ICH – SECONDARY PREVENTION...

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Disclosures

- NIH/NINDS
  - U01 NS 074425
    *Futility study of deferoxamine mesylate in ICH*

- AHA Collaborative Sciences Award
  - 15CSA24540001
    *Injectable Biomaterial Matrix for Hemorrhagic Stroke: Mechanisms and Therapies*
Objectives

To Discuss:

- The epidemiology of ICH recurrence
- Importance of preventing ICH recurrence
- Secondary preventive strategies
  - BP Control
  - Judicious use of anti-thrombotic agents
    - Antiplatelets
    - Anticoagulants
  - Judicious use of statins
Epidemiology

- ICH survivors are at high risk for a recurrent event

- The cumulative risk of ICH recurrence varies from 1% to 5% per year

- In PROGRESS, the risk of ICH recurrence in patients with ICH was higher than the risk of a first ICH in IS patients (HR = 6.5; 95% CI 4.5 – 9.7)

- The risk of ICH recurrence is ongoing and extends for years especially in patients with lobar ICH, i.e. the frequency of recurrent ICH does not seem to significantly decline over time
Epidemiology – Risk Factors

The risk factors for ICH recurrence are:

- Location of the initial ICH (lobar vs. deep)
  - Annual risk for ICH recurrence after deep ICH ~ 2% to 3%
  - Annual risk for ICH recurrence after lobar ICH ~ 7% to 14%

- HTN
  - High BP increases the recurrence of both deep & lobar ICH
  - The only known intervention for secondary prevention of ICH is lowering BP

- Older age
  - Higher prevalence of CAA
  - Increased use of anti-thrombotic drugs
Epidemiology – Risk Factors

- Carriers of APO-E ε2 or ε4 genotype

- Greater number of microbleeds (especially in lobar locations) on GRE or T2* MRI

- Detection of superficial siderosis on MRI

- Patients with recurrent ICHs

- Race:
  - In Whites, most of the initial & recurrent ICHs tend to be lobar
  - In Asians, deep ICHs tend to be more common
Prerequisites of Secondary Prevention

Identification of the etiology/mechanism of the initial ICH is an important first step. It allows:

- Stratification of the risk of ICH recurrence
- Tailoring of preventive strategies to decrease the risk of recurrence
Secondary Prevention of ICH: Why Not?

- ICH is a frequent cause of morbidity and mortality
  - Mortality up to 40%
  - Most patients are left with serious and permanent disability

- Is it really worth the cost and resources to prevent ICH recurrence?
Secondary Prevention of ICH: Why YES?

- Up to 30% of ICH patients achieve mRS ≤2 by 90 days, and slightly more by 6 months!

- 70,000 patients are admitted with ICH to hospitals in the United States & 400,000 in the Far East each year

- Worldwide, the overall incidence of ICH is approximately 25 per 100,000 person years
BP Management

- Inappropriate BP control increases risk of ICH recurrence
- Adequate control of BP reduces risk of ICH recurrence
Long-term BP control is inadequate in ICH patients...

Poor Long-Term Blood Pressure Control After Intracerebral Hemorrhage

Darin B. Zahurancic, MD, MS; Jeffrey J. Wing, MPH; Dorothy F. Edwards, PhD; Ravi S. Menon, MD; Stephen J. Fernandez, MPH; Richard E. Burgess, MD, PhD; Ian A. Sobocik, BS; Laura Geman, BS; Anna J. Troth, MD; Ninar M. Shani, PhD; M. Chris Gibson, MD, MPH; Bernadette Boden-Alba, MPH, DrPH; Chelsea S. Kidwell, MD

Background and Purpose—Hypertension is the most important risk factor associated with intracerebral hemorrhage. We explored racial differences in blood pressure (BP) control after intracerebral hemorrhage and assessed predictors of BP control at presentation, 30 days, and 1 year in a prospective cohort study.

Methods—Subjects with spontaneous intracerebral hemorrhage were identified from the Diffusion Lesion Imaging of Primary Hemorrhage (DISCERN) Project. BP was measured by race at each time point. Multivariable linear regression was used to determine predictors of presenting mean arterial pressure, and longitudinal linear regression was used to assess predictors of mean arterial pressure at follow-up.

Results—A total of 622 patients were included (mean age, 59 years; 52% male; 77% black). Mean arterial pressure at presentation was 9.6 mm Hg higher in blacks than whites despite adjustment for confounders (P = 0.065). Fewer than 20% of patients had normal BP (<120/80 mm Hg) at 30 days or 1 year. Although there was no difference at 30 days (P = 0.31), blacks were more likely than whites to have Stage 2 hypertension at 1 year (P = 0.056). Factors associated with lower mean arterial pressure at follow-up in multivariable analysis were being married at baseline (P = 0.032) and living in a facility (versus personal residence) at the time of BP measurement (P = 0.023).

Conclusions—Long-term BP control is inadequate in patients after intracerebral hemorrhage, particularly in blacks. Further studies are needed to understand the role of social support and barriers to control to identify optimal approaches to improve BP in this high-risk population. (Stroke. 2013;43:2580-2585.)

