Brief Report

The Effect of Medical Treatments on Stroke Risk in Asymptomatic Carotid Stenosis

Alice King, PhD; Martin Shipley, MSc; Hugh Markus, FRCP; for the ACES Investigators

Background and Purpose—Recent evidence suggests current best medical treatment may be sufficient to prevent stroke in patients with asymptomatic carotid stenosis. If this is the case, then it is important to determine risk reduction provided by treatments. Using Asymptomatic Carotid Emboli Study (ACES) prospective data, the effect of current treatment and risk factors on future stroke and transient ischemic attack risk were determined.

Methods—Four-hundred seventy-seven patients with asymptomatic carotid stenosis were followed-up every 6 months for 2 years. Changes in risk factors and stroke prevention therapies were reviewed at each visit. Using time-dependent Cox regression, the relationship between current treatment over time was determined and presented as hazard ratios and 95% confidence intervals for risk of stroke, transient ischemic attack, and cardiovascular death end points.

Results—On multivariate analysis, antiplatelets (P=0.001) and lower mean blood pressure (P=0.002) were independent predictors of reduced risk of ipsilateral stroke and transient ischemic attack. Antiplatelets (P<0.0001) and antihypertensives (P<0.0001) were independent predictors of a lower risk of any stroke or cardiovascular death.

Conclusions—Antiplatelet therapy and blood pressure control are the most important factors in reducing short-term stroke and cardiovascular risk in patients with asymptomatic carotid stenosis. More prospective data are required for medical treatments in asymptomatic carotid stenosis in particular for current statin usage. (Stroke. 2013;44:XXX-XXX.)

Key Words: carotid stenosis  ▪ risk prediction  ▪ stroke

The optimal treatment for primary prevention in patients with asymptomatic carotid stenosis is controversial. Carotid endarterectomy reduced the risk of stroke in 2 large trials. However, the absolute benefit was small, mainly because of the low risk of stroke in the medically treated group of ≈2% per annum. Recent evidence suggests that with newer more effective medical therapy, stroke risk is lower. There has been a reduction in stroke risk over the past 2 decades, which may mean there is little benefit from carotid endarterectomy.1,2

If this patient group is treated without surgery, then it is important to establish which medical approaches add to stroke prevention. Prospective studies have related risk factors (RFs) and medication at baseline to future risk,3–5 but there are little data on how taking into account changes in current medication influences risk in asymptomatic carotid stenosis. We used prospective Asymptomatic Carotid Emboli Study (ACES) data to address this question. ACES was an international, multicenter study of patients with asymptomatic carotid stenosis, with clinical follow-up over 2 years.6 Current medications, blood pressure (BP), and recurrent stroke or transient ischemic attack (TIA) were recorded at each 6-month follow-up visit. We evaluated treatment changes every 6 months and compared the effects of baseline treatments with current treatments and RFs over the 6-month intervals on the risk of stroke, TIA, and cardiovascular disease (CVD) death within the 2-year follow-up.

Methods

Patients

Inclusion and exclusion criteria and RF definitions for ACES have been published previously.6 RF treatment was left to the discretion of local physicians.

End Points

The predefined primary end point of ACES was ipsilateral stroke or TIA over 2 years of follow-up.4 A secondary end point was any stroke or CVD death.

Statistical Analysis

Treatments and RFs were compared to examine changes over follow-up and were stratified according to their values at baseline. Current treatment at the start of each 6-month period was used to define risk over the subsequent 6 months until next clinical follow-up using time-dependent Cox regression to calculate hazard ratios and 95% confidence intervals for primary and secondary end points. P<0.05 was considered significant. SPSS statistical software (version 18.0) was used. See online-only Data Supplement for further details of analysis.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.112.673608/-/DC1.

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Results
During follow-up, there were the following end points: ipsilateral stroke or TIA in 32; ipsilateral stroke alone in 10; any stroke in 18; and stroke death or CVD in 37; 29.1% of patients were using all 3 medical therapies and none of these patients experienced ipsilateral stroke during follow-up.

The proportions of demographics, treatments, and RFs at each visit are shown in the Table and as follows.

