Status Epilepticus in Europe

- Status epilepticus classification
- Drug available in Europe
- Efficacy of new AED iv in status epilepticus
- New standard practice in Europe

General concern in SE

1. VPA are sufficient for inclusion in protocol
2. Continuous EEG monitoring (20%)
3. Protocol at AE
4. PB is still justified

Pre-hospital management

- Prognosis of SE related with time to control
- Success rate to control seizure related early treatment
- Mortality rate related success rate of seizure control
- Pre-hospital treatment is very important
- IV or rectal benzodiazepine
- Buccal or intranasal midazolam

Survey of Adult GCSE

- 45 physicians from 26 countries
- 41/45 were neurologist
- 79% from university hospital
- 16% from private, public hospital
- 5% from research institute
- 64% have protocol for SE at AE
**Annex 1. Availability and licensing of drugs for SE in European countries.**

<table>
<thead>
<tr>
<th>Valproate</th>
<th>Phenytoin</th>
<th>Lorazepam</th>
<th>Diazepam</th>
<th>Midazolam</th>
<th>Clonazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>yes no yes yes yes no yes yes no yes no no</td>
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<td>Denmark</td>
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<tr>
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<tr>
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<tr>
<td>Ireland</td>
<td>yes no yes yes yes no yes yes no yes no yes</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Italy</td>
<td>yes no yes no yes yes yes yes no yes no yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>no no yes yes yes no yes yes no yes no no</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reg.SE: registered for use SE.
*Valproate intravenous (IV) is licensed but not marketed.

**Survey of licensed drug for SE: 25 countries in Europe**

- **Sodium valproate 2:22 (registered: available)**
- **Phenytoin 24:24 (registered: available)**
- **Sodium valproate**: Hungary, Norway
- **No Phenytoin**: Russia

---

**Intravenous benzodiazepine**

- **First line**
  - DZP 66%
  - LOR 29.5%
  - MID 4.5%

- **Second line**
  - DZP 26%
  - LOR 18%
  - MID 56%

---

**Intravenous AED after BZP**

<table>
<thead>
<tr>
<th></th>
<th>First line (%)</th>
<th>Second line (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>FOS</td>
<td>23</td>
<td>2.5</td>
</tr>
<tr>
<td>PB</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>VPA</td>
<td>16</td>
<td>43.5</td>
</tr>
</tbody>
</table>
Anesthetic agent in RSE

<table>
<thead>
<tr>
<th></th>
<th>First line (%)</th>
<th>Second line (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>Phenobarb</td>
<td>8.5</td>
<td>14</td>
</tr>
<tr>
<td>Propofol</td>
<td>23.5</td>
<td>30</td>
</tr>
<tr>
<td>Midazolam</td>
<td>28</td>
<td>14</td>
</tr>
</tbody>
</table>

New generation of anticonvulsant
- Non-GABAergic mechanisms
- Topiramate
- Levetiracetam
- Blockade of NMDA receptor
- MK-801

Newer therapy
- IV VPA is another choice for treatment in elderly
- Loading dose 15 mg/kg – 70 mg/kg
- Safety and tolerability of rapid infusion rate
- Low risk of hypotension, respiratory depression, sedative

Valproate is an effective, well-tolerated drug for treatment of status epilepticus/serial attacks in adults

Outcome of seizure control
- Complete seizure controlled 56.8%
- Stop, then recurrent seizure 15.9%
- Partially seizure controlled 11.9%
- No seizure controlled 13.6%

VPA for SE in Srinagarind hospital
- First line drug 41%
- Second line drug 54.5%
- Third line drug 4.5%
- Dosage 15-25 mg/kg/dose, mean 16.82
- Total dose/day 750-2700 mg, mean 1025

Somsak Tiamkao, et al 2007

Somsak Tiamkao, et al 2007

Valproic acid is effective, well-tolerated treatment for status epilepticus/serial attacks in adults.

Somsak Tiamkao, et al 2007

Valproic acid is effective, well-tolerated treatment for status epilepticus/serial attacks in adults.

