low (<0.2% per month)    | 43     | <0.0001 | <u>1</u>                                | <u>2</u> | <u>3</u> | 4        | 5        | 6        | 7            | 8              | 9             | 10          |
| Risk of death in control, high (>0.2% per month)   | 41     | <0.0001 | <u>2</u>                                | <u>1</u> | 3        | 4        | 5        | 6        | 7            | 8              | 9             | 10          |
| Risk of stroke in control, low (<0.17% per month)  | 40     | <0.0001 | <u>1</u>                                | <u>2</u> | <u>3</u> | 4        | 5        | 6        | 7            | 8              | 9             | 10          |
| Risk of stroke in control, high (>0.17% per month) | 41     | <0.0001 | <u>2</u>                                | <u>1</u> | 5        | 6        | 3        | 4        | 7            | 8              | 9             | 10          |
| Time from index event, short (<87 days)            | 22     | <0.0001 | <u>1</u>                                | <u>2</u> | <u>3</u> | 4        | 5        | 6        | 8            | 7              | 9             | 10          |
| Time from index event, long (>87 days)             | 22     | <0.0001 | <u>2</u>                                | <u>1</u> | <u>3</u> | 6        | <u>4</u> | <u>5</u> | 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.<sup>16</sup>

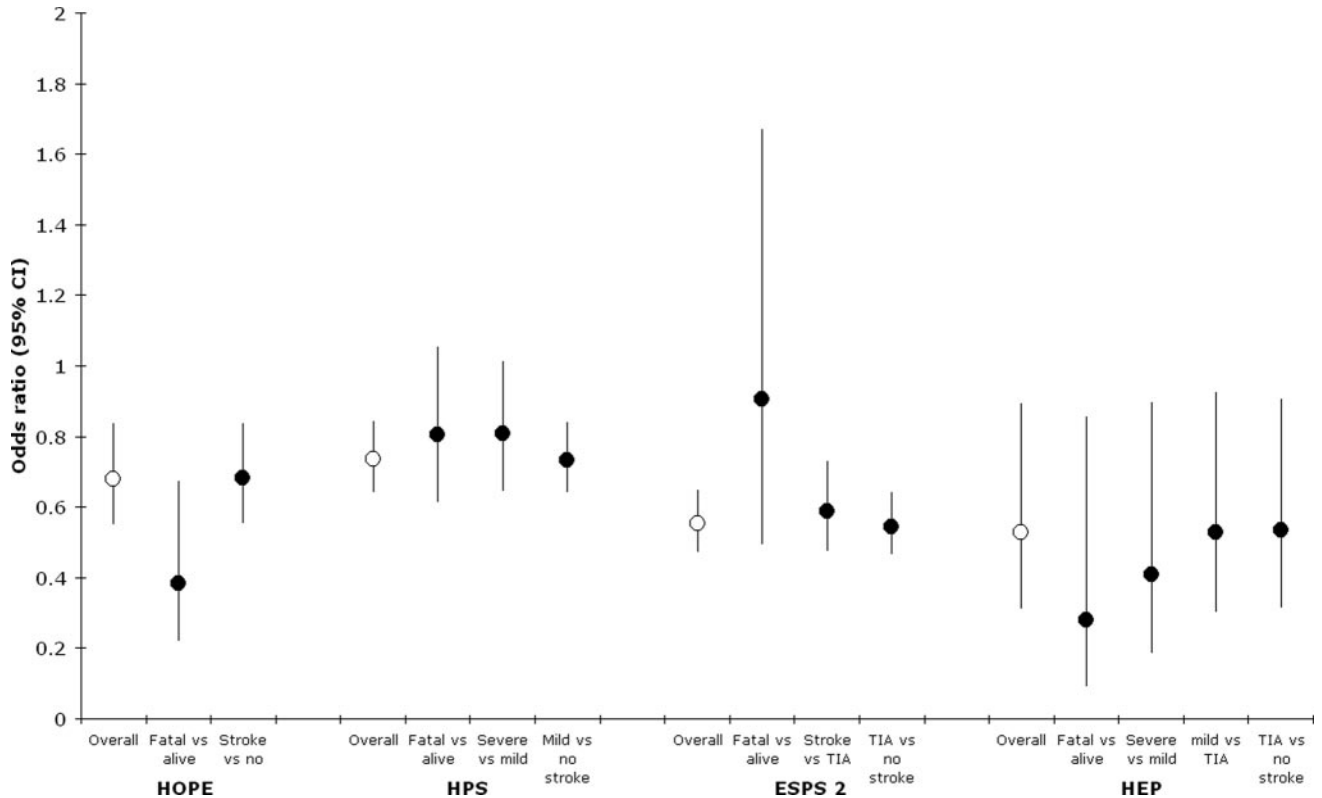
Second, there is existing published evidence that interventions do alter severity: simvastatin reduced the risk of stroke of different severities by similar risk reductions in the Heart Protection Study (HPS),<sup>17</sup> hormone replacement therapy increased both stroke and its severity in the Women’s Estrogen for Stroke Trial (WEST),<sup>18</sup> and antiplatelet agents reduced

both fatal and nonfatal vascular events in the Antithrombotic Trialists’ (ATT) Collaboration meta analysis.<sup>19</sup> 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,<sup>20</sup> 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<sup>13</sup> 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%.<sup>21,22</sup> Logistic and Cox models give similar results when the overall event frequency is less than 10%.<sup>23,24</sup> Where the frequency of events is higher, ordinal data may be analyzed by time to event.<sup>25,26</sup> 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,<sup>3,27</sup> 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

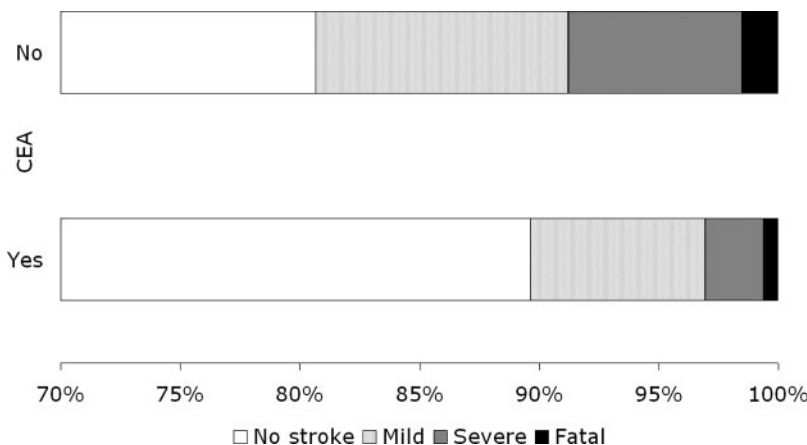


**Figure 2.** Odds ratios across trial (by ordinal logistic regression) and by individual outcome levels for 4 trials to illustrate the assumption of proportionality of odds.

