Comparison of Stroke Guidelines: Similarities and Differences between Japanese and European Recommendations for the Management and Prevention of Acute Ischemic and Hemorrhagic Strokes

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Cerebrovascular Diseases celebrated its 20th anniversary in 2010 with a Europe/Japan Stroke symposium in Barcelona, Spain, 20 years after the first *European Stroke Conference*. The session addressed different aspects of acute stroke management and strategies for stroke prevention from two viewpoints with specific traditional and historical backgrounds in modern neurovascular medicine, Europe and Japan [1].

During this meeting, speakers and participants in a large auditorium experienced a surprisingly high coincidence of identical or very close proposals and perspectives as well as less common but remarkable differences.

Cerebrovascular Diseases had published the 2003 European guidelines (GLs) for the management of ischemic stroke and transient ischemic attacks [2] with an update in 2008 [3], the European stroke initiative recommendations for the management of ICH in 2006 [4], and very recently, the guidelines for the management of intracranial aneurysms and subarachnoid hemorrhage (2013) [5], based on western evidence. On the other hand, the first English version of Japanese GLs for the management of stroke were published in 2011 [6], although the first Japanese GLs for the management of stroke appeared in 2004 in Japan [7, 8]. The reasons why Japan made their own GLs are as follows: (1) some of the approved drugs

and generally used drug dosages are different in Japan as compared with other American or European countries and vice versa, (2) there may be racial differences, and (3) there have been many publications concerning stroke therapy in Japan, not written in English, which have not been taken into consideration in the development of western stroke GLs. These timely associations and the joint conviction of evidence-based backgrounds for regulated treatment on one side and best medical insight into pathomechanisms in the absence of such data challenged an improved mutual cooperation among European and Japanese stroke clinicians.

Since then, the authors of the following articles met repeatedly and compared the latest versions of the European and Japanese GLs for ischemic and hemorrhagic strokes. From the beginning, we were well aware about the important differences in structure, style, history and interests that members of the original writing committees in Europe and Japan might have had – as a result, many aspects have only been addressed in one but left out in the other GL, which consequently founded the basis for the comparison tables and chapters listed in the following two articles. Aspects of major importance were surprisingly similar, and hence did not need extensive interpretation even though the classification of evidence levels and recom-

Table 1a. Classification of evidence levels of stroke (Japan)

Level of evidence	Type of evidence
Ia	Meta-analysis (with homogeneity) of RCTs
Ib	At least one RCT
IIa	At least one well-designed, controlled study but without randomization
IIb	At least one well-designed, quasi-experimental study
III	At least one well-designed, nonexperimental descriptive study (e.g. comparative/correlation/case study)
IV	Expert committee reports, opinions, and/or experience of respected authorities

This Japanese Guidelines classification was established based on the classification in the National Clinical Guidelines for Stroke (1999) adopted by the UK Royal College of Physicians, with a partial adoption of proposals by the Oxford Center for Evidence-Based Medicine (2001). RCT = Randomized controlled trial.

Table 1b. Classification of evidence levels on stroke (Europe)

Level of evidence	Classification scheme for a therapeutic intervention
I	An adequately powered, prospective, clinical RCT with masked outcome assessment in a representative population or an adequately powered systematic review of prospective, clinical RCTs with masked outcome assessment in representative populations. The following are required: (a) randomized concealment (b) primary outcome(s) is/are clearly defined (c) exclusion/inclusion criteria are clearly defined (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have a minimal potential for bias (e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
II	Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or RCT in a representative population that lacks one criterion of a–e
III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion
RCT = Randomized controlled trial.	

mendation grades defined by the individual committees differed between both original GLs (tables 1, 2).

Interestingly, some aspects of ischemic stroke management differed significantly, e.g. the dosage of recombinant tissue plasminogen activator approved in Japan is lower (0.6 mg/kg) than in Europe (0.9 mg/kg), which derived from different customs in cardiovascular treatment prior to the design of acute ischemic stroke trials. Furthermore, comedication with neuroprotective agents

(edaravon), intravenous anticoagulant (argatroban) or antiplatelet agents within 1–2 days after stroke onset is recommended in Japan but not in Europe. For cardioembolic stroke prevention, a major difference consists in a higher target international normalized ratio (2.0–3.0) in younger subjects versus those >70 years (1.6–2.6), without age restrictions in Europe.

Patients with hemorrhagic stroke/intracerebral bleedings were treated surgically – in the absence of clear evi-

Table 2. Grades of Recommendation

Japanese guidelines	European guidelines (ESO)
Grade A: Implementation is highly recommended (based on Ia or at least one datum-rated level Ib).	Level A: Established as useful/predictive or not useful/predictive for a diagnostic measure or established as effective, ineffective or harmful for a therapeutic intervention; requires at least one convincing class I study or at least two consistent, convincing class II studies.
Grade B: Implementation is recommended (based on at least one datum-rated level II).	Level B: Established as useful/predictive or not useful/predictive for a diagnostic measure or established as effective, ineffective or harmful for a therapeutic intervention; requires at least one convincing class II study or overwhelming class III evidence.
Grade C1: Implementation can be considered, but it lacks an adequate scientific basis.	Level C: Established as useful/predictive or not useful/predictive for a diagnostic measure or established as effective, ineffective or harmful for a therapeutic intervention; requires at least two class III studies.
Grade C2: It is not recommendable because of a lack of scientific evidence.	Good Clinical Practice (GCP) points: Recommended best practice based on the experience of the guideline development group. Usually based on class IV evidence indicating large clinical uncertainty, such GCP points can be useful for health workers.
Grade D: Implementation is not recommended.	

dence-based recommendations worldwide – more often depending on the association with hypertension in Japan but not in Europe. Infra- and supratentorial differences were similarly addressed in both regions. However, due to lacking evidence from appropriate trials, patients with large or intraventricular bleedings were only treated if life-saving performance was considered irrespective of neurological outcome – thus treatment of patients in appropriate randomized clinical trials is frequently recommended in Europe and Japan, but often with different concepts and study designs in participating centers.

We hope that this brief survey – when compared with the lengthy original recommendations – provides a stimulating basis for an extended interest among Japanese and European stroke clinicians to learn from their individual experiences and to strengthen efforts for a joint cooperation in treating and preventing stroke all around the globe.

The next Europe/Japan Stroke symposium is planned to take place at the European Stroke Conference 2014 in Nice, France

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