1. Lipid-lowering therapy. The proportion of patients using any lipid-lowering or statin therapy changed significantly (both $P<0.0001$) between visits (Table). Lipid-lowering therapy increased from baseline (65.8%) to 24 months (72.1%). Because statins were the predominant lipid-lowering therapy, only effects of statins are presented in further analyses.

2. Antihypertensive therapy and hypertension. The proportion of patients using $\geq 3$ antihypertensives increased from baseline (18.9%) to 24 months (23.6%) (Table). Corresponding with this, there was a reduced proportion of patients who were hypertensive (BP $\geq 140/90$ mm Hg) from baseline (14.7%) to 24 months (8.5%), and reduced mean systolic BP from baseline (147.5 mm Hg) to 24 months (141.5 mm Hg) over the same time period (Table).

3. Antithrombotic therapy. The proportion of patients prescribed antithrombotics over the study duration altered significantly ($P=0.003$). However, overall, antithrombics were prescribed at $\geq 95\%$ of follow-ups. Antiplatelet use or dual antiplatelet therapy was uncommon; therefore, only any antiplatelet (including dual) is presented in further analysis. Antiplatelets altered over follow-ups ($P<0.0001$); the major change was an increase at 6 months. There was no positive trend between use and study duration.

4. Smoking. Smoking status of patients varied between visits ($P=0.017$; Table).

Relationship Between Treatments, Risk Factors, and Clinical End Points

Univariate Analysis
None of the baseline treatments predicted risk of ipsilateral stroke or TIA (Figure 1). However, baseline mean BP weakly predicted any stroke or CVD death ($P=0.03$). In comparison to baseline measures, univariate associations between current treatments or RFs and subsequent risk are shown in Figure 2A and as follows.

1. Statins. Statins were associated with a lower risk of ipsilateral stroke or TIA ($P=0.04$) and of any stroke or CVD death ($P<0.0001$).

2. Antihypertensives and BP. Antihypertensives predicted a lower risk of ipsilateral stroke or TIA ($P=0.01$) and any stroke or CVD death ($P<0.0001$). BP was strongly associated with ipsilateral stroke or TIA and any stroke or CVD death (all $P<0.0001$). The association of antihypertensives with ipsilateral stroke or TIA was largely mediated via BP control (Figure 2B).

3. Antiplatelets. Antiplatelets predicted a lower risk of ipsilateral stroke or TIA and any stroke or CVD death (both $P<0.0001$).

4. Smoking. Smoking was a predictor of risk of ipsilateral stroke or TIA ($P=0.01$) and any stroke or CVD death ($P<0.0001$).

Multivariate Analysis
Multivariate analyses were performed including antihypertensives, antiplatelets, and statins (Figure 2C). Antiplatelets ($P<0.0001$) were an independent predictor of a reduced risk of ipsilateral stroke or TIA. Statins, antihypertensives, age, and sex were not predictors of ipsilateral stroke or TIA. Antiplatelets ($P<0.0001$) and antihypertensives ($P<0.0001$) were independent predictors of a lower risk of any stroke or CVD death. Male sex (hazard ratios, 4.12; 95% confidence interval, 1.26–13.51; $P=0.02$) also was an independent predictor of any stroke or CVD death. Statins and age were not significant predictors of any stroke or CVD death.

A multivariate analysis also was performed replacing antihypertensives with mean BP to determine the effectiveness of BP control for future risk (Figure 2D). Antiplatelets ($P=0.001$) and mean BP ($P=0.002$) were independent predictors of a reduced risk of ipsilateral stroke or TIA. Statins, age, and sex were not significant predictors of ipsilateral stroke or TIA. Antiplatelets ($P<0.0001$) were independent predictors of a lower risk of any stroke or CVD death. Mean BP ($P=0.006$) and male sex (hazard ratios, 4.72; 95% confidence interval, 1.45–15.38; $P=0.01$) also were independent predictors of any stroke or CVD death. Statins and age were not significant predictors of any stroke or CVD death.

Discussion
These results emphasize the importance of controlling conventional cardiovascular RFs in patients with asymptomatic carotid stenosis.