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.<sup>28</sup> 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.<sup>28</sup> 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,<sup>4</sup> analogous approaches exist for ordinal tests.<sup>29</sup> 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.<sup>29</sup> 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<sup>1</sup> of carotid endarterectomy (CEA).

Hypertension in Elderly Patients (HEP) trial<sup>30</sup> 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;<sup>29</sup> 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<sup>11</sup> 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.<sup>1,2</sup> 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)<sup>3</sup>; (9) *t* test; (10) bootstrap of difference in mean rank (with 3×3000 cycles).<sup>4,5</sup> 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<sup>3</sup> 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.<sup>5</sup>
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)<sup>6</sup> 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 ( $\leq 65$ ,  $> 65$  years); trial size ( $< 2520$ ,  $\geq 2250$  participants); length of follow up ( $\leq 36$  months,  $> 36$  months); baseline severity (control group death rate adjusted for length of follow up,  $\leq$  median [0.2],  $>$  median [0.2]); time from index event ( $\leq 87$  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 I 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  $P = 0.04$ ,<sup>6</sup> TPT-I  $P = 0.0002$ ,<sup>7</sup> TPT-II  $P = 0.03$ , HOPE  $P = 0.02$ ,<sup>3</sup> ANBP2  $P = 0.04$ ,<sup>8</sup> WEST  $P = 0.05$ <sup>9</sup>). 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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# Stroke