Key Words: hypertension • intracerebral hemorrhage • secondary prevention • racial differences
Inadequate BP control is associated with higher risk for ICH recurrence…

- 1145 ICH patients
- Median follow-up = 36.8 months (minimum = 9.8)
- <50% of patients achieved consistent BP control in line with AHA/ASA guidelines

**Recurrence:**

- 102/505 among survivors of lobar ICH (~ 20%)
  - 84 vs. 49 per 1000 person-years among patients with inadequate BP control compared with adequate BP control
  - HR 3.53 (95% CI 1.65-7.54)
- 44/640 among survivors of non-lobar (~ 7%)
  - 52 vs. 27 per 1000 person-years among patients with inadequate BP control compared with adequate BP control
  - HR 4.23 (95% CI 1.02-17.52)

*Biffi et al. JAMA. 2015;314(9):904-912*
All hypertensive stages above normotension (90-119/60-79 mmHg) were associated with increased risk for ICH recurrence.

HR for lobar ICH (1.33; 95% CI 1.02-1.76) and non-lobar ICH (1.54; 95% CI 1.03-2.30) per 10 mmHg increase in BP.

Both elevated SBP & DBP are associated with increased risk of ICH recurrence.
BP lowering is beneficial in ICH survivors

**PROGRESS**

- 6,015 patients with history of IS, TIA, or ICH were randomized to perindopril w/ or w/o indapamide or placebo
- Mean follow-up ~ 3.9 years
- Mean difference in BP between active treatment & placebo was 9/4 mm Hg
  - 12/5 mmHg with combination therapy
  - 5/3 mmHg with single-drug therapy
- Overall stroke risk reduction with active treatment was 28% (95% CI 17-38)
  - RRR 43% with combination therapy
  - RRR 5% with single therapy

*Lancet. 2001; 358:1033–1041*
BP lowering is beneficial across all stroke types, particularly ICH

Effects of a Perindopril-Based Blood Pressure–Lowering Regimen on the Risk of Recurrent Stroke According to Stroke Subtype and Medical History
The PROGRESS Trial

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Background and Purpose — The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed that blood pressure lowering reduced stroke risk in patients with a history of cerebrovascular events. Here, we report the consistency of treatment effects across different stroke subtypes and among major clinical subgroups.

Methods — PROGRESS was a randomized, double-blind trial among 6105 people with a prior history of cerebrovascular events. Participants were assigned to active treatment (perindopril for all participants and indapamide for those with neither an indication nor a contraindication to a diuretic) or matching placebo(s).

Results — During a mean of 3.9 years of follow-up, active treatment reduced the absolute rates of ischemic stroke from 10% to 8% (relative risk reduction [RRR], 24%; 95% confidence interval [CI], 10 to 35) and the absolute rates of intracerebral hemorrhage from 2% to 1% (RRR, 50%; 95% CI, 26 to 67). The relative risk during follow-up was reduced by 26% (95% CI, 12 to 38) among patients whose baseline cerebrovascular event was an ischemic stroke and by 49% (95% CI, 18 to 68) among those whose baseline event was an intracerebral hemorrhage. There was no evidence that treatment effects were modified by other drug therapies (antiplatelet or other antihypertensive agents), residual neurological signs, atrial fibrillation, or the time since the last cerebrovascular event.

Conclusions — Beneficial effects of a perindopril-based treatment regimen were observed for all stroke types and all major clinical subgroups studied. These data suggest that effective blood pressure–lowering therapy should be routinely considered for all patients with a history of cerebrovascular events. (Stroke. 2004;35:116-121.)
727 participants had 886 strokes during follow up
- 656 ischemic
- 123 ICH
- 107 unknown type

Risk of IS was reduced in the active treatment group by 24\% (95\% CI 10-35)

RRR of ICH was 50\% (95\% CI 26-67)
~ 11% of participants in each arm had a history of ICH

- Overall, active treatment reduced absolute rates of ICH from 2% to 1% (RRR 50%; 95% CI 26-67%) during a mean follow-up of 3.9 years
- RRR was 76% with combination therapy and -1% with single therapy
- 50% of recurrent strokes were hemorrhagic & 35% ischemic
- RRR for stroke among patients with a baseline ICH was 49% (95% CI 18-68)
Effects of Perindopril-Based Lowering of Blood Pressure on Intracerebral Hemorrhage Related to Amyloid Angiopathy

The PROGRESS Trial

Hisatomi Arima, MD; Christophe Tzourio, MD; Craig Anderson, MD; Mark Woodward, PhD; Marie-Germaine Bousser, MD; Stephen MacMahon, PhD; Bruce Neal, MD; John Chalmers, MD; for the PROGRESS Collaborative Group

Background and Purpose—Patients with cerebral amyloid angiopathy (CAA) are at high risk for intracerebral hemorrhage (ICH), but no effective prevention strategies have been established. The objective is to determine whether lowering of blood pressure (BP) provides protection for this high-risk patient group.