Somsak Tiamkao, et al 2007
Newer therapy

- Topiramate nasogastric
- Effective dose 300 – 1600 mg/day
- Most of cases : CPSE

Status epilepticus : SE

- Non-convulsive SE : NCSE
  - NCSE in neonatal, childhood, adult
  - NCSE : absence, CPS, subtle
- Convulsive SE : CSE
  - CSE in childhood, adult
  - CSE : tonic-clonic, myoclonic, EPC

Table 1. Classification of SE

1. NCSE occurring in the neonatal and infantile epilepsy syndromes
   1a. Ohtahara syndrome
   1b. West syndrome
   1c. Severe myoclonic encephalopathy of infancy (SMEI; Dravet syndrome)
   1d. NCSE in other forms of neonatal or infantile epilepsy
2. NCSE occurring only in childhood
   2a. NCSE in early-onset benign childhood occipital epilepsy (Paraytropoulos syndrome)
   2b. NCSE in other forms of childhood epileptic encephalopathies, syndromes, and etiologies
      (e.g., Rett syndrome, Angelman syndrome, Dravet syndrome, myoclonic-astatic epilepsies,
      other childhood myoclonic encephalopathies)
   2c. Electrical status epilepticus in slow wave sleep (ESES)
   2d. Landau-Kleffner syndrome
3. Convulsive SE occurring only in childhood
   3a. Febrile SE
   3b. NCSE in other forms of childhood epileptic syndromes
   3c. NCSE in early childhood syndromes (e.g., Angelman, Dravet, Rett syndromes, myoclonic-astatic epilepsy)
   3d. NCSE in early-onset benign childhood occipital epilepsy (Paraytropoulos syndrome)
   4. NCSE occurring in both childhood and adult life with epileptic encephalopathy
      4a. NCSE in the Lennox-Gastaut syndrome
      i. Atypical absence SE
      ii. Tonic SE
      4b. Other forms of NCSE in patients with learning disability or disturbed cerebral development
         (cryptogenic or symptomatic) without epileptic encephalopathy
   4c. Typical absence SE in idiopathic generalized epilepsy
   4d. Complex partial SE:  
      i. Limbic
      ii. Nonlimbic
   4e. NCSE in the postictal phase of tonic-clonic seizures
   4f. Subtle SE (myoclonic SE occurring in the late stage of convulsive SE)
   4g. Aura continua (with (i) sensory, (ii) special sensory, (iii) autonomic, (iv) cognitive symptoms)
5. Convulsive forms of SE occurring in childhood and adult life
   5a. Tonic-clonic status epilepticus
   5b. Epilepsia partialis continua (EPC; simple partial motor SE)
   5c. Myoclonic SE
   6. NCSE occurring in late adult life
   6a. De novo absence SE of late onset
   7. Boundary syndromes
      7a. Some cases of epileptic encephalopathy
      7b. Some cases of coma due to acute brain injury with epileptiform EEG changes
      7c. Some cases of epileptic behavioral disturbance or psychosis
      7d. Some cases of drug induced or metabolic confusional state with epileptiform EEG changes

*Boundary syndromes are defined as cases in which it is not clear to what extent the continuous epileptiform electrographic abnormalities are contributing to the clinical impairment.

Outcome of treatment

- Complete recovery 27.9%
- Death recovery 41.9%
- Partial recovery 16.3%
- Recovery to same previous neurological deficit 14%

Somsak Tiamkao, et al 2007
Pre-hospital management

- Prognosis of SE related with time to control
- Success rate to control seizure related early treatment
- Mortality rate related success rate of seizure control
- Pre-hospital treatment is very important
- IV or rectal benzodiazepine
- Buccal or intranasal midazolam

Protocol for in-hospital treatment of tonic-clonic SE

Stage 1: stage of early status (0 - 10/30 min)
- Lorazepam: 4 mg IV bolus
  (can be replaced once 5-10 min)
- If seizures continue after 30 min

Stage 2: stage of established status (10/30 – 60/90 min)

Stage 3: stage of refractory status (> 60/90 min)