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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 <sup>1</sup>          | 1989                               | Chronic nonrheumatic AF:1                            | Warfarin                                      | Placebo         | 335/336                   | 74          |     |
|                               | BAATAF <sup>2</sup>          | 1990                               | Non rheumatic AF:1                                   | Warfarin                                      | Control         | 212/208                   | 68          |     |
|                               | SPAF 1 <sup>3</sup>          | 1991                               | Non rheumatic AF:1                                   | Warfarin                                      | Placebo         | 210/211                   | 67          |     |
|                               | VASPNAF <sup>4</sup>         | 1992                               | Non rheumatic AF:1                                   | Warfarin                                      | Placebo         | 260/265                   | 67          |     |
|                               | VASPNAF <sup>4</sup>         | 1992                               | Previous ischaemic stroke:2                          | Warfarin                                      | Placebo         | 21/25                     | 67          |     |
|                               | ASPECT <sup>5</sup>          | 1994                               | Post MI:2  | Anticoagulant                                 | Placebo         | 1700/1704                 | 61          |     |
|                               | SPAF 2 <sup>6</sup>          | 1994                               | Non rheumatic AF:1                                   | Warfarin                                      | Aspirin         | 555/545                   | ...         |     |
|                               | SPAF3 <sup>7</sup>           | 1998                               | Nonvalvular AF:1                                     | W+ Asp  | Adjusted dose W | 521/523                   | 72          |     |
|                               | TPT <sup>8</sup>             | 1998                               | At risk of IHD:1                                     | W+ Asp  | Placebo         | 1277/1272                 | 57          |     |
|                               | TPT <sup>8</sup>             | 1998                               | At risk of IHD:1                                     | Warfarin                                      | Placebo         | 1268/1272                 | 57          |     |
|                               | NASPEAF-IM risk <sup>9</sup> | 2004                               | Patients with MS without prior embolism:1            | Combined (A+ triflusal)                       | Anticoagulant   | 222/232                   | ...         |     |
|                               | NASPEAF-H risk <sup>9</sup>  | 2004                               | Non valvular AF with prior embolism:2                | Combined (A+ triflusal)                       | Anticoagulant   | 223/247                   | ...         |     |
|                               | Antiplatelets                | Acheson <sup>10</sup>              | 1969   | Post stroke:2                                 | Dipiridamole    | Placebo                   | 69/70       | 58  |
|                               |                              | Canadian Co-op <sup>11</sup>       | 1978   | Recent cerebral or retinal ischaemic attack:2 | Sulphinpyrazone | Placebo                   | 156/139     | ... |
| Breddin <sup>12</sup>         |                              | 1980                               | Post MI:2  | Aspirin                                       | Placebo         | 317/309                   | ...         |     |
| Breddin <sup>12</sup>         |                              | 1980                               | Post MI:2  | Aspirin                                       | Phenprocoumon   | 317/320                   | ...         |     |
| Herskovits <sup>13</sup>      |                              | 1981                               | Post TIA:2   | Pentoxifylline                                | Antiaggregant   | 30/36                     | 61          |     |
| ARIS <sup>14</sup>            |                              | 1982                               | Post MI  | Sulphinpyrazone                               | Placebo         | 365/362                   | ...         |     |
| AICLA <sup>15</sup>           |                              | 1983                               | Atherothrombotic cerebral or retinal ischaemic event | Aspirin                                       | Placebo         | 198/204                   | 63          |     |
| ACCSG <sup>16</sup>           |                              | 1985                               | Recent carotid territory TIAs:2                      | Dip+ Asp                                      | Aspirin         | 448/442                   | 63          |     |
| Matus-Guiu <sup>17</sup>      |                              | 1987                               | Post stroke:2  | Asp+ Dip                                      | Dipiridamole    | 115/71                    | 56          |     |
| Swedish Co-op <sup>18</sup>   |                              | 1987                               | Post minor or major stroke                           | Aspirin                                       | Placebo         | 253/252                   | 68          |     |
| TASS <sup>19</sup>            |                              | 1989                               | Post TIA/stroke:2                                    | Ticlopidine                                   | Aspirin         | 1529/1540                 | 63          |     |
| STIMS <sup>20</sup>           |                              | 1990                               | PAD  | Ticlopidine                                   | Placebo         | 346/341                   | 60          |     |
| UKTIA high dose <sup>21</sup> |                              | 1991                               | Post stroke-TIA:2                                    | Asp high dose                                 | Placebo         | 815/814                   | ...         |     |
| UKTIA low dose <sup>21</sup>  |                              | 1991                               | Post stroke-TIA:2                                    | Asp low dose                                  | Placebo         | 806/814                   | ...         |     |
| SALT <sup>22</sup>            |                              | 1991                               | Post stroke, TIA                                     | Aspirin                                       | Placebo         | 676/684                   | 67          |     |
| SPAF 1 <sup>3</sup>           |                              | 1991                               | Non rheumatic AF:1                                   | Aspirin                                       | Placebo         | 552/568                   | 67          |     |
| Fornaro <sup>23</sup>         |                              | 1993                               | Chronic non valvular AF:1                            | Indobufen                                     | Placebo         | 98/98                     | 62          |     |
| CAPRIE <sup>24</sup>          |                              | 1996                               | Atherosclerotic vascular disease:2                   | Clopidogrel                                   | Aspirin         | 9599/9586                 | 62          |     |
| ESPS 2 <sup>25</sup>          |                              | 1997                               | Post stroke-TIA:2                                    | Aspirin                                       | Placebo         | 1649/1649                 | 67          |     |
| TISS <sup>26</sup>            |                              | 1997                               | Post TIA, minor stroke, amaurosis fugax              | Ticlopidine                                   | Indobufen       | 821/811                   | 65          |     |
| TPT <sup>8</sup>              |                              | 1998                               | At risk of IHD:1                                     | Aspirin                                       | Placebo         | 1268/1272                 | 57          |     |
| Taylor <sup>27</sup>          |                              | 1999                               | Carotid stenosis:2                                   | LD Aspirin                                    | HD Aspirin      | 1395/1409                 | 69          |     |
| TACIP <sup>28</sup>           | 2001                         | Post TIA or non disabling stroke:2 | Triflusal  | Aspirin                                       | 1058/1055       | 65                        |             |     |
| AAASPS <sup>29</sup>          | 2003                         | Post stroke:2                      | Ticlopidine  | Aspirin                                       | 902/907         | 61                        |             |     |
| Ridker (WHS) <sup>30</sup>    | 2005                         | Healthy women 45 years or older:1  | Aspirin  | Placebo                                       | 19 934/19 942   | 55                        |             |     |
| BP control                    | VACS1970 <sup>31</sup>       | 1970                               | Hypertension   | Active treatment                              | Placebo         | 186/194                   | 49          |     |
|                               | Mild HT Oslo <sup>32</sup>   | 1980                               | Mild hypertension:1                                  | Active treatment                              | Control         | 406/379                   | 45          |     |
|                               | IPPSH <sup>33</sup>          | 1985                               | Essential Hypertension:1                             | BB  | Non BB          | 3185/3172                 | 52          |     |