Methods—This study is a subsidiary analysis of the PROGRESS trial—a randomized, placebo-controlled trial that established the beneficial effects of BP lowering in patients with cerebrovascular disease; 6105 patients were randomly assigned to either active treatment (perindopril for all participants plus indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo. Outcomes were probable CAA-related ICH as defined by the Boston criteria, probable hypertension-related ICH, and unclassified ICH.

Results—Over a mean follow-up of 3.9 years, 16 probable CAA-related ICH, 51 probable hypertension-related ICH, and 44 unclassified ICH occurred. Active treatment reduced the risk of CAA-related ICH by 77% (95% CI, 19%–93%), that of hypertension-related ICH by 46% (95% CI, 4%–69%), and that of unclassified ICH by 43% (95% CI, −5%–69%). There was no evidence of differences in the magnitude of the effects of treatment among different types of ICH (P homogeneity=0.4).

Conclusions—BP-lowering treatment is likely to provide protection against all types of ICH. (Stroke. 2010;41:394-396.)
Lowering BP is beneficial across all ICH subtypes…

- 88% of patients with CAA-related ICH had pre-existing ICH
- 84% of patients with HTN-related ICH had pre-existing IS
- Active treatment reduced risk of CAA-ICH by 77%, HTN-ICH by 46%, and unclassified ICH by 43%
- There was no difference in the magnitude of the effects of treatment among different types of ICH

**Figure.** Effects of randomized treatment on the risks of different types of ICH. Solid boxes indicate estimates of treatment effect on the risks of ICH types; horizontal lines, 95% CI; diamond, the estimate and 95% CI for overall effect. Areas of the boxes are proportional to the event number.
What is the target BP?

AHA/ASA Guideline

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage
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, the Congress of Neurological Surgeons, and the Neurocritical Care Society

J. Claude Hemphill III, MD, MAS, FAHA, Chair; Steven M. Greenberg, MD, PhD, Vice-Chair; Craig S. Anderson, MD, PhD; Kyra Becker, MD, FAHA; Bernard R. Bendok, MD, MS, FAHA; Mary Cushman, MD, MSc, FAHA; Gordon L. Fung, MD, MPH, PhD, FAHA; Joshua N. Goldstein, MD, PhD, FAHA; R. Loch Macdonald, MD, PhD, FRCS; Pamela H. Mitchell, RN, PhD, FAHA; Phillip A. Scott, MD, FAHA; Magdy H. Selim, MD, PhD; Daniel Woo, MD, MS; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology

BP should be controlled in all ICH patients (Class I; Level of Evidence A). (Revised from the previous guideline) Measures to control BP should begin immediately after ICH onset (Class I; Level of Evidence A). (New recommendation) A long-term goal of BP <130 mm Hg systolic and 80 mm Hg diastolic is reasonable (Class IIa; Level of Evidence B). (New recommendation)
Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial

The SPS3 Study Group*  

Summary  
Background: Lowering of blood pressure prevents stroke but optimum target levels to prevent recurrent stroke are unknown. We investigated the effects of different blood-pressure targets on the rate of recurrent stroke in patients with recent lacunar stroke.  

Methods: In this randomised open-label trial, eligible patients lived in North America, Latin America, and Spain and had recent, MRI-defined symptomatic lacunar infarctions. Patients were recruited between March, 2003, and April, 2011, and randomly assigned, according to a two-by-two multifactorial design, to a systolic blood-pressure target of 130-149 mm Hg or less than 130 mm Hg. The primary endpoint was reduction in all stroke (including ischaemic strokes and intracranial haemorrhages). Analysis was done by intention to treat. This study is registered with ClinicalTrials.gov, number NCT 00059366.  

Findings: 3020 enrolled patients: 1519 in the higher-target group and 1501 in the lower-target group, were followed up for a mean of 3.7 (SD 2.9) years. Mean age was 63 (SD 11) years. After 1 year, mean systolic blood pressure was 138 mm Hg (95% CI 137-139) in the higher-target group and 127 mm Hg (95% CI 126-128) in the lower-target group. Non-significant rate reductions were seen for all stroke (hazard ratio 0.81, 95% CI 0.64-1.03, p=0.08), ischaemic stroke or unknown (0.84, 0.66-1.09, p=0.19), intracranial haemorrhage (0.61, 0.41-0.91, p=0.06), and disabling or fatal stroke (0.87, 0.69-1.10, p=0.26) with the lower target. The rate of intracerebral haemorrhage was reduced significantly (0.31, 0.1-1.22, p=0.016) in the higher-target group.  

Interpretation: Although the reduction in stroke was not significant, our results suggest that in patients with recent lacunar strokes, the use of a systolic blood-pressure target of less than 130 mm Hg is likely to be beneficial.

