Atherosclerosis and stroke

Prof. Natan M. Bornstein M.D.
Director of Brain Division,
Shaare Zedek Medical Center, Jerusalem
Chairman of the Israeli Neurological Association
Vice President of the WSO
natanb@szmc.org.il

Supported by Bayer, Bristol-Myers Squibb and Pfizer Alliance, Boehringer Ingelheim, Daiichi Sankyo Europe GmbH and Medtronic in the form of educational grants. The scientific programme has not been influenced in any way by its sponsors.
ESC Heart & Brain Workshop

Declaration of Interest:

none

Supported by Bayer, Bristol-Myers Squibb and Pfizer Alliance, Boehringer Ingelheim, Daiichi Sankyo Europe GmbH and Medtronic in the form of educational grants. The scientific programme has not been influenced in any way by its sponsors.
Cerebrovascular Disease: Stroke

**Subtype**

**Hemorrhagic Stroke (15%)**
- Intracerebral Hemorrhage (59%)

**Ischemic Stroke (85%)**
- Atherothrombotic Cerebrovascular Disease (20%)
- Cryptogenic (30%)
- Embolism (20%)
- Lacunar (25%)
- Small vessel disease

**Subarachnoid Hemorrhage (41%)**

Stroke

ICH

Small vessel Occlusive (lacunar)

Large vessel Atherothrombosis

Other determined

Undetermined

Cardioembolic

STROKE
Atherosclerosis leads to any number of four possible types of thrombus formation:

1. Rupture of Fibrous Cap
2. Erosion of Endothelium
3. Erosion of Calcium Nodule
4. Intraplaque Hemorrhage

References:
Antiplatelets

- **Clopidogrel**: Block ADP receptors
- **Aspirin**: Inhibits cyclooxygenase and thromboxane A$_2$
- **Dipyridamole**: Increases plasma adenosine

**Inhibition of platelet activation and aggregation**
ESO recomandation - 2008

• Patients are recommended to take antithrombotic therapy (Class I, Level A).

• Those not requiring anticoagulation are recommended to take antiplatelet therapy (Class I, Level A). Where possible, combined aspirin and dipyridamole, or clopidogrel alone, should be taken. Alternatively, aspirin alone, or triflusal alone, may be used (Class I, Level A).

• The combination of aspirin and clopidogrel is not recommended in patients with recent ischemic stroke except in patients with specific indications, e.g. unstable angina or non-Q-wave MI during the last 12 months; treatment should be given for up to 9
Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Walter N. Kernan, MD, Chair; Bruce Ovbiagele, MD, MSc, MAS, Vice Chair; Henry R. Black, MD; Dawn M. Bravata, MD; Marc I. Chimowitz, MBChB, FAHA; Michael D. Ezekowitz, MBChB, PhD; Margaret C. Fang, MD, MPH; Marc Fisher, MD, FAHA; Karen L. Furie, MD, MPH, FAHA; Donald V. Heck, MD; S. Claiborne (Clay) Johnston, MD, PhD; Scott E. Kasner, MD, FAHA; Steven J. Kittner, MD, MPH, FAHA; Pamela H. Mitchell, PhD, RN, FAHA; Michael W. Rich, MD; DeJuran Richardson, PhD; Lee H. Schwamm, MD, FAHA; John A. Wilson, MD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease

Abstract—The aim of this updated guideline is to provide comprehensive and timely evidence-based recommendations on the prevention of future stroke among survivors of ischemic stroke or transient ischemic attack. The guideline is addressed to all clinicians who manage secondary prevention for these patients. Evidence-based recommendations are provided for control of risk factors, intervention for vascular obstruction, antithrombotic therapy for cardioembolism, and antiplatelet therapy for noncardioembolic stroke. Recommendations are also provided for the prevention of recurrent stroke in a variety of specific circumstances, including aortic arch atherosclerosis, arterial dissection, patent foramen ovale, hyperhomocysteinemia, hypercoagulable states, antiphospholipid antibody syndrome, sickle cell disease, cerebral venous sinus thrombosis, and pregnancy. Special sections address use of antithrombotic and anticoagulation therapy after an intracranial hemorrhage and implementation of guidelines. (Stroke. 2014;45:2160-2236.)

