Intravenous Thrombolysis in Nonagenarians With Ischemic Stroke

Hakan Sarikaya, MD; Marcel Arnold, MD; Stefan T. Engelter, MD; Philippe A. Lyser, MD; Patrik Michel, MD; Céline Odier, MD; Bruno Weder, MD; Barbara Tettenborn, MD; Felix Mueller, MD; Lucka Sekoranja, MD; Roman Sztajzel, MD; Pietro Ballinari, PhD*; Heinrich P. Mattle, MD; Ralf W. Baumgartner, MD

Background and Purpose—Demographic changes will result in a rapid increase of patients age ≥90 years (nonagenarians), but little is known about outcomes in these patients after intravenous thrombolysis (IVT) for acute ischemic stroke. We aimed to assess safety and functional outcome in nonagenarians treated with IVT and to compare the outcomes with those of patients age 80 to 89 years (octogenarians).

Methods—We analyzed prospectively collected data of 284 consecutive stroke patients age ≥80 years treated with IVT in 7 Swiss stroke units. Presenting characteristics, favorable outcome (modified Rankin scale [mRS] 0 or 1), mortality at 3 months, and symptomatic intracranial hemorrhage (SICH) using the National Institute of Neurological Disorders and Stroke (NINDS) and Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria were compared between nonagenarians and octogenarians.

Results—As compared with octogenarians (n=238; mean age, 83 years), nonagenarians (n=46; mean age, 92 years) were more often women (70% versus 54%; P=0.046) and had lower systolic blood pressure (161 mm Hg versus 172 mm Hg; P=0.035). Patients age ≥90 years less often had a favorable outcome and had a higher incidence of mortality than did patients age 80 to 89 years (14.3% versus 30.2%; P=0.034; and 45.2% versus 22.1%; P=0.002; respectively), while more nonagenarians than octogenarians experienced a SICH (SICHNINDS, 13.3% versus 5.9%; P=0.106; SICHSITS-MOST, 13.3% versus 4.7%; P=0.037). Multivariate adjustment identified age ≥90 years as an independent predictor of mortality (P=0.017).

Conclusions—Our study suggests less favorable outcomes in nonagenarians as compared with octogenarians after IVT for ischemic stroke, and it demands a careful selection for treatment, unless randomized controlled trials yield more evidence for IVT in very old stroke patients. (Stroke. 2011;42:1967-1970.)

Key Words: outcome ■ thrombolysis ■ ischemic stroke ■ nonagenarian

Age is the most important nonmodifiable risk factor for stroke and is a major predictor of clinical outcome after ischemic stroke, with increased mortality and higher risk of intracranial hemorrhage by advancing age.1,2 In elderly patients, evidence from randomized controlled trials for benefit of intravenous thrombolysis (IVT) with alteplase is scarce, as patients over 80 years of age are either underrepresented or excluded in these trials.3,4 Several observational studies reported outcomes in patients age ≥80 years with ischemic stroke and suggested potential benefit of IVT,5–7 but little is known about outcome specifically in nonagenarians. Nonetheless, demographic changes result in excessive growing of the “oldest-old” population. Thus, the number of nonagenarians will increase almost 8-fold to 57 million people worldwide by 2050.8 Therefore, we undertook this study to assess rates of symptomatic intracranial hemorrhage (SICH), mortality, and favorable outcome in nonagenarians treated with IVT for ischemic stroke and compared the data with outcomes in octogenarians.

Patients and Methods

As a joint initiative of 7 stroke centers in Switzerland, we designed a study to compare outcomes in nonagenarians with octogenarians after IVT for ischemic stroke. All participating centers used IVT according to current guidelines.9 Neither center applied an upper age limit for IVT, because in Switzerland alteplase is licensed for

Received August 29, 2010; Accepted January 25, 2011.

From the Department of Neurology (H.S., R.W.B.), University Hospital of Zurich, Switzerland; Department of Neurology (M.A., H.P.M.), University Hospital of Bern, Switzerland; Department of Neurology (S.T.E., P.A.L.), University Hospital of Basel, Switzerland; Department of Neurology (P.M., C.O.), University Hospital of Lausanne, Switzerland; Department of Neurology (B.W., B.T.), Cantonal Hospital of St. Gallen, Switzerland; Department of Neurology (F.M.), Cantonal Hospital of Muensterlingen, Thurgau, Switzerland; Department of Neurology (L.S., R.S.), University Hospital of Geneva, Switzerland; Institute of Psychology (P.B.), University of Bern, Switzerland.

*Statistical analysis performed by P.B.