|                               | MRC mild <sup>34</sup>       | 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 causes                    | ...         | 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 <sup>35</sup>        | 1986                     | Hypertension (old)                                   | Atenolol/<br>Bendrofluzide  | Control                  | 348/377                   | 69          |
|                          | SHEP <sup>36</sup>       | 1991                     | hypertension:2 (systolic)                            | Active treatment            | Placebo                  | 2365/2371                 | 72          |
|                          | MRC old <sup>37</sup>    | 1992                     | Hypertension (old)                                   | Diuretic                    | Placebo                  | 1081/2213                 | 70          |
|                          | MRC old <sup>37</sup>    | 1992                     | Hypertension (old)                                   | Beta blocker                | Placebo                  | 1102/2213                 | 70          |
|                          | PATS <sup>38</sup>       | 1995                     | Hypertension + post stroke/TIA:2                     | Indapamide                  | Placebo                  | 2841/2824                 | 60          |
|                          | Syst China <sup>39</sup> | 1998                     | Hypertension (systolic)                              | Active treatment            | Placebo                  | 1253/1141                 | 67          |
|                          | UKPDS 38 <sup>40</sup>   | 1998                     | Diabetes   | Tight                       | Less tight               | 758/390                   | 56          |
|                          | ABCD <sup>41</sup>       | 1998                     | Hypertension   | Nisoldipine                 | Enalapril                | 235/235                   | 58          |
|                          | UKPDS-39 <sup>42</sup>   | 1998                     | Type 2 diabetes                                      | Captopril                   | Atenolol                 | 400/358                   | 56          |
|                          | CAPP <sup>43</sup>       | 1999                     | Hypertension:2                                       | Captopril                   | Conventional treatment   | 5492/5493                 | 52          |
|                          | NICH-EH <sup>44</sup>    | 1999                     | Elderly hypertension:1                               | Nicardipine                 | Trichlormethiazide       | 204/210                   | 70          |
|                          | Syst-Eur <sup>45</sup>   | 1999                     | Hypertension (systolic)                              | Active treatment            | Placebo                  | 2398/2297                 | 70          |
|                          | STOP-HT <sup>46</sup>    | 1999                     | Hypertension:2                                       | ACE inhibitors              | Conventional drugs       | 2205/2213                 | 76          |
|                          | STOP-HT <sup>46</sup>    | 1999                     | Hypertension:2                                       | Calcium antagonists         | Conventional drugs       | 2196/2213                 | 76          |
|                          | HOPE <sup>47</sup>       | 2000                     | Having cardiovascular risk factors:2                 | Ramipril                    | Placebo                  | 4645/4652                 | 66          |
|                          | INSIGHT <sup>48</sup>    | 2000                     | Hypertension   | Nifedipine                  | Co-amilozide             | 3157/3164                 | 65          |
|                          | NORDIL <sup>49</sup>     | 2000                     | Hypertension   | Diltiazem                   | Diuretics + beta blocker | 5410/5471                 | 60          |
|                          | MacMahon <sup>50</sup>   | 2000                     | Post MI, TIA, PVD                                    | Ramipril                    | Placebo                  | 308/309                   | 61          |
|                          | PROGRESS <sup>51</sup>   | 2001                     | Hypertension, post stroke/TIA:2                      | Perindopril +<br>Indapamide | Placebo                  | 3051/3054                 | 64          |
|                          | OPTIMAL <sup>52</sup>    | 2002                     | Post MI:2  | Losartan                    | Captopril                | 2744/2733                 | 67          |
|                          | ANBP2 <sup>53</sup>      | 2003                     | Hypertension (old)                                   | Enalapril                   | Hydrochlorothiazide      | 3044/3039                 | 80          |
|                          | DIABHYCAR <sup>54</sup>  | 2004                     | Type 2 diabetes                                      | Ramipril                    | Placebo                  | 2443/2469                 | 65          |
|                          | SCOPE <sup>55</sup>      | 2004                     | Hypertension (old, systolic)                         | Candesartan                 | Control                  | 754/764                   | 77          |
| Statins                  | 4S <sup>56</sup>         | 1994                     | Patients with coronary heart disease;2               | Simvastatin                 | Placebo                  | 2221/2223                 | ...         |
|                          | KAPS <sup>57</sup>       | 1995                     | Atherosclerosis:1                                    | Pravastatin                 | Placebo                  | 212/212                   | 57          |
|                          | REGRESS <sup>58</sup>    | 1995                     | Coronary atherosclerosis:2                           | Pravastatin                 | Placebo                  | 450/434                   | 56          |
|                          | WOSCOPS <sup>59</sup>    | 1995                     | Coronary heart disease:2                             | Pravastatin                 | Placebo                  | 3302/3293                 | 55          |
|                          | CARE <sup>60</sup>       | 1996                     | Post MI:2  | Pravastatin                 | Placebo                  | 2081/2078                 | 59          |
|                          | Post CABG <sup>61</sup>  | 1997                     | Coronary heart disease:2                             | Aggressive treatment        | Moderate treatment       | 676/675                   | 62          |
|                          | LIPID <sup>62</sup>      | 1998                     | Coronary heart disease:2                             | Pravastatin                 | Placebo                  | 4512/4502                 | 62          |
|                          | BIP <sup>63</sup>        | 2000                     | Coronary heart disease:2                             | Bezafibrate                 | Placebo                  | 1548/1542                 | 60          |
|                          | GISSIP-P <sup>64</sup>   | 2000                     | Coronary heart disease:2                             | Pravastatin                 | Control                  | 2138/2133                 | ...         |
|                          | SCAT <sup>65</sup>       | 2000                     | Coronary heart disease:2                             | Simvastatin                 | Placebo                  | 230/230                   | 61          |
|                          | MIRACL <sup>66</sup>     | 2001                     | Coronary heart disease:2                             | Atorvastatin                | Placebo                  | 1538/1548                 | 65          |
|                          | HPS <sup>67</sup>        | 2002                     | CHD (stroke):2                                       | Simvastatin                 | Placebo                  | 10 269/10 267             | 64          |
|                          | PROSPER <sup>68</sup>    | 2002                     | Elderly with risk factors for cardiovascular disease | Pravastatin                 | Placebo                  | 2891/2913                 | 75          |
| ALLHAT-LLT <sup>69</sup> | 2002                     | Coronary heart disease:2 | Pravastatin  | Control                     | 5170/5185                | 66                        |             |
| ALERT <sup>70</sup>      | 2003                     | Renal transplant         | Fluvastatin  | Placebo                     | 1050/1052                | 50                        |             |
| CARDS <sup>71</sup>      | 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) |
|--------------|----------------------|------|-------------------------------|----------------------|-------------------|---------------------------|-------------|
| Surgery      | SPARCL <sup>72</sup> | 2006 | Post TIA/stroke:2             | Atorvastatin         | Placebo           | 2365/2366                 | 63          |
|              | NASCET <sup>73</sup> | 1991 | Post stroke:2                 | CEA                  | Medical           | 328/331                   | 66          |
|              | VACS <sup>74</sup>   | 1993 | Asymptomatic carotid stenosis | Surgical treatment   | Medical treatment | 211/233                   | 64          |
|              | ACAS <sup>75</sup>   | 1995 | Asymptomatic carotid stenosis | Immediate surgery    | Deferred surgery  | 825/834                   | 67          |
|              | ACST <sup>76</sup>   | 2004 | Asymptomatic carotid stenosis | Immediate surgery    | Deferred surgery  | 1560/1560                 | 68          |
| HRT          | ERA <sup>77</sup>    | 2000 | Coronary heart disease:2      | HRT                  | Placebo           | 204/105                   | 66          |
|              | WEST <sup>78</sup>   | 2001 | Post stroke, TIA:2            | Estradiol            | Placebo           | 337/327                   | 71          |
|              | Clarke <sup>79</sup> | 2002 | Coronary heart disease:2      | HRT                  | Control           | 134/121                   | 67          |
|              | WHI-EP <sup>80</sup> | 2003 | Post menopausal women:1       | Estrogen + Progestin | Placebo           | 8506/8102                 | 63          |