Key Words: AHA Scientific Statements □ atrial fibrillation □ carotid stenosis □ hypertension □ ischemia □ ischemic attack, transient □ prevention □ stroke
Antiplatelets

• Aspirin offers 15% relative risk reduction for stroke after TIA or stroke
• Most widely studied dosages of aspirin are 50-150mg
• Aspirin, ASA+Dipyridamole, Clopidogrel are all acceptable initial therapy.
Long term Clopidogrel + Aspirin
Clopidogrel 300 mg loading followed by 75 mg daily for 90 days + aspirin at a dose of 75 mg daily for the first 21 days VS. aspirin only in a Chinese population
Platelet-Oriented Inhibition in New TIA and minor ischemic stroke

High-risk TIA (ABCD² ≥4) or Minor ischemic stroke (NIHSSS ≤3)

R < 12 h
N=5,840

Placebo + ASA (Loading placebo + ASA)

Clopidogrel 75mg + ASA (Loading 600 mg + ASA)

90 days

Ischemic stroke, MI and ischemic vascular death
Ticagrelor — Is There Need for a New Player in the Antiplatelet-Therapy Field?

Albert Schömig, M.D.
SOCRATES
Acute Stroke Or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes

Sponsor
AstraZeneca

R < 24 h
N=13,600

Aspirin 100mg
(Loading 300 mg)

Ticagrelor 90 mg bid
(Loading 180 mg)

A P2Y12 inhibitor

Composite of stroke, MI and death

90 days

High-risk TIA (ABCD² ≥ 4)
or
Minor ischemic stroke
(NIHSSS ≤ 5)

Sponsor
AstraZeneca
Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack

S. Claiborne Johnston, M.D., Ph.D., Pierre Amarenco, M.D., Gregory W. Albers, M.D., Hans Denison, M.D., Ph.D., J. Donald Easton, M.D., Scott R. Evans, Ph.D., Peter Held, M.D., Ph.D., Jenny Jonasson, Ph.D., Kazuo Minematsu, M.D., Ph.D., Carlos A. Molina, M.D., Yongjun Wang, M.D., and K.S. Lawrence Wong, M.D., for the SOCRATES Steering Committee and Investigators*
A Primary End Point: Stroke, Myocardial Infarction, or Death

Cumulative Probability (%)

Days since Randomization

No. of Patients

Ticagrelor 6589 6265 6216 6186 6153 6141 6118 6094 6058 4574
Aspirin 6610 6228 6186 6162 6129 6100 6078 6053 6030 4502

Ticagrelor 442 6.8
Aspirin 497 7.5

Hazard ratio, 0.89 (95% CI, 0.78–1.01); P=0.07

No. with Event

No. at Risk

Aspirin 6610 6228 6186 6162 6129 6100 6078 6053 6030 4502
Ticagrelor 6589 6265 6216 6186 6153 6141 6118 6094 6058 4574
B Ischemic Stroke

Cumulative Probability (%)

Aspirin

Ticagrelor

Days since Randomization

No. of Patients
Ticagrelor 6589
Aspirin 6610

No. with Event
Ticagrelor 385
Aspirin 441

Hazard ratio, 0.87 (95% CI, 0.76–1.00)

No. at Risk
Aspirin 6610 6230 6193 6169 6134 6112 6092 6065 6046 4518
Ticagrelor 6589 6272 6230 6204 6169 6157 6133 6102 6073 4587
Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: a subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial

Pierre Amarenco, Gregory W Albers, Hans Denison, J Donald Easton, Scott R Evans, Peter Held, Michael D Hill, Jenny Jonasson, Scott E Kasner, Per Ladenvall, Kazuo Minematsu, Carlos A Molina, Yongjun Wang, K S Lawrence Wong, S Clairemain Johnston, for the SOCRATES Steering Committee and Investigators

Summary

Background Ticagrelor is an effective antiplatelet therapy for patients with coronary atherosclerotic disease and might be more effective than aspirin in preventing recurrent stroke and cardiovascular events in patients with acute cerebral ischaemia of atherosclerotic origin. Our aim was to test for a treatment-by-ipsilateral atherosclerotic stenosis interaction in a subgroup analysis of patients in the Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial.