Correspondence to Hakan Sarikaya, MD, Neurology Department, University Hospital of Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland. E-mail hakan.sarikaya@usz.ch

© 2011 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.110.601252

1967
ischemic stroke without age restrictions. Patients and relatives were informed about limited evidence for the effectiveness of alteplase in patients age ≥80 years, and informed consent was obtained prior to the treatment. A standardized form was used to collect data with predefined variables as done in a previous study with similar methodology. We analyzed data of consecutive patients age 80 years or older who were treated with intravenous alteplase for acute ischemic stroke between January 1, 2000, and December 31, 2008. The following variables were ascertained: age, sex, vascular risk factors according to predefined criteria, history of coronary artery disease, antithrombotic medication at stroke onset, baseline National Institutes of Health Stroke Scale (NIHSS) score, stroke etiology according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria, time-to-treatment, blood pressure, and blood glucose level obtained at admission. All patients treated with IVT were admitted to intermediate or intensive care units for at least 24 hours. All patients underwent brain imaging with computed tomography or magnetic resonance imaging 24 to 48 hours after IVT and in any case of clinical deterioration. Clinical outcome was assessed by outpatient visits or structured telephone interviews using the modified Rankin Scale (mRS) score at 3 months.

The primary outcome measure was favorable outcome, defined as mRS score 0 to 1 and mortality at 3 months. Secondarily, we assessed rate of SICH by applying the definition from the National Institutes of Health Stroke Scale (SICHSITS-MOST). In addition, we also used the more conservative definition from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SICHSTS-MOST). 

### Statistical Analysis

Normally distributed data were expressed as mean±SD and compared using unpaired, 2-tailed t-test. The 2 groups (nonagenarians and octogenarians) were compared using Mann-Whitney U test for continuous variables and a χ² or a Fisher exact test (the latter if some expected counts in the 2-by-2 table were <5) for binary variables. Multiple logistic regression analyses were performed to assess the joint effects of age and stroke risk factors on the outcome parameters SICH, mortality, and favorable outcome. In the first step, the influence of every single potential predictor on the outcomes was evaluated using univariate logistic regression analyses. The parameters excluded were baseline NIHSS score, time-to-treatment, systolic and diastolic blood pressure, blood glucose level on admission (continuous variables), age (80–89 years versus 90–99 years), sex, arterial hypertension, smoking, diabetes mellitus, hypercholesterolemia, coronary heart disease, and antithrombotic medication with antiplatelets or anticoagulants at stroke onset (categorical variables). In the second step, a multivariate logistic regression analysis was performed, including all potential predictors with a probability value <0.2 from univariate analyses in the model. Significance was declared at P<0.05.

### Results

Forty-six nonagenarians (mean age, 92; range, 90–99 years) and 238 octogenarians (mean age, 83; range, 80–89 years) were eligible for this study. As compared with their counterparts, nonagenarians were more often women (70% versus 54%; P=0.046), had a lower systolic blood pressure (160 mm Hg versus 172 mm Hg; P=0.035), and tended to have slightly more severe strokes by a mean NIHSS score of 1.5 points, which was not significant (Table 1). Nine of 46 nonagenarians (19.6%) and 52 of 238 octogenarians (21.8%) were treated beyond the 3-hour time window (P=0.730), while 10 of 237 octogenarians (4.2%) and none of nonagenarians were treated with oral antiocoagulants at stroke onset (P=0.375). Time-to-treatment and other vascular risk factors did not differ significantly between the 2 groups (Table 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonagenarian (n=46)</th>
<th>Octogenarian (n=238)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>14/46 (30.4)</td>
<td>110/237 (46.4)</td>
<td>0.046</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>39/46 (84.8)</td>
<td>193/238 (81.1)</td>
<td>0.554</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>3/45 (6.7)</td>
<td>29/238 (12.2)</td>
<td>0.284</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>5/45 (11.1)</td>
<td>33/238 (13.9)</td>
<td>0.619</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>12/44 (27.3)</td>
<td>93/235 (39.6)</td>
<td>0.122</td>
</tr>
<tr>
<td>Antplatelet medication at stroke onset (%)</td>
<td>24/46 (52.2)</td>
<td>107/237 (45.1)</td>
<td>0.382</td>
</tr>
<tr>
<td>Anticoagulation at stroke onset (%)</td>
<td>0/46 (0)</td>
<td>10/237 (4.2)</td>
<td>0.375†</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>13/45 (28.9)</td>
<td>50/238 (21.0)</td>
<td>0.244</td>
</tr>
<tr>
<td>Mean NIHSS score±SD</td>
<td>14.4±6.7</td>
<td>12.9±5.9</td>
<td>0.126†</td>
</tr>
<tr>
<td>Time to treatment±SD</td>
<td>148.8±51.1</td>
<td>159.6±40.7</td>
<td>0.116†</td>
</tr>
<tr>
<td>Mean systolic blood pressure±SD, mm Hg</td>
<td>161.1±28.7</td>
<td>172.0±25.9</td>
<td>0.035†</td>
</tr>
<tr>
<td>Mean diastolic blood pressure±SD, mm Hg</td>
<td>85.7±20.8</td>
<td>90.1±18.0</td>
<td>0.175†</td>
</tr>
<tr>
<td>Mean blood glucose±SD, mmol/L</td>
<td>7.0±2.9</td>
<td>7.1±2.3</td>
<td>0.842†</td>
</tr>
<tr>
<td>Cause of stroke</td>
<td></td>
<td></td>
<td>0.312</td>
</tr>
<tr>
<td>Large artery atherosclerosis (%)</td>
<td>10/45 (22.2)</td>
<td>79/238 (33.2)</td>
<td></td>
</tr>
<tr>
<td>Cardiac embolism (%)</td>
<td>22/45 (48.9)</td>
<td>80/238 (33.6)</td>
<td></td>
</tr>
<tr>
<td>Small artery disease (%)</td>
<td>2/45 (4.4)</td>
<td>13/238 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Other determined etiology (%)</td>
<td>0/45 (0)</td>
<td>4/238 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Undetermined etiology (%)</td>
<td>11/45 (24.4)</td>
<td>62/238 (26.1)</td>
<td></td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; IVT, intravenous thrombolysis; SD, standard deviation. 
*P-values apply to χ² tests unless otherwise indicated. 
†t test. 
‡Fisher exact test.