<table>
<thead>
<tr>
<th></th>
<th>Higher-target group (n=1519)</th>
<th>Lower-target group (n=1501)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All stroke</td>
<td>152</td>
<td>125</td>
<td>0.81</td>
<td>0.08</td>
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<tr>
<td>Ischaemic stroke or unknown</td>
<td>131</td>
<td>112</td>
<td>0.84</td>
<td>0.19</td>
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<tr>
<td>Intracranial haemorrhage</td>
<td></td>
<td></td>
<td>0.61</td>
<td>0.16</td>
</tr>
<tr>
<td>All</td>
<td>21</td>
<td>13</td>
<td>0.38</td>
<td></td>
</tr>
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<td></td>
<td></td>
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<tr>
<td>Intracerebral</td>
<td>16</td>
<td>6</td>
<td>0.29</td>
<td>0.03</td>
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<tr>
<td>Subdural or epidural</td>
<td>5</td>
<td>6</td>
<td>0.09</td>
<td>0.78</td>
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<tr>
<td>Other</td>
<td>2</td>
<td>4</td>
<td>0.03</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>40</td>
<td>36</td>
<td>0.70</td>
<td>0.59</td>
</tr>
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<td>Major vascular event*</td>
<td>188</td>
<td>160</td>
<td>3.46</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>101</td>
<td>206</td>
<td>1.16</td>
<td>0.01</td>
</tr>
<tr>
<td>Vascular death</td>
<td>41</td>
<td>36</td>
<td>0.70</td>
<td>0.52</td>
</tr>
<tr>
<td>Non-vascular</td>
<td>35</td>
<td>40</td>
<td>0.60</td>
<td>0.62</td>
</tr>
<tr>
<td>Uncertain</td>
<td>25</td>
<td>30</td>
<td>0.43</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*One classified as both intracerebral and other, and one as both intracerebral and subdural or epidural. 1One classified as intracerebral and subdural or epidural, and two as both intracerebral and other. 1Disabling strokes classified as modified Rankin score 3 or higher after 3-6 months.

Table 2: Primary and secondary outcomes
Achieved BP and Outcomes in SPS3

- Post-hoc examination of the association of mean achieved BP 6 months after randomization with recurrent stroke, major vascular events, and all-cause mortality

- Mean follow up = 3.7 years

Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial
Hisatomi Arima\textsuperscript{a}, John Chalmers\textsuperscript{a}, Mark Woodward\textsuperscript{a}, Craig Anderson\textsuperscript{a}, Anthony Rodgers\textsuperscript{b}, Stephen Davis\textsuperscript{c}, Stephen MacMahon\textsuperscript{a}, Bruce Neal\textsuperscript{a} for the PROGRESS Collaborative Group

Objective To explore the likely optimum blood pressure (BP) level for patients with a history of cerebrovascular disease.

Methods The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a randomized, placebo-controlled trial that established the beneficial effects of BP lowering in 6105 patients with cerebrovascular disease. The present study comprises two series of post hoc analyses. The first was designed to investigate the effects of randomized treatment on recurrent stroke by baseline BP levels, and the second was a corresponding observational analysis investigating the association between achieved follow-up BP levels and recurrent stroke risk.

Results Analyses of the randomized treatment comparisons showed that BP lowering with combination therapy produced similar risk reductions in each of four subgroups defined by baseline BP of less than 120, 120–139, 140–159, and 160 mmHg or greater ($P$ homogeneity $= 0.5$). The effects of single-drug therapy were also comparable across these subgroups ($P$ homogeneity $= 0.2$), but consistently greater benefits were observed with combination compared to single-drug therapy. The analyses of achieved follow-up BP showed that the lowest risk of recurrence was among the one-quarter of participants with the lowest follow-up BP levels (median 112/72 mmHg), and that risks rose progressively with higher follow-up BP levels. Minor side-effects were progressively more common at lower BP levels ($P$ homogeneity $= 0.04$), but there was no excess of serious complications (all $P$ homogeneity $> 0.2$).

Conclusion These analyses provide no evidence of a J-curve relationship between BP level and stroke risk among patients with cerebrovascular disease, and identify no patient group among whom more intensive BP lowering would not be expected to produce greater risk reductions. \textit{J Hypertens} 24:1201–1208 © 2006 Lippincott Williams & Wilkins.

Journal of Hypertension 2006, 24:1201–1208

Keywords: blood pressure, indapamide, perindopril, randomized controlled trial, recurrent stroke

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Correspondence and requests for reprints to John Chalmers, PROGRESS Collaborative Group, \textsuperscript{a}The George Institute for International Health, University of Sydney, PO Box M201, Maseman Road, NSW 2000, Australia. Tel: +61 2 9993 4587; fax: +61 2 9993 4588; e-mail: j.chalmers@thegeorgeinstitute.org

Sponsorship: PROGRESS was funded by grants from Servier, the Health Research Council of New Zealand, and the National Health and Medical Research Council of Australia. The study was designed, conducted, analysed and interpreted by the investigators independently of all sponsors.

Conflict of interest: J.C. and S.M. have received research grants from Servier, as chief investigators for PROGRESS and ADVANCE administered by the University of Sydney. J.C., M.W., C.A., A.R., S.M., and B.N. have received honoraria from Servier for presentations regarding the study at scientific meetings.

A free communication on a portion of this study was presented at the Annual Scientific Meeting of the Stroke Society of Australia held in Melbourne in September 2005.

Received 29 October 2005 Revised 1 February 2006 Accepted 23 February 2006
- The beneficial effects of treatment in preventing ICH extend down to patients with baseline BP levels ~ 115/75 mmHg

- Progressive lowering BP to 115/75 mmHg in ICH patients over time was safe in PROGRESS
The association of stroke recurrence with achieved follow-up SBP level was strong and continuous in the range of achieved follow-up SBP from 112 to 168 mmHg.