Methods SOCRATES was a randomised, double-blind, controlled trial of ticagrelor versus aspirin in patients aged 40 years or older with a non-cardioembolic, non-severe acute ischaemic stroke, or high-risk transient ischaemic attack from 674 hospitals in 33 countries. We randomly allocated patients (1:1) to ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2-90, given orally) or aspirin (300 mg on day 1 followed by 100 mg daily for days 2-90, given orally) within 24 h of symptom onset. Investigators classified all patients into atherothrombotic and non-atherothrombotic groups for the prespecified, exploratory analysis reported in this study. The primary endpoint was the time to occurrence of stroke, myocardial infarction, or death within 90 days. Efficacy analysis was by intention to treat. The SOCRATES trial is registered with ClinicalTrials.gov, number NCT01994720.

Findings Between Jan 7, 2014, and Oct 29, 2015, we randomly allocated 13199 patients (6589 [50%] to ticagrelor and 6610 [50%] to aspirin). Potentially symptomatic atherosclerotic stenosis was reported in 3081 (23%) of 13199 patients. We found a treatment-by-atherosclerotic stenosis interaction (p=0.017). 103 (6.7%) of 1542 patients with ipsilateral stenosis in the ticagrelor group and 147 (9.6%) of 1539 patients with ipsilateral stenosis in the aspirin group had an occurrence of stroke, myocardial infarction, or death within 90 days (hazard ratio 0.68; 95% CI 0.53–0.88; p=0.003). In 10118 patients with no ipsilateral stenosis, 339 (6.7%) of 5047 patients in the ticagrelor group had an occurrence of stroke, myocardial infarction, or death within 90 days compared with 350 (6.9%) of 5071 in the aspirin group (0.97 [0.84–1.13]; p=0.72). There were no significant differences in the proportion of life-threatening bleeding or major or minor bleeding events in patients with ipsilateral stenosis in the ticagrelor group compared with the aspirin group.

Interpretation In this prespecified exploratory analysis, ticagrelor was superior to aspirin at preventing stroke, myocardial infarction, or death at 90 days in patients with acute ischaemic stroke or transient ischaemic attack when associated with ipsilateral atherosclerotic stenosis. An understanding of stroke mechanisms and causes is important to deliver safe and efficacious treatments for early stroke prevention.
Fatal or nonfatal stroke
Atorvastatin 80mg vs. placebo after stroke/TIA, LDL-C 100-190mg/dL and no known CHD

Any coronary event

AHA/ASA Secondary prevention guidelines

Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and CV events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL (Class I; Level of Evidence B)
Reduction of LDL cholesterol and stroke incidence

Estimates of relative risk reduction

- 10% LDL reduction:
  - relative risk reduction 7.5% (2.3-12.5) overall
  - relative risk reduction 13.5% (7.7-18.8) for primary prevention of stroke

- 1 mmol/L (39 mg/dL) LDL reduction:
  - relative risk reduction 21.1% (6.3-33.5) overall
  - relative risk reduction 35.9% (21.7-47.6) for primary prevention of stroke
Monoclonal antibodies targeting PCSK9 result in large reductions in plasma LDL cholesterol.
Surgery vs Stenting for Symptomatic Carotid Stenosis
Treatment options for symptomatic carotid stenosis:

- Revascularization
- CEA (Carotid Endarterectomy)
- CAS (Carotid Artery Stenting)
- Medical treatment
- Risk factor management
any stroke at 5 years including operative risk