At 3 months, 6 of 42 nonagenarians reached a favorable outcome (Table 2). In comparison, the frequency of favorable outcome in octogenarians was significantly higher (30.2% versus 14.3%; P=0.034). Logistic regression analyses identified NIHSS score (<0.001), antiplatelet medication (P=0.003), diabetes mellitus (P=0.006), and anticoagulants (P=0.007) to be independently associated with clinical outcome at 3 months, while the association with age ≥90 years was no longer significant (P=0.147).

Within the nonagenarian group, 6 of 10 men (60%; 95% CI, 23.1 to 96.9) experienced a favorable outcome, whereas all 32 women (100%) had an unfavorable outcome (P<0.001). Furthermore, nonagenarians with a favorable outcome had less severe strokes (mean NIHSS score, 11 versus 16 points; P=0.028), whereas no association was identified with time-to-treatment and the age of nonagenarians. Mortality in nonagenarians was significantly higher as compared with octogenarians (45.2% versus 22.1%; P=0.002; Table 2). After multivariable adjustment, independent predictors of mortality were age ≥90 years (P=0.017), anticoagulants (P=0.049), and NIHSS score (P<0.001).

Classification of SICH was available in 45 of 46 nonagenarians. Six patients age ≥90 years experienced a SICH (according to NINDS and SITS-MOST criteria), of which 5 were fatal, and 1 caused severe disability (mRS, 5). Com-
pared with octogenarians, the risk of SICH in nonagenarians was about 2-fold higher. The difference was statistically significant by using the SITS-MOST criteria (13.3% versus 4.7%; \( P=0.034 \)), but not the NINDS criteria (13.3% versus 5.9%; \( P=0.106 \); Table 2). Multivariate analyses did not identify an independent predictor of SICH. In nonagenarians, 5 of 6 SICH (83.3%) were fatal. In comparison, 5 of 14 SICH (35.7%) were fatal in octogenarians, but the difference was statistically not significant (\( P=0.141 \)). Fatal SICH in nonagenarians (5 of 19; 26.3%) tended to account more often for mortality as compared with octogenarians (5 of 52; 9.6%). The difference was not statistically significant (\( P=0.118 \)).

### Discussion

This multicenter observational study assessed clinical outcomes in stroke patients age \( \geq 90 \) years treated with IVT, and it suggests poor outcomes for this age group; about 1 of 7 patients reached a favorable outcome and nearly half of the population died within the first 3 months after stroke. Also, 13% of patients experienced a SICH, all of which caused either death or severe disability. Nonagenarians had about a 2-fold higher risk for unfavorable outcome, mortality, and SICH, as compared with octogenarians.