Drug used in the stage early tonic-clonic SE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>IV bolus (not exceed 2-5 mg/min)</td>
<td>10-30 mg</td>
<td>0.03-0.1 mg/kg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>IV bolus</td>
<td>4 mg (0.07 mg/kg)</td>
<td>0.01-0.04 mg/kg</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Buccal, intranasal</td>
<td>5-10 mg</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Table 4. Drugs used in the stage of early tonic-clonic SE (Stage 1)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>IV bolus (not exceeding 100 mg/min)</td>
<td>15-30 mg</td>
<td>0.25-0.5 mg/kg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>IV bolus</td>
<td>4 mg (0.07 mg/kg)</td>
<td>0.01-0.04 mg/kg</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Buccal, intranasal</td>
<td>5-10 mg</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Table 5. Drugs used in the stage of established tonic-clonic SE (Stage 2)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>IV bolus (not exceeding 2 mg/min)</td>
<td>1-2 mg</td>
<td>0.025-0.05 mg/kg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>IV bolus</td>
<td>0.1 mg/kg (usually 1 mg)</td>
<td>0.1 mg/kg</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Buccal, intranasal</td>
<td>5-10 mg</td>
<td>0.1-0.2 mg/kg</td>
</tr>
</tbody>
</table>

**Note:** FF: phenytoin equivalent; IV: intravenous; n/a: not applicable.
Stage 2: established status (10/30 – 60/90 min)

- Phenobarbital: IV infusion 10 mg/kg at a maximum rate of 100 mg/min
- Phenytoin: IV infusion 15 mg/kg at a maximum rate 50 mg/min
- Fosphenytoin: IV infusion 15 mg/kg at a maximum rate 50 mg/min
- Valproate: IV infusion 25 mg/kg at 3-6 mg/kg/min
- Levetiracetam: IV bolus 2000 – 4000 mg

Prevention Regimen For Effectively avoiding Second Strokes – The PRoFESS™ Trial

Ralph L. Sacco, MS, MD on behalf of the PRoFESS Study Group
Division of Neurological Disorders
Miller Professor of Neurology, Epidemiology, and Human Genetics
University of Miami, Miami, FL

Trial was sponsored by Boehringer Ingelheim
Dr. Sacco received honorarium from Eli as a consultant.

ASA for Secondary Prevention
**Objective**

- To assess the relative efficacy of Clopidogrel and ASA in reducing the incidence of ischemic stroke, MI, or vascular death among patients who had survived a recent ischemic stroke, recent MI, or had symptomatic atherosclerotic peripheral arterial disease.

- To assess the relative safety and tolerability of Clopidogrel and ASA.

**Primary End Point**

- First occurrence of ischemic stroke, MI, or vascular death.

**Follow-up**

1 to 3 years

**Study Subjects**

1384 centers, 16 countries

**Study Drug Permanently Discontinued**

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>Clopidogrel 75 mg</th>
<th>Aspirin 325 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>0.30%</td>
<td>0.41%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.45%</td>
<td>0.27%</td>
</tr>
<tr>
<td>Indigestion/vomiting</td>
<td>1.00%</td>
<td>2.41%</td>
</tr>
<tr>
<td>Any bleeding disorder</td>
<td>1.20%</td>
<td>1.37%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.21%</td>
<td>0.30%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0.53%</td>
<td>0.99%</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>0.23%</td>
<td>0.20%</td>
</tr>
</tbody>
</table>

**Management of Atherothrombosis with Clopidogrel in High-risk patients with recent TIA or IS**

**Rationale**

- Patients with a recent TIA or ischemic stroke remain at high risk of subsequent major vascular events.
- Prevention of major ischemic events in high-risk patients requires aggressive antiplatelet therapy.
- Synergy between clopidogrel and ASA is supported by pre-clinical and clinical data.
- Benefit of clopidogrel is amplified in high-risk patients.