This association remained strong even after controlling for the effects of other cardiovascular risk factors and of randomized treatment, and was not altered after adjustment for baseline BP.

Similar associations were observed for both IS & ICH although the relationship of ICH with achieved follow-up SBP level was stronger.
Targeting SBP <120 mm Hg could be beneficial...
Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Treatment</th>
<th>Standard Treatment</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>% per year</td>
<td>no. of patients (%)</td>
<td>% per year</td>
</tr>
<tr>
<td>All participants</td>
<td>(N = 4678)</td>
<td></td>
<td>(N = 4683)</td>
<td></td>
</tr>
<tr>
<td>Primary outcome†</td>
<td>243 (5.2)</td>
<td>1.65</td>
<td>319 (6.8)</td>
<td>2.19</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>97 (2.1)</td>
<td>0.65</td>
<td>116 (2.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>40 (0.9)</td>
<td>0.27</td>
<td>40 (0.9)</td>
<td>0.27</td>
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<tr>
<td>Stroke</td>
<td>62 (1.3)</td>
<td>0.41</td>
<td>70 (1.5)</td>
<td>0.47</td>
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<tr>
<td>Heart failure</td>
<td>62 (1.3)</td>
<td>0.41</td>
<td>100 (2.1)</td>
<td>0.67</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>37 (0.8)</td>
<td>0.25</td>
<td>65 (1.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>155 (3.3)</td>
<td>1.03</td>
<td>210 (4.5)</td>
<td>1.40</td>
</tr>
<tr>
<td>Primary outcome or death</td>
<td>332 (7.1)</td>
<td>2.25</td>
<td>423 (9.0)</td>
<td>2.90</td>
</tr>
</tbody>
</table>

*Data from reference [1].

**Patients with DM, Stroke & difficult-to-treat HTN were excluded from SPRINT!**
Intensive lowering of BP requires >2 anti-HTN agents & comes with a price!
My Thoughts..

- ICH patients would likely have the lowest risk of ICH recurrence if their SBP could be lowered to ≤120-130 mmHg in the long term, provided that they can tolerate it.

- INTERACT-II suggests that this can be safely started within a few days after ICH...... ATTACH-II!!

- How best to achieve & maintain greater BP reduction is challenging
  - Combination therapy might be preferable
  - Lifestyle modifications, and management of OSA and obesity are important
  - Improved support from health care providers & care takers, and patient education and involvement in BP monitoring are key to improve adherence to therapy.
Use of antithrombotic agents

○ A large number of ICH patients have cardiovascular comorbidities and are taking aspirin

○ ~12% to 14% of ICH patients are taking an OAC at the time of ICH onset

○ Survivors of ICH often have compelling indications for anticoagulant or antiplatelet medications

○ OAC use is associated with increased mortality after ICH (up to 70%)

○ The dilemma is whether to resume antithrombotic drugs or to discontinue them in ICH survivors lest they should raise the risk of recurrent ICH and/or worsen the outcome of any recurrence
Resumption of antithrombotic agents after ICH

- Should we?
- When?
- What agent?
- Under what circumstances?
  - Patient characteristics
  - ICH characteristics (location/etiology)

- No consensus
- No data from RCTs
- Various opinions based on a combination of observational data, small studies, pathophysiological considerations, and competing benefit/risk assessment
Does aspirin increase the risk of ICH recurrence?

If so, is there a preferential difference based on ICH location (lobar vs. non-lobar)?

- Prospective, observational
- 13 German centers
- 496 ICH patients; 141 (28.4%) received APL agents after ICH
- Mean follow up ~ 2 years

- Annual rate of ICH recurrence:
  - Non-lobar ICH = 2.9% (95% CI 1.6-4.1)
  - Lobar ICH = 7.2% (95% CI 3.8-10.6)

- No difference could be found for recurrent ICH under antiplatelet agents vs. no antithrombotic medication


- Prospective, observational
- Single center (USA)
- 207 ICH patients; 127 lobar & 80 non-lobar
- 27 lobar & 19 non-lobar ICH patients received APL agents after ICH
- Follow up ~ 2 years

- Cumulative 2-year ICH recurrence rate:
  - Lobar ICH = 22%
  - Non-lobar ICH = 4%

- APL use was not associated with ICH recurrence
  - HR 0.8, 95% CI 0.3-2.3) for lobar ICH
  - HR 1.2, 95% CI 0.1-14.3) for non-lobar ICH

- Prospective, observational
- Single center (Chinese)
- 440 ICH patients (predominantly non-lobar); 55 (12.7%) received ASA after ICH
- Follow up ~ 62.2±1.8 months

- 10.7% had recurrent ICH

- Patients prescribed aspirin did not have a higher risk of recurrent ICH compared with those not prescribed aspirin (22.7 per 1,000 patient-aspirin years vs. 22.4 per 1,000 patient years)