On univariate analysis hypertension, BP, smoking, statins, and antiplatelets all were associated with the end points. On multivariate analysis, hypertension, BP, smoking, and antiplatelets were associated with reduced ipsilateral TIA and stroke, whereas antiplatelets, mean BP, and antihypertensives were associated with any stroke or CVD death.

Patients were followed-up every 6 months and changes in treatment were recorded. Therefore, we associated current treatments and current RF with events in each subsequent 6-month period. This showed current treatments such as antiplatelets reduced the risk of stroke or TIA. The estimates for ipsilateral stroke or TIA favored statin and antihypertensives treatment, and for any stroke or CVD death the estimates favored statin treatment.

Antiplatelets are widely used in the secondary prevention of stroke, but evidence for their efficacy in primary prevention is less clear. One previous trial of aspirin in asymptomatic carotid stenosis found no benefit, although this was performed some time ago (1988–1994) when there was less effective treatment of vascular RF, and the annual rate of ischemic event was high, at $\sim 11\%$. This study included patients with $\geq 50\%$ stenosis compared with the $\geq 70\%$ stenosis cut-off used in our study. Our data suggest antiplatelets are important in patients with asymptomatic carotid stenosis. Because the majority of patients were only using aspirin, we did not
have the power to examine efficacy between different or dual antiplatelets.

Limitations of this study include a lack of knowledge of the treatment duration before recruitment and lack of blood tests to assess efficacy of statin therapy, for example, achieved low-density lipoprotein cholesterol level; therefore, these could not be used to assess treatment efficacy. There was also an increase in statin and aspirin usage and a decrease in smoking from 1999 to 2009. However, the number of patients using statins in ACES is likely to be less than in current clinical practice, which may account for the nonsignificance of statins in the multivariate model. In addition, the study had a small sample size and follow-up for this study was 2 years; further data are required to show the effect of medical therapies

Table. Risk Factors, Demographics, and Proportions of Patients Using Lipid-Lowering Antithrombotics and Antihypertensives at 6-Month Intervals

<table>
<thead>
<tr>
<th>Time</th>
<th>Baseline</th>
<th>6 Months</th>
<th>12 Months</th>
<th>18 Months</th>
<th>24 Months</th>
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<tr>
<td>Total Patients</td>
<td>477</td>
<td>450</td>
<td>411</td>
<td>377</td>
<td>365</td>
</tr>
<tr>
<td></td>
<td>n (%) or Mean (SD)</td>
<td>n (%) or Mean (SD)</td>
<td>n (%) or Mean (SD)</td>
<td>n (%) or Mean (SD)</td>
<td>n (%) or Mean (SD)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>355 (74.4)</td>
<td>337 (74.9)</td>
<td>297 (72.3)</td>
<td>272 (72.2)</td>
<td>263 (72.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>98 (20.6)</td>
<td>95 (21.1)</td>
<td>85 (20.7)</td>
<td>81 (21.5)</td>
<td>76 (20.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>35 (7.3)</td>
<td>32 (7.1)</td>
<td>25 (6.1)</td>
<td>22 (5.8)</td>
<td>21 (5.8)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>177 (37.1)</td>
<td>167 (37.1)</td>
<td>144 (35)</td>
<td>127 (33.7)</td>
<td>120 (32.9)</td>
</tr>
<tr>
<td>Previous ischemia</td>
<td>139 (29.1)</td>
<td>133 (29.6)</td>
<td>123 (29.9)</td>
<td>116 (30.8)</td>
<td>113 (31)</td>
</tr>
<tr>
<td>Any lipid-lowering drug</td>
<td>314 (65.8)</td>
<td>310 (68.9)</td>
<td>296 (72)</td>
<td>268 (71.1)</td>
<td>263 (72.1)</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>297 (62.3)</td>
<td>298 (66.2)</td>
<td>286 (69.3)</td>
<td>258 (68.4)</td>
<td>256 (70.1)</td>
</tr>
<tr>
<td>Any Antihypertensive</td>
<td>376 (78.8)</td>
<td>361 (80.2)</td>
<td>336 (81.8)</td>
<td>299 (79.3)</td>
<td>292 (80)</td>
</tr>
</tbody>
</table>