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(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 |
|----------|-------------------------|--------------------|-------------------------|---------------------|--|-------------|--------------|
| ...      | ...                     | 59                 | 13.5                    | ...                 | Fatal stroke+non fatal stroke                    | +           | +            |
| 69       | 4                       | 33                 | 19.3                    | ...                 | Ipsilateral stroke                               |             | +            |
| 100      | 4                       | 48                 | 9.4                     | ...                 | TIA+transient monocular blindness stroke+death   | ...         | +            |
| 66       | ...                     | 32                 | 10.3                    | ...                 | Ipsilateral stroke+perioperative 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 <sup>1</sup>              | 1967          | Male hypertensive patients  | 143                  | Relevant outcome data not available |
|             | Co-op RCT <sup>2</sup>          | 1973          | Patients with diastolic BP 100–120  | 58                   | Relevant outcome data not available |
|             | Sprackling <sup>3</sup>         | 1981          | Elderly hypertensive patients   | 123                  | Relevant outcome data not available |
|             | EWPH <sup>4</sup>               | 1985          | Elderly hypertensive patients   | 840                  | Relevant data not available         |
|             | Wikstrand <sup>5</sup>          | 1986          | Elderly hypertensive patients   | 562                  | Relevant data not given             |
|             | BBB <sup>6</sup>                | 1988          | Hypertension  | 2127                 | Neutral                             |
|             | TOMHS <sup>7</sup>              | 1993          | Patients with hypertension aged 45 to 69 years  | 902                  | Neutral                             |
|             | ASIST <sup>8</sup>              | 1994          | Patients with coronary artery disease   | 306                  | Relevant outcome data not available |
|             | CIBIS <sup>9</sup>              | 1994          | Patients with chronic heart failure   | 641                  | Relevant outcome data not available |
|             | HYCAR <sup>10</sup>             | 1995          | Patients with hypertension and LVH  | 115                  | Relevant outcome data not available |
|             | GLANT <sup>11</sup>             | 1995          | Patients with mild to moderate essential hypertension   | 1936                 | Neutral                             |
|             | STONE <sup>12</sup>             | 1996          | Patients with hypertension  | 1632                 | Relevant data not given             |
|             | MIDAS <sup>13</sup>             | 1996          | Patients with hypertension  | 883                  | Relevant data not given             |
|             | ACCT <sup>14</sup>              | 1996          | Patients with essential hypertension  | 1084                 | Relevant outcome data not available |
|             | ELITE <sup>15</sup>             | 1997          | Patients aged 65 or more with heart failure   | 722                  | Relevant outcome data not available |
|             | VHAS <sup>16</sup>              | 1997          | Patients with hypertension  | 1414                 | Relevant outcome data not available |
|             | LOA <sup>17</sup>               | 1997          | Patients with hypertension  | 898                  | Relevant outcome data not available |
|             | AIREX <sup>18</sup>             | 1997          | Patients with heart failure after MI  | 603                  | Relevant outcome data not available |
|             | VHAS <sup>19</sup>              | 1998          | Patients with hypertension  | 456                  | Relevant outcome data not available |
|             | FACET <sup>20</sup>             | 1999          | Patients with hypertension and NIDDM  | 380                  | Relevant data not given             |
|             | HOT <sup>21</sup>               | 1998          | Patients with hypertension  | 18 790               | Neutral                             |
|             | Tuomilehto <sup>22</sup>        | 1999          | Older patients with diabetes and systolic hypertension  | 4695                 | Relevant outcome data not available |
|             | ALLHAT <sup>23</sup>            | 2000          | Patients with hypertension 55 years or older  | 33 357               | Relevant outcome data not available |
|             | PREVENT <sup>24</sup>           | 2000          | Patients with coronary atherosclerosis  | 825                  | Relevant outcome data not available |
|             | ATIME <sup>25</sup>             | 2000          | Patients with hypertension  | 2935                 | Relevant outcome data not available |
|             | CALM <sup>26</sup>              | 2000          | Patients with type 2 diabetes having hypertension and microalbuminuria                                      | 197                  | Relevant data not given             |
|             | ELITE-2 <sup>27</sup>           | 2001          | Patients with symptomatic heart failure   | 3152                 | Relevant outcome data not available |
|             | CONVINCE <sup>28</sup>          | 2001          | Patients with hypertension  | 16 602               | Relevant outcome data not available |
|             | CAPRICON <sup>29</sup>          | 2001          | Patients had MI   | 1959                 | Relevant data not available         |
|             | CASTLE <sup>30</sup>            | 2001          | Patients with mild hypertension   | 251                  | Relevant data not available         |
|             | AASK <sup>31</sup>              | 2002          | Patients 18–70 years with hypertensive renal disease.   | 1094                 | Relevant outcome data not available |
|             | LIFE <sup>32</sup>              | 2002          | Patients with essential HT and LVH ascertained by ECG   | 9193                 | Relevant outcome data not available |
|             | ELSA <sup>33</sup>              | 2002          | Patients with hypertension  | 2334                 | Relevant outcome data not available |
|             | EUROPA <sup>34</sup>            | 2003          | Patients with previous MI, coronary revascularisation, angiographic evidence of CAD or positive stress test | 18 328               | Relevant outcome data not available |
|             | CHARM-preserved <sup>35</sup>   | 2003          | Patients had NYHA class 11-1V CHF and LVEF >40%   | 3023                 | Relevant outcome data not available |
|             | CHARM-alternative <sup>36</sup> | 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 <sup>37</sup>       | 2003          | Patients had NYHA class 11-1V, LVEF 40% or less and being treated with ACEIs                                | 2548                 | Relevant outcome data not available |
|             | NICOLE <sup>38</sup>            | 2003          | Patients who has undergone successful coronary angioplasty  | 826                  | Relevant data not given             |
|             | E-COST <sup>39</sup>            | 2003          | Patients with essential hypertension  | 2048                 | Relevant outcome data not available |
|             | SHELL <sup>40</sup>             | 2003          | Elderly patients with isolated systolic hypertension  | 1882                 | Neutral                             |
|             | Berl <sup>41</sup>              | 2003          | Patients with diabetic nephropathy and hypertension   | 1715                 | Relevant outcome data not available |
|             | CAMELOT <sup>42</sup>           | 2004          | Patients with coronary artery disease and normal blood pressure   | 1991                 | Relevant outcome data not available |
|             | JMIC-B <sup>43</sup>            | 2004          | Patients with hypertension and coronary artery disease  | 1650                 | Relevant outcome data not available |
|             | PEACE <sup>44</sup>             | 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 <sup>45</sup>      | 2006                      | Patients with hypertension and high cardiovascular risk   | 15 245  | Relevant outcome data not available |                                     |