**Objectives**

- Evaluate the relative efficacy of Clopidogrel plus ASA versus monotherapy in patients with a recent TIA or ischemic stroke and at high risk of recurrent ischemic events.
- Evaluate safety of long-term administration of combined clopidogrel and ASA treatment in patients with cerebrovascular disease.
**MATCH**

**Study Design**

\[ N = 7,959 \]

- **Patient Population**
  - Patients with recent TIA or IS, and at high risk for recurrent events
  - Previous TIA, MI, angina, DM, or asymptomatic PAD

- **Primary End Point**
  - First occurrence of MI, IS, and at high risk for recurrent events, or at high risk for symptomatic PAD

- **Follow-up**
  - 18 months
  - 28 countries

**Main Safety Outcomes**

<table>
<thead>
<tr>
<th>Type of Bleeding Events (%)</th>
<th>Placebo + Clopidogrel (n=3,797)</th>
<th>ASA + Clopidogrel (n=3,759)</th>
<th>% Absolute Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-Threatening Events (%)</td>
<td>16 (1%)</td>
<td>81 (2%)</td>
<td>1.15 (0.59, 1.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fatal</td>
<td>3 (1%)</td>
<td>81 (2%)</td>
<td>1.15 (0.59, 1.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>21 (5%)</td>
<td>73 (2%)</td>
<td>1.36 (0.86, 1.86)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major Bleeding (%)</td>
<td>11 (1%)</td>
<td>73 (2%)</td>
<td>1.36 (0.86, 1.86)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Primary End Point: MI, IS, Vascular Death, or Rehospitalization for an Acute Ischemic Event**

\[ N = 7,959 \]

- **Relative Risk Reduction**
  - 6.4% (P = 0.0016)

**Stroke Mortality Rate by Age**

Blood Pressure and Stroke Mortality

- Stroke mortality rates in each decade of age vs. usual blood pressure at the start of the decade.

**The first randomized trial of ACE inhibitor-based treatment in patients with a history of cerebrovascular disease**

**PERINDOPRIL PROTECTION AGAINST RECURRENT STROKE STUDY**

- The first randomized trial of ACE inhibitor-based treatment in patients with a history of cerebrovascular disease
**PROGRESS Primary Outcome Stroke**

28% risk reduction (95% CI 17 - 38%)

- Placebo
- Active

Follow-up time (years)

**LIFE**

The Losartan Intervention For Endpoint Reduction in Hypertension Study

An investigator initiated community-based study in 945 sites in 7 countries enrolling 9,193 patients

Steering Committee Chair/ Vice-Chair B. Dahlf, D. Devereux

European/ US Coordinators S.E. Kjeldsen, S. Julius

Data and Safety Monitoring Committee Chair J. Kjekshus

Clinical Endpoint Classification Committee D. Lvy, K. Thygesen

**LIFE Reduction in the Risk of Stroke**

- Losartan
- Atenolol

Proportion of patients with first event (%)

67 70 72 73 74 75 76 77 78 79 80 81 82

Time (months)

Losartan

Adjusted risk reduction 24.9%, p = 0.0010

Unadjusted risk reduction 25.8%, p = 0.0006

**Antithrombotic Therapy**

Recommendations (1/4)

- Patients should receive antithrombotic therapy (Class I, Level A)

- Patients not requiring anticoagulation should receive antiplatelet therapy (Class I, Level A). Where possible, combined aspirin and dipyridamole, or clopidogrel alone, should be given. Alternatively, aspirin alone, or triflusal alone, may be used (Class I, Level A)

**Stroke prevention?**

- ASA
- Clopidogrel
- ASA + Dipyridamole
- Antiplatelet + ACE I/ ARB
A Global Study Among 20,332 Patients in 695 Sites from 35 Countries

PRoFESS

Objectives:

- To compare the efficacy and safety of the combination of extended-release dipyridamole and aspirin to clopidogrel (non-inferiority first then superiority)
- To compare telmisartan to placebo in the prevention of recurrent stroke (superiority)

Study Design

2x2 Factorial design 20,332 stroke patients over age 50

<table>
<thead>
<tr>
<th>Telmisartan</th>
<th>Clopidogrel*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-DP+ASA</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>ER-DP+ASA placebo</td>
</tr>
<tr>
<td>Telmisartan placebo</td>
<td>Telmisartan</td>
</tr>
<tr>
<td>Telmisartan placebo</td>
<td>ER-DP+ASA placebo</td>
</tr>
</tbody>
</table>