N of antihypertensives

1 | 171 (35.9) | 153 (34) | 135 (32.9) | 115 (30.5) | 116 (31.8) | <0.001 |
2 | 115 (24.1) | 117 (26) | 115 (28) | 102 (27.1) | 93 (25.5) |
≥3 | 90 (18.9) | 91 (20.2) | 86 (20.9) | 82 (21.8) | 86 (23.6) |
Blood pressure ≥140/90 mm Hg | 70 (14.7) | 55 (12.2) | 57 (13.9) | 51 (13.5) | 31 (8.5)  | <0.0001 |
Systolic BP, mm Hg | 147.51 (18.6) | 145.1 (18.8) | 145.2 (21.0) | 145.6 (17.8) | 141.5 (17.7) | 0.0001 |
Antithrombotics | 447 (93.7) | 429 (95.3) | 393 (95.6) | 358 (95) | 346 (94.8) | 0.003 |
Any antiplatelets | 419 (87.8) | 429 (95.3) | 369 (89.8) | 333 (88.3) | 321 (88)  | <0.001 |
Dual AP or clopidogrel alone | 88 (18.5) | 87 (19.3) | 91 (22.1) | 81 (21.5) | 76 (20.8)  | <0.001 |
Smoking status

Never | 185 (38.8) | 170 (37.8) | 161 (39.2) | 148 (39.3) | 144 (39.5) | 0.017 |
Current | 70 (14.7) | 72 (16) | 66 (16.1) | 61 (16.2) | 52 (14.3) |
Former | 222 (46.5) | 205 (45.6) | 184 (44.8) | 170 (45.1) | 170 (46.6) |

AP indicates antiplatelets; BP, blood pressure; NS indicates not significant.

*P value for test of whether patients changed treatment throughout the study period.
and controlling risk factors over longer follow-up in larger studies.

Our data emphasize the importance of BP control in asymptomatic carotid stenosis. Mean BP was related to risk of stroke and TIA. On univariate analysis, antihypertensive use was related to a reduced ipsilateral stroke or TIA risk, but this association disappeared after controlling for mean BP level.

A considerable body of evidence has shown that statins reduce risk in stroke and atherosclerosis; the lack of effect we found with statin therapy may partly reflect the short time duration of follow-up. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, a reduction in risk only started appearing after 1 to 2 years of follow-up.

In summary, our data show that medical treatments can reduce risk in asymptomatic stenosis over relatively short time periods. This is consistent with recent clinical trials and epidemiological studies suggesting that intensive RF treatment significantly reduces stroke rate in asymptomatic carotid stenosis. Importantly, there were no ipsilateral strokes in any patient receiving all 3 medical therapies. Further trials are required to determine whether more intensive treatments will reduce the risk of stroke below that at which patients may benefit from interventions, such as carotid endarterectomy. Interestingly, in ACES, the risk of stroke was nearer to 1% (10/477) than 2%, suggesting stroke rates already may have decreased since the trials of endarterectomy in asymptomatic carotid stenosis were performed.

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Disclosures
None.

References


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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/11/27/STROKEAHA.112.673608.DC1

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Supplemental Material

Supplemental Methods

ACES was designed to assess whether detection of embolic signals could predict stroke risk in patients with asymptomatic carotid stenosis. This was a post-hoc analysis of ACES data.

Study inclusion criteria were: carotid stenosis (70-99% luminal occlusion, established by carotid duplex ultrasound), which had been asymptomatic for ≥2 years. Patients with previous symptoms in the contralateral carotid or vertebrobasilar territory were only eligible if symptoms were ≥2 years prior to recruitment. Patients with previous contra-lateral carotid endarterectomy (CEA) were eligible 1 year following surgery assuming they had remained asymptomatic in the territory of the operated artery since operation.

Exclusion criteria were: concurrent diseases likely to limit life expectancy to less than 3 years; if the patient, physician or surgeon was unwilling to manage asymptomatic carotid stenosis medically; absence of an acoustic window necessary for TCD, and the presence of non-biological prosthetic heart valves.