Only 6 of 42 nonagenarians (14%) reached a favorable outcome at 3 months, while clinical outcome was favorable in 30% of octogenarians (\( P=0.034 \)). Our results are in concordance with the study from the Mayo Clinic that reported favorable outcome in 2 of 20 alteplase-treated nonagenarians (10%) at 30 days. In contrast, the recently published posthoc analysis of the Canadian Activase for Stroke Effectiveness Study (CASES) showed similar outcomes in nonagenarians at 30 days as compared with octogenarians (30% versus 26%). In our population of nonagenarians, age, stroke severity, and time-to-treatment were similar to those observed in the CASES registry, and thus they do not explain different outcomes. Comorbidities (eg, previous stroke, cancer, dementia, and congestive heart failure) and prestroke disability might have differed between the 2 populations as a probable explanation. Another finding of our study is worse clinical outcome in women age \( \geq 90 \) years as compared with their male counterparts. This may have implications for clinical practice, since women comprise higher population proportions in advanced age, and the female-male ratio will dramatically increase by every decade of age in future. However, the wide 95% CI preclude any definite conclusion.

The 3-month mortality in nonagenarians treated with IVT reached 45%, which was 2-fold higher as compared with that of octogenarians. Our finding is in accordance with 3 recent studies that reported 3-month mortality of 51% to 59% in stroke patients age \( \geq 90 \) years undergoing IVT. The higher incidence of SICH in nonagenarians may have contributed to the difference in mortality between the 2 populations. Furthermore, age is an independent predictor of mortality, and studies on IVT reported an increased 3-month mortality with older age up to 40% in stroke patients age \( \geq 80 \) years. The same is true for elderly stroke patients who are not treated with IVT. The 3-month mortality of 45% reported in stroke patients age \( \geq 80 \) years without thrombolysis is consistent with that observed in nonagenarians from our study. Finally, mean NIHSS score in nonagenarians was 1.5 points higher than in octogenarians, and multivariate analyses identified NIHSS score as an independent predictor of mortality. These data suggest that, rather than IVT alone, other factors such as older age, comorbid conditions, and stroke severity may be substantially related to the high mortality in nonagenarians; this was consistent with the natural history reported in this age group.

The rate of SICH in nonagenarians was higher as compared with octogenarians, and the difference was significant according to the SITS-MOST criteria, but not according to the NINDS criteria. Age \( \geq 90 \) years did not predict SICH after multivariate logistic regression analyses, but all SICH in this age category were severe, with most of them leading to death. In comparison, data from CASES registry showed a relative risk of 1.7 for SICH in nonagenarians as compared with octogenarians after IVT, which was not statistically significant. The higher incidence of SICH in patients age \( \geq 90 \) years may be explained by impaired ability to clear alteplase and higher frequency of cerebral amyloid angiopathy and leukoaraiosis by advancing age; this might be more pronounced in nonagenarians than in octogenarians. In contrast, the risk of SICH in octogenarians was comparable to that in the NINDS trial and is line with findings of a systematic review and a recently published large-scale study that reported a similar risk of SICH in stroke patients age \( \geq 80 \) years and <80 years of age.
This study has some limitations. It is a multicenter observational study performed in clinical setting, and IVT was performed at the discretion of the treating physicians. Thus, a selection bias is likely, and baseline characteristics such as age, stroke severity, blood pressure, glycaemia, and imaging findings might have influenced the decision whether to administer IVT. Some baseline variables that could potentially influence stroke outcome, such as previous stroke in past medical history, prestroke disability, and atrial fibrillation, were not available for analysis. Furthermore, the cohort size of nonagenarians was small, so the possibility of a type II error must be admitted. Finally, there is no age-matched control group, and assessment of the mRS score at 3 months was not blinded to the clinical condition of the patients during the hospital stay and at discharge.

In conclusion, the observational design of this study does not allow us to judge the efficacy and safety of IVT in nonagenarians with ischemic stroke. Nonetheless, our data suggest less frequent favorable outcomes, higher mortality, and more frequent SICH in nonagenarians as compared with octogenarians. These findings may be useful for accurate adjusting of patient and family expectations. Furthermore, a careful selection of patients age ≥90 years for IVT is needed in view of less favorable outcomes in this age population. Randomized controlled trials such as the ongoing International Stroke Trial-3 would yield more evidence on the balance of risk and benefit of IVT in stroke patients age 90 years and older. Our study will hopefully stimulate additional research interest in this progressively growing very-elderly patient population.

Disclosures

None.