<table>
<thead>
<tr>
<th>stenosis</th>
<th>CEA</th>
<th>BMT</th>
<th>AR</th>
<th>NNT</th>
<th>strokes prev/1000 CEAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30%</td>
<td>18.36%</td>
<td>15.71%</td>
<td>-2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-49%</td>
<td>22.80%</td>
<td>25.50%</td>
<td>2.6</td>
<td>38</td>
<td>26</td>
</tr>
<tr>
<td>50-69%</td>
<td>20.00%</td>
<td>27.70%</td>
<td>7.8</td>
<td>13</td>
<td>78</td>
</tr>
<tr>
<td>70-99%</td>
<td>17.13%</td>
<td>32.70%</td>
<td>15.6</td>
<td>6</td>
<td>156</td>
</tr>
<tr>
<td>nr occln</td>
<td>16.82%</td>
<td>15.15%</td>
<td>-1.7</td>
<td>n/b</td>
<td>n/b</td>
</tr>
</tbody>
</table>

ECST, NASCET & VA studies combined and reanalysed after standardisation to NASCET angiographic measurement method (n>6000)

Lancet 2004;363:915-924
Lancet 2003;361:107-116
Stroke 2004;35:2855-2861
### Symptomatic carotid stenosis

**Is CAS as safe as CEA?**

Stroke or death within 30 days of treatment (per protocol analysis)

<table>
<thead>
<tr>
<th>Study</th>
<th>CAS</th>
<th>CEA</th>
<th>Peto OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA-3S</td>
<td>25/260</td>
<td>10/257</td>
<td></td>
</tr>
<tr>
<td>SPACE</td>
<td>44/591</td>
<td>35/567</td>
<td></td>
</tr>
<tr>
<td>ICSS</td>
<td>61/828</td>
<td>28/821</td>
<td></td>
</tr>
<tr>
<td>Subtotal*</td>
<td>130/1679</td>
<td>73/1645</td>
<td></td>
</tr>
<tr>
<td>CREST</td>
<td>40/668</td>
<td>21/653</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>170/2347</td>
<td>94/2298</td>
<td></td>
</tr>
</tbody>
</table>

**Absolute risks**

- **EVA-3S**: CAS 9.6, CEA 3.9
- **SPACE**: CAS 7.4, CEA 6.2
- **ICSS**: CAS 7.4, CEA 3.4
- **CREST**: CAS 6.0, CEA 3.2

**OR (Fixed) = 1.80 (1.40 – 2.31), p = 0.000**

**Heterogeneity p = 0.23**

*P. Amarenco, Lancet 2010*
Symptomatic carotid stenosis

CAS vs. CEA: effect of age

Carotid Stenting Trialists’ Collaboration, Lancet 2010

Any stroke or death within 120 days of randomization

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>CAS</th>
<th>CEA</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 70</td>
<td>5.8%</td>
<td>5.7%</td>
<td>1.0 (0.68 to 1.47)</td>
</tr>
<tr>
<td>&gt;= 70</td>
<td>12.0%</td>
<td>5.9%</td>
<td>2.04 (1.48 to 2.82)</td>
</tr>
</tbody>
</table>
Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.
Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Walter N. Kernan, MD, Chair; Bruce Ovbiagele, MD, MSc, MAS, Vice Chair; Henry R. Black, MD; Dawn M. Bravata, MD; Marc I. Chimowitz, MBChB, FAHA; Michael D. Ezckowitz, MBChB, PhD; Margaret C. Fang, MD, MPH; Marc Fisher, MD, FAHA; Karen L. Furie, MD, MPH, FAHA; Donald V. Heck, MD; S. Claiborne (Clay) Johnston, MD, PhD; Scott E. Kasner, MD, FAHA; Steven J. Kittner, MD, MPH, FAHA; Pamela H. Mitchell, PhD, RN, FAHA; Michael W. Rich, MD; DeJurana Richardson, PhD; Lee H. Schwamm, MD, FAHA; John A. Wilson, MD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease

Abstract—The aim of this updated guideline is to provide comprehensive and timely evidence-based recommendations on the prevention of future stroke among survivors of ischemic stroke or transient ischemic attack. The guideline is addressed to all clinicians who manage secondary prevention for these patients. Evidence-based recommendations are provided for control of risk factors, intervention for vascular obstruction, antithrombotic therapy for cardioembolism, and antiplatelet therapy for noncardioembolic stroke. Recommendations are also provided for the prevention of recurrent stroke in a variety of specific circumstances, including aortic arch atherosclerosis, arterial dissection, patent foramen ovale, hyperhomocysteinemia, hypercoagulable states, antiphospholipid antibody syndrome, sickle cell disease, cerebral venous sinus thrombosis, and pregnancy. Special sections address use of antithrombotic and anticoagulation therapy after an intracranial hemorrhage and implementation of guidelines. (Stroke. 2014;45:2160-2236.)

Key Words: AHA Scientific Statements • atrial fibrillation • carotid stenosis • hypertension • ischemia • ischemic attack, transient • prevention • stroke
Extracranial Carotid Disease Recommendations

For patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis as documented by noninvasive imaging, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6% (Class I; Level of Evidence A).

For patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging with corroboration (eg, magnetic resonance angiogram or computed tomography angiogram), CEA is recommended depending on patient-specific factors, such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6% (Class I; Level of Evidence B).
Extracranial Carotid Disease Recommendations

• For patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis as documented by noninvasive imaging, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6% (Class I; Level of Evidence A).

• For patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging with corroboration (eg, magnetic resonance angiogram or computed tomography angiogram), CEA is recommended depending on patient-specific factors, such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6% (Class I; Level of Evidence B).
• When the degree of stenosis is <50%, CEA and CAS are not recommended *(Class III; Level of Evidence A).*

• When revascularization is indicated for patients with TIA or minor, nondisabling stroke, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay surgery if there are no contraindications to early revascularization *(Class IIa; Level of Evidence B).*

• CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the ICA is reduced by >70% by noninvasive imaging or >50% by catheter-based imaging or noninvasive imaging with corroboration and the anticipated rate of periprocedural stroke or death is <6% *(Class IIa; Level of Evidence B).* *(Revised recommendation)*

• It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (ie, older than ≈70 years), CEA may be associated with
Intracranial Atherosclerosis
SAMMPRIS Trial

Medical Management:
Aspirin 325mg per day + Clopidogrel 75mg per day for 90 days
Symptomatic intracranial artery stenosis: *Aggressive medical treatment ± stenting*

SAMMPRIS Trial

**AHA/ASA secondary prevention guidelines 2014**

For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable (*Class IIb: Level of Evidence B*).

*Lancet* 2014;383:333-41
Effect of a Balloon-Expandable Intracranial Stent vs Medical Therapy on Risk of Stroke in Patients With Symptomatic Intracranial Stenosis

The VISSIT Randomized Clinical Trial

Osama O. Zaidat, MD, MS; Brian-Fred Fitzsimmons, MD; Britton Keith Woodward, MD; Zhigang Wang, MD; Monika Killer-Oberpfalzer, MD; Ajay Wakhloo, MD, PhD; Rishi Gupta, MD, MBA; Howard Kirshner, MD; J. Thomas Megerian, MD, PhD; James Lesko, PhD; Pamela Pitzer; Jandira Ramos, MPH; Alicia C. Castonguay, PhD; Stanley Barnwell, MD; Wade S. Smith, MD; Daryl R. Gress, MD; for the VISSIT Trial Investigators

Figure 2. Kaplan-Meier Estimate of Event-Free Survival Rates in Treatment Groups Intent-to-Treat Population

Log-rank test was used to test the hypothesis that event-free survival rates (primary end point) between groups were the same.
Management of patients with Aortic arch atheroma
Ulcerated Plaques in the Aortic Arch and Brain Infarction: Autopsy

500 Autopsy Cases *

Adjusted OR 4.0 [95% CI, 2.1-7.8]


Event Rates

Risk of Recurrent BI 12%/yr *

Risk of Vasc Event 26%/yr *

Aortic Arch Plaque and Brain Infarction: TEE *

Adjusted Odds Ratio (95% CI)