Brain imaging with CT or MRI was performed at baseline. Subjects were followed at 6, 12, 18 months with final follow up at 24 months. If stroke or transient ischaemic attack (TIA) occurred during follow-up, a further brain CT or MRI was performed.

In addition to follow-up for new ischaemic events every 6 months, details of anti-platelets, anti-coagulants, anti-hypertensives and lipid-lowering agents was recorded. Smoking status was confirmed every 6 months. Blood pressure (BP) was measured with recordings of systolic and diastolic pressures every 6 months. Hypertension was defined as taking antihypertensive medication, and/or systolic or diastolic BP >140 or >90 mmHg respectively. Mean BP was calculated where mean arterial pressure = Diastolic BP + 1/3 (Systolic BP - Diastolic BP). Diabetes mellitus included clinical diagnoses of type I and type II disease. Ischaemic heart disease represented a history of angina or previous myocardial infarction. Peripheral vascular disease was recorded if
there was a history of symptomatic disease. The presence of atrial fibrillation (AF) was recorded either on history or, if evident, on electrocardiogram (ECG) evaluation at recruitment. Lipid-lowering agents that were used were statins, fibrates and ezetimibe and their combinations. Anti-hypertensives used included calcium channel blockers, ACE inhibitors, angiotensin 2 receptor blockers, diuretics, beta-blockers, nitrates and alpha 1 blockers. Anti-thrombotics prescribed were aspirin, Dipyridamole, Clopidogrel, Ticlopidine and other antplatelets [trifusal, indobufene, picotamide] or any anticoagulation (heparin or warfarin) and combinations of anti-thrombotic therapies. This study was approved by the local ethics committees and all subjects gave written informed consent.

Atrial fibrillation(AF) was not an exclusion criteria and there were 35 patients with AF. Five had ipsilateral stroke/TIA and four of these were treated with CEA. One additional patient had vertebrobasilar stroke.

During follow-up there were 32 ipsilateral stroke/TIA, 10 ipsilateral stroke, 18 any stroke, 37 any stroke/CVD death 37. 34 patients had CEA: 16 after ipsilateral TIA, one after ipsilateral stroke, and 17 for asymptomatic stenosis. Follow up visits continued if a patient had a TIA, but stopped after a stroke or CEA.

**Statistical methods**

To analyse differences in treatments and BP between each follow-up period, Cochrans Q (dichotomous outcomes) or Friedmans ANOVA (continuous outcomes) test was performed in order to assess whether patients remained on the same treatments throughout the study period. Post-hoc Wilcoxon or McNemar tests for proportions were used (Bonferroni correction and p value ≤0.005 considered significant) where Cochrans Q was p<0.05 to observe where the difference in time points lay.

In standard Cox proportional hazards the risk of an event over time is related to variables which are assessed only at baseline, at the start of the follow-up period, however it relies on the assumption that these variables stay constant over time. During follow-up in studies with long duration (especially in observational studies), and with repeated follow-up these variables are likely to change and use of the baseline values will often not reflect
subjects’ current risk status. These changes can be incorporated into the prediction of stroke risk, by using time-dependent Cox regression (which relaxes the assumption that variable stay constant over time) to calculate hazard ratios (HR) and their 95% confidence intervals (CI) for primary and secondary endpoints. Using the Time program (SPSS), time-dependent variables were defined and used to calculate risk at each time-point throughout the study. The current status of each time-dependent variable (e.g. statin treatment) at the start of each 6 month period was included and the time was defined until the start of the next 6 month period. Current treatment at the start of each six month period was therefore used to define risk over the subsequent 6 months until next clinical follow-up. The one HR given is the hazard ratio of outcome events over the subsequent 6 month period for not being currently on the treatment. P values <0.05 were considered statistically significant.