| ACTION <sup>46</sup>     | 2004                      | Patients with treated stable symptomatic coronary disease | 3825  | Relevant outcome data not available |                                     |
| ASCOT-BPLA <sup>47</sup> | 2005                      | Hypertension  | 19 257  | Relevant data not given             |                                     |
| ADVANCE <sup>48</sup>    | 2005                      | Hypertension  | 11 140  | Relevant data not given             |                                     |
| MOSES <sup>49</sup>      | 2005                      | Hypertensive stroke patients                              | 1405  | Relevant data not given             |                                     |
| Gradman <sup>50</sup>    | 2005                      | Patients with hypertension                                | 652   | Relevant data not given             |                                     |
| Hermida <sup>51</sup>    | 2005                      | Patients with essential hypertension                      | 200   | Relevant data not given             |                                     |
| Stokes <sup>52</sup>     | 2005                      | Patients with systolic hypertension                       | 16  | Relevant outcome data not available |                                     |
| Ernst <sup>53</sup>      | 2006                      | Untreated hypertensive patients                           | 30  | Relevant data not given             |                                     |
| Kushiro <sup>54</sup>    | 2006                      | Patients with hypertension                                |   | Relevant data not given             |                                     |
| HRT                      | Marmorston <sup>55</sup>  | 1962  | Previous cerebrovascular disease  | 200                                 | Relevant outcome data not available |
|                          | VACS <sup>56</sup>        | 1966  | Males with atherosclerotic myocardial infarction and cerebral infarction    | 582                                 | Relevant data not given             |
|                          | McDowell <sup>57</sup>    | 1967  | Post-menopausal women with non embolic cerebral infarction                  | 176                                 | Relevant data not given             |
|                          | Nachtigall <sup>58</sup>  | 1979  | Post-menopausal women 2 or more years after menopause                       | 329                                 | Relevant data not given             |
|                          | Hall <sup>59</sup>        | 1994  | Post menopausal women with rheumatoid arthritis                             | 200                                 | Relevant data not given             |
|                          | PEPI <sup>60</sup>        | 1995  | Post-menopausal women age 45 to 64  | 875                                 | Relevant data not given             |
|                          | Hall <sup>61</sup>        | 1998  | Post-menopausal women with coronary heart disease                           | 60                                  | Relevant data not given             |
|                          | Hulley <sup>62</sup>      | 1998  | Post menopausal women with established coronary heart disease               | 2763                                | Relevant outcome data not available |
|                          | Mijatovic <sup>63</sup>   | 1998  | Post menopausal women   | 52                                  | Relevant data not given             |
|                          | HERS <sup>64</sup>        | 1998  | Post-menopausal women with established coronary heart disease               | 2763                                | Relevant outcome data not available |
|                          | Ravn <sup>65</sup>        | 1999  | Post menopausal women 45 to 59 years of age                                 | 1609                                | Relevant outcome data not given     |
|                          | Recker <sup>66</sup>      | 1999  | Women older than 65 years and having low bone mass                          | 128                                 | Relevant outcome data not available |
|                          | Komulainen <sup>67</sup>  | 1999  | Non osteoporotic early post menopausal women                                | 464                                 | Relevant outcome data not available |
|                          | MORE <sup>68</sup>        | 1999  | Osteoporotic post-menopausal women  | 7705                                | Relevant outcome data not available |
|                          | Mulnard <sup>69</sup>     | 2000  | Women with mild to moderate AD, MMSE 12–28 and had a hysterectomy           | 120                                 | Relevant outcome data not available |
|                          | EWA <sup>70</sup>         | 2000  | Post-menopausal women with angiographically verified coronary heart disease | 118                                 | Relevant data not given             |
|                          | EVTET <sup>71</sup>       | 2000  | Post-menopausal women who suffered previous DVT or PE                       | 140                                 | Relevant data not given             |
|                          | Mosekilde <sup>72</sup>   | 2000  | Post menopausal women   | 2016                                | Relevant outcome data not available |
|                          | Gallagher <sup>73</sup>   | 2001  | Post menopausal women with normal bone density                              | 489                                 | Relevant outcome data not available |
|                          | PHOREA <sup>74</sup>      | 2001  | Post-menopausal women   | 264                                 | Relevant outcome data not available |
|                          | Binder <sup>75</sup>      | 2001  | Post-menopausal women 75 years of age or older                              | 59                                  | Relevant data not given             |
|                          | EPAT <sup>76</sup>        | 2001  | Post menopausal women without pre-existing cardiovascular disease           | 222                                 | Relevant outcome data not available |
|                          | WAVE <sup>77</sup>        | 2002  | Post-menopausal women with coronary stenosis                                | 423                                 | Relevant outcome data not available |
|                          | ESPRIT <sup>78</sup>      | 2002  | Post-menopausal women survived first MI                                     | 1017                                | Relevant outcome data not available |
|                          | Giske <sup>79</sup>       | 2002  | Apparently healthy peri and post menopausal women                           | 166                                 | Relevant outcome data not given     |
|                          | Arrenbrecht <sup>80</sup> | 2002  | Non osteoporotic post menopausal volunteers                                 | 160                                 | Relevant outcome data not given     |
|                          | Haines <sup>81</sup>      | 2003  | Post menopausal Chinese women   | 152                                 | Relevant outcome data not available |
|                          | HABITS <sup>82</sup>      | 2004  | Female patients with previous breast cancer                                 | 434                                 | Relevant outcome data not available |
| Anticoagulants           | Olsson <sup>83</sup>      | 1980  | Patients who had TIA or RIND  | 156                                 | Neutral                             |
|                          | CAFA <sup>84</sup>        | 1991  | Patients with chronic atrial fibrillation                                   | 378                                 | Relevant outcome data not available |
|                          | EAF <sup>85</sup>         | 1995  | Patients with non rheumatic AF and recent minor IS                          | 214                                 | Relevant outcome data not available |
|                          | SPRIT <sup>86</sup>       | 1997  | Patients after cerebral ischaemia of presumed arterial origin               | 1316                                | Relevant outcome data not available |
|                          | CARS <sup>87</sup>        | 1997  | Patients who had MI   | 8803                                | Neutral                             |
|                          | Hellemons <sup>88</sup>   | 1999  | Atrial fibrillation   | 729                                 | Neutral                             |