- In a subgroup analysis including 127 patients with indications for aspirin of whom 56 were prescribed aspirin
  - The incidence of combined vascular events including recurrent ICH, ischemic stroke, and acute coronary syndrome was lower in patients prescribed aspirin than those not prescribed aspirin (52.4 per 1,000 patient-aspirin years, vs. 112.8 per 1,000 patient-years, p=0.04)

- Observational
- Tayside, Scotland
- 417 ICH patients
  - 235 (56.4%) lobar
  - 139 (33.3%) non-lobar
  - 120 (28.7%) were prescribed APL agents
- Median follow-up ~ 36.5 months

ICH recurrence:
- Overall = 9.7 per 1000 patient-years (95% CI 5.3-16.4)
- Non-lobar ICH = 6.4 per 1000 patient-years (95% CI 1.32-18.7)
- Lobar ICH = 11.2 per 1000 patient-years (95% CI 5.1-21.3). All except one were lobar ICHs; 78% of recurrent ICHs occurred in patients not exposed to APLs.

HR for recurrent ICH with APL use:
- Overall = 1.07 (95% CI 0.24-4.84)
- Lobar ICH = 1.52 (95% CI, 0.31–7.39)
- Non-lobar ICH - No ICH events occurred among APL-treated patients

APL use did not appear to have a clinically significant impact on the risk of recurrent ICH or subsequent IS/MI
Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy

ABSTRACT

Objective: To identify and compare clinical and neuroimaging predictors of primary lobar intracerebral hemorrhage (ICH) recurrence, assessing their relative contributions to recurrent ICH.

Methods: Subjects were consecutive survivors of primary ICH drawn from a single-center prospective cohort study. Baseline clinical, imaging, and laboratory data were collected. Survivors were followed prospectively for recurrent ICH and intercurrent aspirin and warfarin use, including duration of exposure. Cox proportional hazards models were used to identify predictors of recurrence stratified by ICH location, with aspirin and warfarin exposures as time-dependent variables adjusting for potential confounders.

Results: A total of 104 primary lobar ICH survivors were enrolled. Recurrence of lobar ICH was associated with previous ICH before index event [hazard ratio [HR] 7.7, 95% confidence interval [CI] 1.4–15.7], number of lobar microbleeds (HR 2.93 with 2–4 microbleeds present, 95% CI 1.3–4.0; HR = 4.12 when ≥5 microbleeds present, 95% CI 1.6–9.3), and presence of CT-defined white matter hypodensity in the posterior region (HR 4.11, 95% CI 1.01–12.2). Although aspirin after ICH was not associated with lobar ICH recurrence in univariate analyses, in multivariate analyses adjusting for baseline clinical predictors, it independently increased the risk of ICH recurrence (HR 3.95, 95% CI 1.6–8.3, p = 0.021).

Conclusions: Recurrence of lobar ICH is associated with previous microbleeds or macrobleeds and posterior CT white matter hypodensity, which may be markers of severity for underlying cerebral amyloid angiopathy. Use of an antiplatelet agent following lobar ICH may also increase recurrence risk. Neurology® 2010;75:693–698
My Thoughts..

- Restarting/continuing aspirin in non-lobar ICH patients with indications for APL is reasonable.

- In ICH patients with suspected CAA or microbleeds on MRI, the use of APLs should be:
  - Reserved for those with compelling indications, i.e. CAD, PVD, or AF.
  - Restricted to the lowest dose (81 mg ASA), if possible.
  - Perhaps avoided in those with recurrent lobar ICHs on APL therapy in whom BP is well controlled.
Does warfarin increase the risk of ICH recurrence?

If so, is there a preferential difference based on ICH location (lobar vs. non-lobar)?

Any role for DOACs?
Poli et al. Neurology. 2014; 82:1020-1026

- The Cerebral Hemorrhage in patients Restarting Oral Anticoagulant Therapy (CHIRONE) Study
- Observational
- 267 patients affiliated with the Italian Federation of Anticoagulation Clinics who had received warfarin after ICH
- Mean follow up ~ 778 patient-years
- ICH recurred in 20 patients (7.5%; rate 2.56 × 100 patient-years) at a median time of 16.5 months, and was fatal in 5 patients (25%; rate 0.4 × 100 patient-years)
- Patients with a history of ICH carry a significant risk of recurrent ICH when treated with warfarin


- 284 consecutive patients with warfarin-related ICH admitted to 13 stroke centres in the Registry of the Canadian Stroke Network
- Warfarin was restarted in-hospital in 91 patients (32%)
- Mortality rates were not higher in those who restarted warfarin in-hospital: 31.9% vs. 54.4% (30-day, P < 0.001) and 48% vs. 61% (1-year, P = 0.04), and bleeding was not increased
- In selected patients at high risk for thromboembolism, reinitiation of warfarin after ICH did not confer increased mortality or bleeding events
Effect of Anticoagulation on Hospitalization Costs After Intracranial Hemorrhage in Atrial Fibrillation
A Registry Study

Anne Sig Vestergaard, MMsc; Flemming Skjøth, MSc, PhD; Gregory Y.H. Lip, MD; Torben Bjerregaard Larsen, MD, PhD

Background and Purpose—Intracranial hemorrhage (ICH) is the most feared adverse event with oral anticoagulant therapy in patients with atrial fibrillation. The health economic aspects of resuming oral anticoagulant therapy after ICH are unknown. The aim was to estimate hospitalization costs of thromboembolism and hemorrhage subsequent to ICH in 2 patient groups with atrial fibrillation surviving the first 90 days post ICH: (1) patients resuming warfarin therapy within 90 days post ICH and (2) patients discontinuing therapy.