20,332 pts

Protocol Amendment 2 - ASA was deleted from C+ASA due to MATCH results in May, 2004; 2027 subjects treated for a maximum of 8 months with C+ASA

Antiplatelet Outcomes

Primary outcome
- Recurrent stroke

Secondary outcome
- Stroke, MI or vascular death

Bleeding Events

- Major hemorrhagic events
  - Assoc. with significant disability
  - Symptomatic Intracranial Hemorrhage
  - Intracranial bleed with loss of vision
  - 2 or more units transfused
  - Life-threatening
    - Fatal, need inotropic med. to maintain BP
    - Requires surgery, 4 or more units needed
  - Intracranial Hemorrhage
    - Intracerebral or hemorrhagic stroke
    - Intracranial
    - Non-stroke intracranial

Patient Disposition

Randomized (20,332)

ASA+ER-DP (10,181)
Prematurely d/c from meds 2961 (29.1%)
Alive at study end 9362 (92.2%)
Died 739 (7.2%)
LTFU 60 (0.6%)

Clopidogrel (10,151)
Prematurely d/c from meds 2226 (22.0%)
Alive at study end 9330 (91.9%)
Died 756 (7.5%)
LTFU 65 (0.6%)
Medical History

<table>
<thead>
<tr>
<th></th>
<th>ASA+ER-DP</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Randomized Patients</td>
<td>10181</td>
<td>10151</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74.4%</td>
<td>73.6%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>28.5%</td>
<td>28.0%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>46.5%</td>
<td>46.8%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>2.7%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Valvular Disease</td>
<td>1.7%</td>
<td>1.7%</td>
</tr>
<tr>
<td>CHF</td>
<td>2.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Deep Venous Thrombosis</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Medical History

<table>
<thead>
<tr>
<th></th>
<th>ASA+ER-DP</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Randomized Patients</td>
<td>10181</td>
<td>10151</td>
</tr>
<tr>
<td>Previous Stroke or TIA</td>
<td>24.2%</td>
<td>24.9%</td>
</tr>
<tr>
<td>Previous Stroke</td>
<td>18.1%</td>
<td>18.4%</td>
</tr>
<tr>
<td>TIA</td>
<td>8.6%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Other Atherosclerotic Disease</td>
<td>19.3%</td>
<td>19.5%</td>
</tr>
</tbody>
</table>

Neurological Status

<table>
<thead>
<tr>
<th></th>
<th>ASA+ER-DP</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Randomized Patients</td>
<td>10181</td>
<td>10151</td>
</tr>
<tr>
<td>Time from Stroke</td>
<td>Median</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>&lt;10 Days</td>
<td>39.6%</td>
</tr>
<tr>
<td></td>
<td>10-20 Days</td>
<td>40.0%</td>
</tr>
<tr>
<td>TOAST Classification</td>
<td>Large-artery Atherosclerosis</td>
<td>28.8%</td>
</tr>
<tr>
<td></td>
<td>Cardioembolism</td>
<td>1.8%</td>
</tr>
<tr>
<td></td>
<td>Small-artery Occlusion (laser)</td>
<td>52.0%</td>
</tr>
<tr>
<td></td>
<td>Acute Stroke of Other Determined Etiology</td>
<td>2.0%</td>
</tr>
<tr>
<td></td>
<td>Stroke of Undetermined Etiology</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

Primary Outcome: Stroke Recurrence

Characterization of First Recurrent Stroke

![Characterization of First Recurrent Stroke Diagram]
**Secondary Outcome:** Stroke, MI, Vascular Death

![Graph showing the comparison of ASA+ER-DP vs Clopidogrel for secondary outcomes](image)

**Stroke Recurrence or Major Hemorrhage Benefit/Risk (ProFESS)**

![Graph showing the comparison of ASA+ER-DP vs Clopidogrel for stroke recurrence or major hemorrhage](image)

**New or worsening CHF**

![Graph showing the comparison of ASA+ER-DP vs Clopidogrel for new or worsening CHF](image)