References


Intravenous Thrombolysis in Nonagenarians With Ischemic Stroke
Hakan Sarikaya, Marcel Arnold, Stefan T. Engelter, Philippe A. Lyrer, Patrik Michel, Céline Odier, Bruno Weder, Barbara Tettenborn, Felix Mueller, Lucka Sekoranja, Roman Sztajzel, Pietro Ballinari, Heinrich P. Mattle and Ralf W. Baumgartner

Stroke. 2011;42:1967-1970; originally published online May 19, 2011;
doi: 10.1161/STROKEAHA.110.601252

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/7/1967

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/10/08/STROKEAHA.110.601252.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
90대의 허혈뇌졸중 환자들에서의 정맥내 혈전용해술

Intravenous Thrombolysis in Nonagenarians With Ischemic Stroke

Hakan Sarikaya, MD; Marcel Arnold, MD; Stefan T. Engelter, MD; Philippe A. Lyrer, MD; Patrik Michel, MD; Céline Odier, MD; Bruno Weder, MD; Barbara Tettenborn, MD; Felix Mueller, MD; Lucka Sekoranja, MD; Roman Sztajzel, MD; Pietro Ballinari, PhD*; Heinrich P. Mattle, MD; Ralf W. Baumgartner, MD


Key Words: outcome ■ thrombolysis ■ ischemic stroke ■ nonagenarian

배경과 목적

인구학적 변화는 90대 환자(nonagenarian)의 빈도 증가를 가져왔으나, 이들 환자에서 급성 허혈뇌졸중(ischemic stroke)의 정맥내 혈전용해술(intravenous thrombolysis, IVT) 이후의 결과에 대하여는 알려져 있지 않다. 저자들은 90대의 환자들에서 시행된 IVT의 안전성 및 가능성 결과를 평가하고, 이들은 80대의 환자들(octogenarian)의 결과와 비교하기 위해 연구를 진행하였다.

방법

저자들은 스위스의 7개 병원에서, 80세 이상에서 IVT를 시행 받은 환자 284명을 전향적으로 모아 분석하였다. 임상적 특징, 양호한 예후(modified Rankin Scale, mRS) 0 또는 1, 3개월째 사망률 및 NINDS (National Institute of Neurological Disorders and Stroke), 혹은 SITS–MOST (Safe Implementation of Thrombolysis in Stroke–Monitoring Study)에서 사용한 중상성 두개내출혈(symptomatic intracranial hemorrhage, SICH) 정도를, 80대의 환자들과 90대의 환자들을 대상으로 비교하였다.

결과

80대의 환자들(238명, 평균 83세)에 비하여 90대의 환자들(46 명, 평균 92세)은 여성이 많았고(70% vs. 54%; P=0.046), 수측 기 혈압은 낮았다(161 mm Hg vs. 172 mm Hg; P=0.035). 90세 이상의 환자들은 80~89세의 환자들에 비하여 양호한 예후를 보이는 경우가 적었고(14.3% vs. 30.2%; P=0.034) 사망률이 더 높은 것으로 나타났으며(45.2% vs. 22.1%; P=0.002), SICH도 더 많은 것으로 나타났다(SICH_nonSICH, 13.3% vs. 5.9%; P=0.106, SICH_nonSICH, 13.3% vs. 4.7%; P=0.037). 다변수 보정 결과, 90세 이상의 환자는 사망률의 독립적인 예측인자였다(P=0.017).

결론

본 연구 결과, 90대의 IVT를 시행받은 허혈뇌졸중 환자들은, 80대의 환자들에 비하여 좋지 않은 예후를 보였다. 따라서 저자들은 나이가 많은 환자들에서 혈전용해술에 대한 무작위 대조군 연구를 통한 객관적 증거들을 얻을 수 있도록 경우에는 환 자들의 치료 선택에 있어 주의가 필요하다는 점을 강조하였다.

### Table 2. Favorable Outcome, Mortality and Symptomatic Intracranial Hemorrhage in Nonagenarians and Octogenarians Treated With Intravenous Thrombolysis

<table>
<thead>
<tr>
<th>Result</th>
<th>Nonagenarians</th>
<th>Octogenarians</th>
<th>P*</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>%</td>
<td>95% CI</td>
<td>Univariate</td>
</tr>
<tr>
<td>Favorable outcome</td>
<td>6/42</td>
<td>14.3</td>
<td>3.2–25.3</td>
<td>0.034</td>
</tr>
<tr>
<td>Mortality</td>
<td>19/42</td>
<td>45.2</td>
<td>28.5–60.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per NINDS</td>
<td>6/45</td>
<td>13.3</td>
<td>3.0–23.7</td>
<td>0.106†</td>
</tr>
<tr>
<td>Per SITS–MOST</td>
<td>6/45</td>
<td>13.3</td>
<td>3.0–23.7</td>
<td>0.037†</td>
</tr>
</tbody>
</table>

ICH indicates intracranial hemorrhage; NINDS, National Institute of Neurological Disorders and Stroke; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

*P-values apply to χ² tests unless otherwise indicated.
†Fisher exact test.