Methods—Retrospective data from Danish national registries were linked to identify patients with atrial fibrillation who suffered an ICH between January 1, 1997, and April 1, 2011. Study start was 90 days after incident ICH. Mortality was evaluated using the Kaplan–Meier estimate. Occurrence of hospitalization-requiring thromboembolism and hemorrhage was used to estimate hospitalization costs by linkage of International Classification of Diseases, Tenth Revision, codes to Danish Diagnosis-Related Group tariffs. The effect of resuming warfarin therapy on average 3-year hospitalization costs was estimated by regression analysis adjusted for between-group differences in baseline characteristics.

Results—In the inclusion period, 2162 patients had an ICH; 1098 survived the first 90 days and were included for analysis, and of those, 267 resumed warfarin therapy. Therapy resumption reduced the mean 3-year hospitalization cost of hospitalized patients significantly by US$ 1588 (95% confidence interval, −2925 to −251) and was significantly correlated with fewer hospitalization days per hospitalized patient (−4.6 [95% confidence interval, −7.6 to −1.6]). The marginal effect of therapy resumption on hospitalization costs per patient was US$ −407 (95% confidence interval, −815 to 2).

Conclusions—Resuming warfarin therapy within 90 days after ICH in patients with atrial fibrillation is associated with a decrease in average hospitalization costs. (Stroke. 2016;47:979-985. DOI: 10.1161/STROKEAHA.115.012338.)
Resumption of warfarin →
- Correlated with fewer hospitalization days per patient
- Reduced 3-year hospitalization costs
Lobar ICH – Do not anticoagulate UNLESS the rate of recurrent ICH is <1.4% per year

Non-lobar ICH -- Do not anticoagulate UNLESS the rate of recurrent ICH is <1.6% per year & the rate of ischemic stroke is >7% per year (CHADS2 ≥ 4 or CHA2DS2-VASc ≥ 5)

All survivors of lobar ICH & most survivors of non-lobar ICH should not be anticoagulated
Balancing the risks…

- ICH results in greater disability & mortality than ischemic stroke.
- Restarting anticoagulation should be avoided, UNLESS the risk of ischemic stroke is MUCH HIGHER than that of recurrent ICH.
- The risk of thromboembolic events depends on the underlying indication for OAC and comorbidities.
- The risk for ICH recurrence depends on ICH subtype/location.

- Risk of ICH recurrence w/o OAC
  - Lobar ICH: 7% to 22% per year
  - Deep ICH: 2% to 3% per year

  *Most anticoagulation-related ICHs are lobar*

- Risk of IS
  - AFib – baseline risk ~ 4.5% per year
    - CHADS2 score 1-4 -- 2.8%- 8.5%
    - CHADS2 score 5 -- 12.5%
    - CHADS2 score 6 -- 18%
  - 12% to 22% in patients with prosthetic valves
Optimal Timing of Resumption of Warfarin After Intracranial Hemorrhage

Ammar Majeed, MD; Yang-Ki Kim, MD; Robin S. Roberts, PhD; Margareta Holmström, MD, PhD; Sam Schulman, MD, PhD

**Background and Purpose**—The optimum timing of resumption of anticoagulation after warfarin-related intracranial hemorrhage in patients with indication for continued anticoagulation is uncertain. We performed a large retrospective cohort study to obtain more precise risk estimates.

**Methods**—We reviewed charts of 2869 consecutive patients with objectively verified intracranial hemorrhage over 6 years at 3 tertiary centers. We calculated the daily risk of intracranial hemorrhage or ischemic stroke with and without resumption of warfarin; we focused on patients who survived the first week and had cardiac indication for anticoagulation or previous stroke. Using a Cox model, we estimated rates for these 2 adverse events in relation to different time points of resumed anticoagulation. The combined risk of either a new intracranial hemorrhage or an ischemic stroke was calculated for a range of warfarin resumption times.

**Results**—We identified warfarin-associated intracranial hemorrhage in 234 patients (8.2%), of whom 177 patients (76%) survived the first week and had follow-up information available; the median follow-up time was 69 weeks (interquartile range [IQR] 19–144). Fifty-nine patients resumed warfarin after a median of 5.6 weeks (IQR 2.6–17). The hazard ratio for recurrent intracranial hemorrhage with resumption of warfarin was 5.6 (95% CI, 1.8–17.2), and for ischemic stroke it was 0.11 (95% CI, 0.014–0.89). The combined risk of recurrent intracranial hemorrhage or ischemic stroke reached a nadir if warfarin was resumed after approximately 10 to 30 weeks.