**Major Hemorrhagic Event**

![Graph showing the comparison of ASA+ER-DP vs Clopidogrel for major hemorrhagic event](image)

**Adverse Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>ASA+ER-DP</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Randomized Patients</td>
<td>10181</td>
<td>10151</td>
</tr>
<tr>
<td>Headache with permanent discontinuation</td>
<td>600 (5.9%)</td>
<td>88 (0.9%)</td>
</tr>
<tr>
<td>Dizziness or Lightheadedness</td>
<td>1365 (13.6%)</td>
<td>908 (9.1%)</td>
</tr>
<tr>
<td>Fainting</td>
<td>149 (1.5%)</td>
<td>76 (0.8%)</td>
</tr>
<tr>
<td>Migraine during first 6 months of study</td>
<td>562 (5.5%)</td>
<td>314 (3.3%)</td>
</tr>
</tbody>
</table>

**Conclusions**

- We were not able to meet our pre-specified non-inferiority criteria for ASA+ER-DP vs CP
- ASA+ER-DP and CP had similar rates of recurrent stroke and major vascular events
- Major hemorrhagic events, including intracranial bleeds, were more frequent among those treated with ASA+ER-DP, but the absolute risks were low and partially offset by fewer ischemic events
- Net benefit/risks were similar with the 2 agents
Ischemic Stroke Risk Increases With Serum Cholesterol

- Estimate adjusted for age, sex, race, hypertension, index year, time to cholesterol measurement, SBP and DBP, coronary heart disease, atrial fibrillation, diabetes, tobacco use, and use of statins.

<table>
<thead>
<tr>
<th>Total Ischemic Stroke (95% CI)</th>
<th>Total Cholesterol (mmol/L)</th>
<th>Total Cholesterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.5</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>175</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>225</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>275</td>
</tr>
<tr>
<td></td>
<td>-27*</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>-48*</td>
<td>325</td>
</tr>
</tbody>
</table>

CI=confidence interval; SBP=systolic blood pressure; DBP=diastolic blood pressure.


Statin Therapy Is Not Associated With Increased Risk for Hemorrhagic Stroke


<table>
<thead>
<tr>
<th>Trials</th>
<th>Odds Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS*</td>
<td>0.96 (0.65-1.42)</td>
</tr>
<tr>
<td>GREACE</td>
<td>0.85 (0.53-1.36)</td>
</tr>
<tr>
<td>MIRACL</td>
<td>1.00 (0.63-1.60)</td>
</tr>
<tr>
<td>KLAS*</td>
<td>1.16 (0.71-1.88)</td>
</tr>
<tr>
<td>LISS*</td>
<td>1.00 (0.64-1.55)</td>
</tr>
<tr>
<td>CASE*</td>
<td>0.84 (0.50-1.42)</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>0.84 (0.50-1.42)</td>
</tr>
</tbody>
</table>

*P=90 (pravastatin vs placebo or usual care).
†P=.024 (atorvastatin vs placebo).
‡P=not reported (atorvastatin vs placebo).

Primary Prevention


**95% CI for the HR = 0.31–0.89.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Atorvastatin 10 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS</td>
<td>4.9</td>
<td>6.95</td>
</tr>
<tr>
<td>ALLHAT-LLT</td>
<td>4.8</td>
<td>10.355</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>3.3</td>
<td>10.395</td>
</tr>
<tr>
<td>CARDS</td>
<td>3.9</td>
<td>2.811</td>
</tr>
</tbody>
</table>

Prevention of Stroke in Patients Without Documented Cardiovascular Disease


<table>
<thead>
<tr>
<th>Trial</th>
<th>Statin dose, mg</th>
<th>FV, y</th>
<th>Number of patients</th>
<th>Between-Group Difference in LDL-C Reduction, mg/dL (%)</th>
<th>Relative Risk Reduction in Stroke of LDL-C Reduction</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin 40</td>
<td>4.9</td>
<td>6.95</td>
<td>–11</td>
<td>37</td>
<td>0.016</td>
</tr>
<tr>
<td>ALLHAT-LLT</td>
<td>Pravastatin 40</td>
<td>4.8</td>
<td>10.355</td>
<td>–9</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Atorvastatin 10</td>
<td>3.3</td>
<td>10.395</td>
<td>–24</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>CARDS</td>
<td>Atorvastatin 10</td>
<td>3.9</td>
<td>2.811</td>
<td>–48</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