(Continued)

Table II. Continued

| Trial                   | Year                          | Patient Group   | n   | Reason for Exclusion                |                                     |
|-------------------------|-------------------------------|---|---|-------------------------------------|-------------------------------------|
| Antiplatelets           | AFASAK 2 <sup>89</sup>        | 1999  | Patients with non valvular chronic atrial fibrillation  | 677                                 | Neutral                             |
|                         | HEAST <sup>90</sup>           | 2000  | Atrial fibrillation   | 449                                 | Relevant outcome data not available |
|                         | Yamaguchi <sup>91</sup>       | 2000  | Atrial fibrillation   |                                     | Relevant outcome data not available |
|                         | WARSS <sup>92</sup>           | 2001  | Patients had noncardioembolic IS within previous 30 days  | 2206                                | Relevant outcome data not available |
|                         | ASPECT 2 <sup>93</sup>        | 2002  | Patients with ischaemic heart disease   | 661                                 | Relevant outcome data not available |
|                         | SPINAF <sup>94</sup>          | 2005  | Patients with non rheumatic atrial fibrillation   | 525                                 | Relevant data not given             |
|                         | WASID <sup>95</sup>           | 2005  | Patients had TIA or stroke  | 569                                 | Neutral                             |
|                         | SPORTIF <sup>96</sup>         | 2005  | Patients with nonvalvular atrial fibrillation   | 3922                                | Neutral                             |
|                         | Elwood <sup>97</sup>          | 1974  | Male patients who had recent MI   | 1239                                | Relevant outcome data not available |
|                         | AITIA <sup>98</sup>           | 1977  | Patients who had carotid TIAs   | 178                                 | Relevant outcome data not available |
|                         | Vogel <sup>99</sup>           | 1979  | Patients with previous MI   | 1340                                | Relevant outcome data not available |
|                         | Elwood <sup>100</sup>         | 1979  | Patients had confirmed MI   | 1682                                | Relevant data not given             |
|                         | ART <sup>101</sup>            | 1980  | Patients with previous MI   | 1558                                | Relevant outcome data not available |
|                         | CDPA <sup>102</sup>           | 1980  | Patients with previous MI   | 2915                                | Relevant outcome data not available |
|                         | PARIS-1 <sup>103</sup>        | 1980  | Patients with previous MI   | 2026                                | Relevant outcome data not available |
|                         | PARIS-2 <sup>104</sup>        | 1986  | Patients recovered from MI 4wks to 4 month previously   | 3128                                | Relevant outcome data not available |
|                         | Boysen <sup>105</sup>         | 1988  | Patients after carotid endarterectomy   | 301                                 | Neutral                             |
|                         | Hass <sup>106</sup>           | 1989  | Patients had previous TIA, amaurosis fugax, RIND or minor stroke                                    | 3069                                | Relevant outcome data not available |
|                         | CATS <sup>107</sup>           | 1989  | Patients with previous thromboembolic stroke  | 1072                                | Relevant outcome data not available |
|                         | Dutch TIA <sup>108</sup>      | 1991  | Patients had TIA or minor ischaemic stroke  | 3131                                | Relevant outcome data not available |
|                         | PACE pilot <sup>109</sup>     | 1994  | Elderly patients without a pre-existing clinical history of cardiovascular disease                  | 400                                 | No outcome data available           |
|                         | EPIC <sup>110</sup>           | 1995  | Patients with coronary artery disease   | 2099                                | Relevant outcome data not available |
|                         | Kereiakes <sup>111</sup>      | 1998  |   |                                     |                                     |
|                         | ESPS 1 <sup>112</sup>         | 1998  | Patients with recent stroke, TIA or RIND  | 1306                                | Relevant outcome data not available |
|                         | EXCITE <sup>113</sup>         | 2000  | Patients with angiographic evidence of clinically significant coronary artery disease               | 7232                                | Neutral                             |
|                         | APLAUD <sup>114</sup>         | 2000  | Patients with recent cardiovascular or cerebrovascular event  | 451                                 | Relevant outcome data not available |
|                         | TACIP <sup>115</sup>          | 2003  | Patients who suffered from TIA or non disabling stroke  | 2113                                | Neutral                             |
|                         | ESPRIT <sup>116</sup>         | 2003  | Patients with recent cerebral ischaemia of arterial origin  | 591                                 | Relevant outcome data not available |
|                         | TAPIRSS <sup>117</sup>        | 2004  | Patients with previous cerebrovascular event  | 431                                 | Neutral                             |
|                         | MATCH <sup>118</sup>          | 2004  | Patients with recent ischaemic stroke or TIA  | 7599                                | Neutral                             |
|                         | PLUTO-Stroke <sup>119</sup>   | 2005  | Patients after ischaemic stroke   | 70                                  | Relevant outcome data not available |
| CARESS <sup>120</sup>   | 2005                          | Patients with symptomatic carotid stenosis              | 107   | Relevant outcome data not available |                                     |
| CHARISMA <sup>121</sup> | 2006                          | Patients with clinically evident cardiovascular disease | 15 603  | Neutral                             |                                     |
| Statins                 | ACAPS <sup>122</sup>          | 1994  | Patients with moderately elevated cholesterol levels and free of symptomatic cardiovascular disease | 1953                                | Relevant outcome data not available |
|                         | CCAIT <sup>123</sup>          | 1994  | Patients with diffuse coronary atherosclerosis  | 331                                 | Relevant data not given             |
|                         | Weintraub <sup>124</sup>      | 1994  | Patients with coronary artery disease   | 404                                 | Relevant outcome data not available |
|                         | Shepherd <sup>125</sup>       | 1995  | Male patients with hypercholesterolemia   | 6595                                | Relevant outcome data not available |
|                         | CCAIT <sup>126</sup>          | 1996  | Patients with coronary atherosclerosis  | 331                                 | Relevant outcome data not available |
|                         | PLAC 1 <sup>127</sup>         | 1995  | Patients with coronary artery disease   | 408                                 | Relevant outcome data not available |
|                         | CIS <sup>128</sup>            | 1997  | Male patients with coronary artery disease and hypercholesterolemia                                 | 254                                 | Relevant outcome data not available |
|                         | AFCAPS/TexCAPS <sup>129</sup> | 1998  | Patients with average TC and LDL-C and below average HDL-C  | 6605                                | Relevant outcome data not available |
|                         | Riegger <sup>130</sup>        | 1999  | Patients with symptomatic coronary heart disease and hyperlipidaemia                                | 365                                 | Relevant outcome data not available |
|                         | Brown <sup>131</sup>          | 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 |                                     |
|---------|--------------------------|---------------|---|----------------------|-------------------------------------|
| Surgery | DIAS <sup>132</sup>      | 1996          | Patients with type 2 diabetes and atherosclerosis | 731                  | Relevant outcome data not available |
|         | LIPIS <sup>133</sup>     | 2002          | Patients underwent their first PCI                | 1677                 | Relevant outcome data not available |
|         | ASCOT-LLA <sup>134</sup> | 2003          | Patients with hypertension                        | 10 305               | Relevant outcome data not available |
|         | Eikelboom <sup>135</sup> | 1988          | Patients undergoing CEA                           | 129                  | Relevant data not available         |
|         | Clagett <sup>136</sup>   | 1989          | Patients undergoing CEA                           | 152                  | Relevant data not available         |
|         | Lord <sup>137</sup>      | 1989          | Patients undergoing CEA                           | 140                  | Relevant outcome data not available |
|         | CASANOVA <sup>138</sup>  | 1991          | Patients with carotid stenosis                    | 410                  | Neutral                             |
|         | Shah <sup>139</sup>      | 1994          | Patients undergoing CEA                           | 873                  | Relevant data not available         |
|         | Katz <sup>140</sup>      | 1994          | Patients undergoing CEA                           | 100                  | Relevant data not available         |
|         | Myers <sup>141</sup>     | 1994          | Patients undergoing CEA                           | 136                  | Relevant data not available         |
|         | Rockman <sup>142</sup>   | 1996          | Patients undergoing CEA                           | 3975                 | Relevant data not available         |
|         | AbuRahama <sup>143</sup> | 1997          | Patients undergoing CEA                           | 399                  | Relevant outcome data not available |
|         | Fiorani <sup>144</sup>   | 1997          | Patients with carotid stenosis                    | 1020                 | Relevant data not available         |
|         | ECST <sup>145</sup>      | 1998          | Patients with carotid stenosis                    | 3018                 | Relevant outcome data not available |
|         | Stoughton <sup>146</sup> | 1998          | Patients with carotid stenosis                    | 208                  | Relevant outcome data not available |
|         | Sbarigia <sup>147</sup>  | 1999          | Patients with carotid stenosis                    | 107                  | Relevant outcome data not available |
|         | McCarthy <sup>148</sup>  | 2002          | Patients with carotid stenosis                    | 240                  | Neutral                             |
|         | CAVATAS <sup>149</sup>   | 2001          | Patients with carotid stenosis                    | 504                  | Neutral                             |
|         | Yadav <sup>150</sup>     | 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**