< 1 mm (1.5-7.7)
1 to 1.9 (2.1-8.9)
2 to 2.9 (2.7-9.0)
3 to 3.9 (3.3-25.2)
≥ 4 mm


Transesophageal echocardiography

« Complex plaques »
THE A.R.C.H. TRIAL

Aortic arch Related Cerebral Hazard

An academic driven trial

Non disabling Brain Infarct, TIA or Peripheral Embolism & Aortic Arch Plaque ≥4 mm

Warfarin
INR 2 to 3

Aspirin 75 mg/d + Clopidogrel 75 mg/d

Source of Funding:
French government through PHRC (1 M€)
Australian MRC (0.5 M€)

Drug supply: Sanofi and Bristol Myers-Squibb
Time to Primary End-point

Adjusted* HR=0.76 [95%CI, 0.36-1.61] p=0.5

*Age, sex, country, history of MI, on-treatment BP (time-dependent covariate)
Conclusions

• We found no significant difference on the incidence of stroke, MI, or vascular death in patients treated with C+A compared to those treated with warfarin.

• No significant difference in major and in intracranial hemorrhages, although we found 2 ICH in C+A vs 1 in W.

• TTR analysis suggests that «super» INR group trended to do better than C+A strategy, which opens the door for testing new drugs with much stable full anticoagulation (e.g., NOACs) over C+A or C.
Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=13447)</th>
<th>Western Europe, North America, Australia (n=1917)</th>
<th>Eastern and central Europe, Middle East (n=1394)</th>
<th>South America (n=1471)</th>
<th>China (n=3987)</th>
<th>South Asia (n=2850)</th>
<th>Southeast Asia (n=855)</th>
<th>Africa (n=973)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤45 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral haemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case-Control Study: 13,477 cases

Martin J O’Donnell, Siu Lim Chin, Sumathy Kangarajan, Denis Xavier, Lisheng Liu, Hongye Zhang, Purnima Rao-Malacini, Xiaohui Zhang, Prem Pais, Steven Agapay, Patricia Lopez-Jaramillo, Albertino Damasceno, Peter Langhorne, Matthew J McQueen, Annika Rosengren, Mahshid Dehghan, Graeme Hankey, Antonio I. Dano, Ahamed Eleyadi, Alvaro Avezum, Charles Mondo, Hans-Christoph Diener, Danuta Ryglewicz, Anna Czlonkowska, Nana Pogosova, Christian Weimar, Romaina Iqbal, Rafael Diaz, Khalid Yusoff, Afzalhussein Yusufali, Aytakin Oguz, Xingyu Wang, Ernesto Penaherrera, Fernando Lanas, Okechukwu S Ojuh, Adesola Oggunniyi, Helle K Iversen, German Malaga, Zvonko Rumboldt, Shahram Owensgharan, Fawaz Al Hussain, Daewoong Magazi, Yongchai Nilanont, John Ferguson, Guillaume Pare, Salim Yusuf; on behalf of the INTERSTROKE investigators.
INTERSTROKE: POPULATION ATTRIBUTABLE RISK

<table>
<thead>
<tr>
<th></th>
<th>Collective PAR (99%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Stroke</td>
<td>90.7% (88.7-92.4)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>91.5% (89.4-93.2)</td>
</tr>
<tr>
<td>ICH</td>
<td>87.1% (82.2-90.8)</td>
</tr>
</tbody>
</table>
Summary

• Stroke is largely a preventable disease.
• Aggressive risk factor management is important.
• All antiplatelets have almost similar efficacy with marginal benefit of clopidogrel or ASA+DP over aspirin.
• Warfarin is indicated for cardioembolic strokes. Newer OAC agents are also effective without any major benefit over warfarin.
• CEA/CAS is beneficial in >50% symptomatic stenosis. CAS is more appropriate in selected cases.
Save the Date

Chicago, USA
June 28-30, 2018

THE HEART & BRAIN SYMPOSIUM

EXPLORE THE INTER-RELATIONSHIP BETWEEN CARDIOVASCULAR HEALTH AND STROKE

hbs.kenes.com