ASCOT-LLA: Atorvastatin Lowers Stroke Risk in Patients With Good Blood Pressure Control

CARDS: Stroke Prevention in Diabetic Patients Without CHD

**Table:**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo*</th>
<th>Atorvastatin*</th>
<th>Hazard Ratio</th>
<th>Relative Risk (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>127 (0.6)</td>
<td>120 (0.6)</td>
<td>0.98</td>
<td>–37% (–52, –11)</td>
</tr>
<tr>
<td>Acute coronary events</td>
<td>77 (5.5)</td>
<td>51 (3.8)</td>
<td>0.65</td>
<td>–36% (–50, –24)</td>
</tr>
<tr>
<td>Cerebral revascularization</td>
<td>24 (1.7)</td>
<td>26 (1.7)</td>
<td>1.02</td>
<td>–1% (–59, +16)</td>
</tr>
<tr>
<td>Stroke</td>
<td>39 (2.4)</td>
<td>21 (1.5)</td>
<td>0.68</td>
<td>–88% (–98, –71)</td>
</tr>
</tbody>
</table>

(n=2841)

CARDS = Collaborative Atorvastatin Diabetes Study.

* Number of patients with an event (%).


Prevention of Stroke in Patients With Documented Cardiovascular Disease

**Figure:**

- **Stroke Reduction in TNT**
  - TNT = Treating to New Targets; RRR = relative risk reduction.
  - Atorvastatin is not indicated for secondary prevention of CVD.

Adapted from Waters DD et al. Circulation. 2002;106:1690-1695.

- **Statin Therapy for Stroke Prevention in ACS: MIRACL**
  - Relative risk = 0.49
  - P = .04
  - 95% CI 0.24–0.98

Adapted from Waters DD et al. Circulation. 2002;106:1690-1695.

**Meta-Analysis of Stroke Outcomes in Statin Trials**

Across 26 Trials, Statins Reduced Stroke by 21% (Pc<.0001)

**Figure:**

- **SPARCL: Study Design**
  - Primary End Point: Time to First Occurrence of a Fatal or Nonfatal Stroke
  - 4732 Patients
  - 240 Planned Primary End Points

SPARCL: Secondary End Points

- Time to occurrence of
  - Cerebrovascular event (includes TIA)
  - Major coronary event, consisting of cardiac death, nonfatal MI, or resuscitated cardiac arrest
  - Major cardiovascular event, defined as a major coronary event or fatal or nonfatal stroke
  - Any CHD event, defined as an acute coronary event, coronary revascularization procedure, or angina/tia requiring emergent hospitalization
  - Any revascularization procedure (coronary, carotid, or peripheral)
  - Any cardiovascular event (any event except noncardiovascular death)
  - All-cause mortality (death from any cause)


SPARCL: Secondary End Points (cont’d)

- MI, resuscitated cardiac arrest, or unstable angina
- Absolute and percent changes in serum lipids/lipoproteins
- Stroke impact as measured by
  - Modified Rankin Scale (MRS) (handicap)
  - Barthel Index (BI) (disability)
  - NIH Stroke Scale (NIHSS) (impairment)

NIH=National Institutes of Health.

SPARCL Addresses a Novel Patient Population

Primary Prevention No Prior Stroke/TIA
- LDL C: <133 mg/dL
- LDLC: <100 mg/dL
- HDLC: >40 mg/dL
- Triglycerides: <150 mg/dL
- Total Cholesterol: <200 mg/dL
- No diabetes

Secondary Prevention Prior Stroke/TIA
- LDL C: <133 mg/dL
- LDLC: <100 mg/dL
- HDLC: >40 mg/dL
- Triglycerides: <150 mg/dL
- Total Cholesterol: <200 mg/dL
- No diabetes

SPARCL: Study Design

Patient Population
- 205 sites worldwide
- Previously documented stroke or TIA within 6 months
- No history of CHD
- LDL-C levels >100 mg/dL and ≤190 mg/dL

Double-Blind Period
- 4,731 Patients
- Atorvastatin 80 mg/day
- Placebo

Primary End Point
- Time to the First Occurrence of a Fatal or Nonfatal Stroke

TIA=transient ischemic attack; CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol; The SPARCL Investigators. Cerebrovasc Dis. 2003;16:389-395.