| Trial    | Odds Ratio (95% Confidence Intervals) |                     |                         |
|----------|---------------------------------------|---------------------|-------------------------|
|          | 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**

| Trial  | Odds Ratio (95% Confidence Intervals) |                     |                     |                       |
|--------|---------------------------------------|---------------------|---------------------|-----------------------|
|        | 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**

| Trial  | Odds Ratio (95% Confidence Intervals) |                     |                     |                      |
|--------|---------------------------------------|---------------------|---------------------|----------------------|
|        | 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**

| Trial  | Odds Ratio (95% Confidence Intervals) |                      |                     |                     |                      |
|--------|---------------------------------------|----------------------|---------------------|---------------------|----------------------|
|        | 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)  |

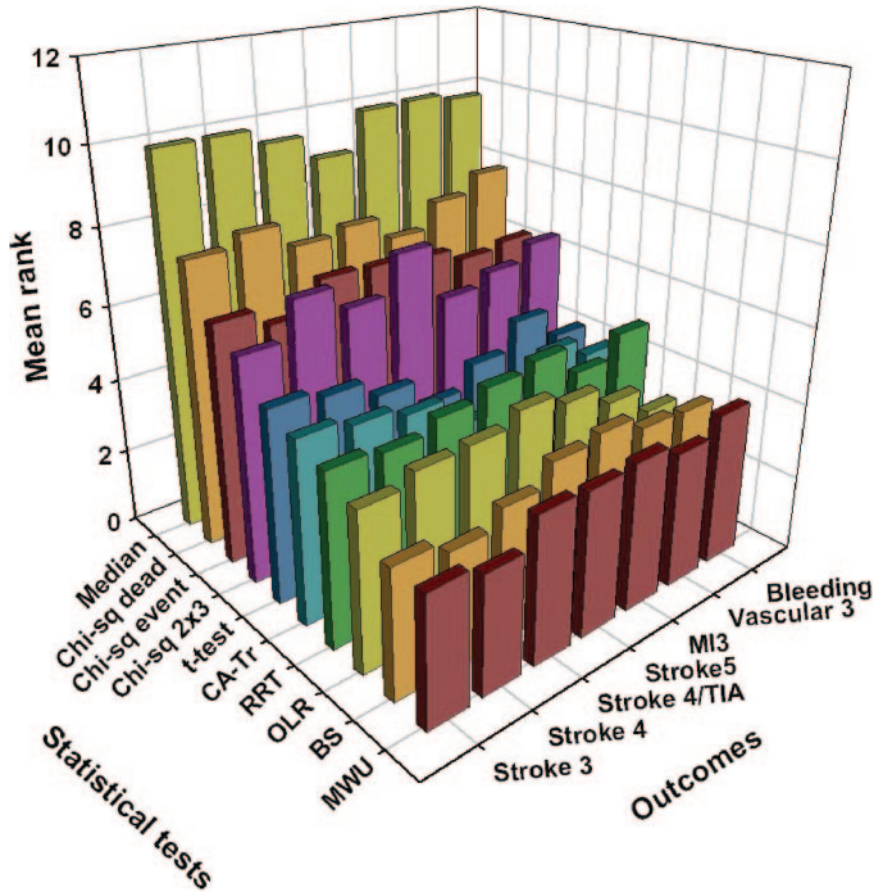


Figure 1. Ordering of statistical tests for stroke (3, 4 and 5-level), myocardial infarction (3-level), vascular events (3-level) and bleeding (3-level). Ordinal tests (Mann-Whitney *U* test, ordinal logistic regression) were superior (lower rank) to dichotomous tests.



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