Univariate analysis of time-dependent covariates adjusted for age and sex was performed. The anti-hypertensive treatment time dependent covariate was analysed in combination with time dependent mean BP to examine whether changes in mean BP was an independent predictor of risk given anti-hypertensive treatment. A multivariate analysis was then performed where all time-dependent covariates were analysed in backward Cox regression model adjusting for age and sex. This was performed by starting with all variables entered into the model. The parameters of all variables are then assessed. Those contributing are included into the final model, with age and sex forced “enter” into the model. The relationship between BP and stroke outcomes has been expressed using HRs associated with a 10mmHg increase in BP.
Supplementary Table. Proportion of patients with treatments at risk factors over follow-up

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<td></td>
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<td>740</td>
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<tr>
<td>Ever</td>
<td>Current smoker</td>
<td>1168</td>
<td>200</td>
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Top panel: Proportion of follow-up visits on treatments (statins, anti-hypertensives and antiplatelets) according to the baseline treatment. Bottom panel: Proportion of follow-up visits with risk factors (smoking and hypertensive) according to the baseline risk factor.
ACES Study personnel

Co-ordinating centre office: St George's University of London, Hugh Markus (Principal investigator), Alice King (Study co-ordinator 17/10/2008 to current) Jennifer Siegel (Study co-ordinator 30/04/2007-17/10/2008), Sheila Reihill (Study co-ordinator 07/03/2003-29/04/2007), Marisa Cullinane (Study co-ordinator 16/08/1999-06/03/2003), Helen McCorie, Emma Morgan, Sun Kwon, Raffi Topakian, Kelly Jones, Ruth Keating. Study statistician: Martin Shipley, University College, London, UK.

Participating centres, study personnel and number of patients recruited.
Bretonneau Hospital, France (Francois Tranquart & Aurore Bleuzen) – 2
Charing Cross Hospital, UK (Alun Davies) – 6
Harbin Medical University, China (Song-Bin Qu) - 20
Institute of Psychiatry and Neurology, Poland (Anna Czlonkowskia, Anna Rozenfeld, Anna Piorkowska & Marta Skowronska) - 5
James Connolly Memorial Hospital, Ireland (Dermot Fitzgerald & Nuala McMahon) - 8
JW Goethe University, Germany (Matthias Sitzer & Oliver Singer) - 14
Kings College Hospital, UK (Paul Baskerville, Colin Deane & David Goss) -31
Leicester Royal Infirmary, UK (Ross Naylor & Jo Walker) - 23
Martini Ziekenhuis Groningen, The Netherlands (Arjen Schaafsma & An Fokkens) - 84
Prince of Wales Hospital, Hong Kong (Lawrence Wong, Sunny Qing Hao, & Roxanna Liu) - 3
Rabin Medical Centre, Israel (Jonathan Streifler & Tilda Sabah) -7
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Singapore General Hospital Campus, National Neuroscience Institute, Singapore (Hui-Meng Chang, Moi Pin Lee, Meng Cheong Wong & Christopher PLH Chen) - 15
South Manchester University Hospital, UK (Charles McCollum, Sarah Welsh & Zoe Bonner) - 26
State Medical Academy, Georgia (Marina Alpaidze, Nana Metreveli) – 12
St George’s University of London, UK (Hugh Markus & Jennifer Siegel) – 71
Tel Aviv Sourasky Medical Centre, Israel (Natan Bornstein, Alex Gur & Sigal Lorenz) - 46
UCL Institute of Neurology, UK (Martin M Brown) - 1
UCLA School of Medicine, USA (Jeffrey Saver & Gina Paek) -5
University Hospital Josep Trueta, Spain (Joaquin Serena & Xavier Ustrell) -19
University Hospital Zagreb, Croatia (Vida Demarin & Vlasta Vukovic) - 12
University Medical Centre Ljubljana, Slovenia (Bojana Zvan & Janja Pretnar) - 4
University of Dusseldorf, Germany (Mario Siebler, Holger Schade, Torge Brosig, Christina Boettcher & Verica Jovanovic) - 8
University of Münster, Germany (E. Bernd Ringelstein, Martin Ritter & Ralf Dittrich) - 19
Vilnius University, Lithuania (Dalius Jatuzis) – 19
Wagner-Jauregg Hospital, Linz (Franz Aichner & Stefan Guggenberger) -1