SPARCL: LDL-C During Follow-Up

Baseline LDL-C: ~133 mg/dL

Mean on-treatment LDL-C:
- Placebo=129 mg/dL
- Atorvastatin=73 mg/dL

Mean Lipid Values During Follow-Up

Atorvastatin was Associated With Lower Levels of LDL-C, TC, and TG and With Higher Levels of HDL-C Compared with Placebo

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Atorvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>72.2</td>
<td>128.5</td>
</tr>
<tr>
<td>HDL-C</td>
<td>52.1</td>
<td>51.1</td>
</tr>
<tr>
<td>TC</td>
<td>147.2</td>
<td>208.4</td>
</tr>
<tr>
<td>TG</td>
<td>111.5</td>
<td>145.5</td>
</tr>
</tbody>
</table>

LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Primary Endpoint: Time to Fatal or Non-Fatal Stroke

Adjusted HR=0.84 (95% CI 0.71, 0.99), P<.03

Prespecified and Post-Hoc Analyses

<table>
<thead>
<tr>
<th>Prespecified Analysis</th>
<th>Atorvastatin (n=2365)</th>
<th>Placebo (n=2366)</th>
<th>HR (95% CI)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>265 (11.3)</td>
<td>311 (13.1)</td>
<td>0.84 (0.71, 0.99)</td>
<td>.03</td>
</tr>
<tr>
<td>Fatal Stroke</td>
<td>24 (1.0)</td>
<td>41 (1.7)</td>
<td>0.87 (0.59, 1.31)</td>
<td>.39</td>
</tr>
<tr>
<td>Non-fatal Stroke</td>
<td>247 (10.4)</td>
<td>260 (11.1)</td>
<td>0.87 (0.73, 1.05)</td>
<td>.11</td>
</tr>
<tr>
<td>Post-Hoc Analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>218 (9.2)</td>
<td>274 (11.5)</td>
<td>0.78 (0.60, 0.94)</td>
<td>.01</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>55 (2.3)</td>
<td>33 (1.4)</td>
<td>1.66 (1.00, 2.80)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Secondary Endpoint: Time to Stroke or TIA

Adjusted HR=0.77 (95% CI 0.67, 0.88), P<.001

Stroke or TIA

<table>
<thead>
<tr>
<th>Stroke or TIA</th>
<th>Atorvastatin (n=2365)</th>
<th>Placebo (n=2366)</th>
<th>HR (95% CI)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>265 (11.2)</td>
<td>311 (13.1)</td>
<td>0.84 (0.71, 0.99)</td>
<td>.03</td>
</tr>
<tr>
<td>TIA</td>
<td>153 (6.5)</td>
<td>208 (8.8)</td>
<td>0.74 (0.50, 0.91)</td>
<td>.004</td>
</tr>
</tbody>
</table>

Number Needed to Treat for Five Years to Prevent One Event

- Stroke: 46
- Major Cardiovascular Event: 29
- Revascularization Procedure: 32

Summary

- Atorvastatin 80 mg/day significantly reduced the risk of stroke (16% RR, P<.03) in patients with recent stroke or TIA and without known CHD
- Atorvastatin 80 mg/day also substantially decreased the risk of major coronary (35% RR, P<.003) and CHD events (45% RR, P<.001) and revascularization procedures (45% RR, P<.001)
- The overall benefit was present despite an increase in the incidence of hemorrhagic stroke in the atorvastatin-treated group
- Atorvastatin 80 mg/day was well-tolerated and the incidence of liver and muscle adverse events was low
Thank you for your attention