**Conclusion**—The optimal timing for resumption of warfarin therapy appears to be between 10 and 30 weeks after warfarin-related intracranial hemorrhage. *(Stroke. 2010;41:2860-2866.)*

**Key Words:** intracranial hemorrhage ■ anticoagulation ■ ischemic stroke ■ management
Table 3. Cox Proportional Hazards Model for Recurrent Intracranial Hemorrhage or for Ischemic Event at Different Time Intervals With and Without Resumption of Warfarin

<table>
<thead>
<tr>
<th>Warfarin Status</th>
<th>Risk of Intracranial Hemorrhage per Day</th>
<th>Risk of Ischemic Stroke per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed rate n (%)</td>
<td>7/3829 (0.18%)</td>
<td>1/2250 (0.044%)</td>
</tr>
<tr>
<td></td>
<td>2/265 (0.75%)</td>
<td>1/504 (0.20%)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>4.13</td>
<td>4.46</td>
</tr>
</tbody>
</table>

Rate used in prediction model*

|                  | 0.18% | 0.044% | 0.0090%† | 0.0012%† | 0.068% | 0.039% | 0.017% |
|                  | 1.02%‡ | 0.25%‡ | 0.049% | 0.0069% | 0.0075%§ | 0.0043%§ | 0.0018%§ |

*The Cox proportional hazard model provided a Warfarin Hazard Ratio for recurrent intracranial hemorrhage of 5.57 (95% CI, 1.80–17.25; \( P=0.0029 \)) and for ischemic stroke of 0.11 (95% CI, 0.0139–0.868; \( P=0.036 \)). The rates used in the prediction model were based on the following hazard ratios:

†Observed rate on warfarin/5.57.
‡Observed rate without warfarin \( \times 5.57 \).
§Observed rate without warfarin \( \times 0.11 \). The remaining proposed rates are those actually observed.
Table:

<table>
<thead>
<tr>
<th>Time of Resumption of OAC</th>
<th>Rate of recurrent ICH</th>
<th>Rate of TTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 2 weeks</td>
<td>36%</td>
<td>4%</td>
</tr>
<tr>
<td>Within 5 weeks</td>
<td>24%</td>
<td>5%</td>
</tr>
<tr>
<td>Within 10 weeks</td>
<td>19%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Figure 2. The “total” risk for a treatment horizon of 3 years of recurrent intracranial hemorrhage and of ischemic stroke according to the time point of resumption of anticoagulation.
Swedish nationwide observational study of 2619 patients w/ AF who survived their first-ever ICH during the period from 2005-2012
Cumulative incidence of IS, MI, systemic embolism, ICH, other fatal hemorrhagic event, or death of other cause within a 3-year follow-up period
When OAC was started within 8-12 weeks after ICH, the incidence of an event (18% vs. 27.5%; 95% CI 4.5-14.3)
Starting OAC before week 8 increased the incidence of severe bleeding (albeit non-significant)
AC reduces the total risk of an event both in low- and high-risk ICH patients w/ AF
The optimal timing of initiating AC is 8-12 weeks following ICH
- LAA closure
- Antiplatelet therapy
- NOACS/DOACS
**DOACS?**

Several trials are being planned.
24 patients with previous ICH underwent LAAO

Mean CHADS2 score = 3.2 ± 1.4

Mean follow-up = 11.9 ± 13.3 months

1 patient died (unrelated to device) and 1 patient had a TIA

No ischemic or hemorrhagic strokes occurred during follow-up

---

Compared outcomes of 147 patients w/ AF & ICH from Nordic countries who underwent LAAO from 2009-1015 to propensity score (HAS-BLED & CHA2DS2-VASc) matched group of 147 Danish patients receiving standard therapy (warfarin 20%; NOACs 23%; APL 37%)

LAAO group had lower risk of the composite endpoint, ischemic stroke, major bleeding, and all-cause mortality; HR 0.19 (95% CI 0.08-0.46); RRR 81%

RRR for ICH = 71%; IS = 65%; major bleeding 61%; and mortality 92%

Phase III (STROKECLOSE) is about to start in Nordic countries
My Thoughts

- In most AF patients with warfarin-associated lobar ICH & suspected CAA, the risk for warfarin-related ICH recurrence seems higher than thromboembolic events and, therefore would be best managed without resumption of warfarin therapy.

- In the subset of patients with lobar ICH at high baseline risk for ischemic stroke (e.g. CHADS2 ≥5), LAA closure (Watchman LAA occlusion device) is a viable option. If LAA is not feasible and OAC is considered, the use of DOACS (e.g. Apixaban) might be an alternative to warfarin.

- In most AF patients with warfarin-related non-lobar (deep) ICH, the risk of warfarin-related ICH recurrence seems equivalent to or lower than the risk of thromboembolic events. Therefore, they may receive net benefit from resumption of OAC. LAA closure or apixaban are reasonable alternatives to warfarin.

- In warfarin-related ICH patients with prosthetic valves, the risk of thromboembolic events is higher than the risk of recurrent ICH (regardless of ICH location). In these patients, resumption of OAC with warfarin is often required. Please note that DOACS are contraindicated in patients with prosthetic valves!

- The optimal time to resumption of anticoagulation after warfarin-related ICH is unclear and may vary from patient to patient. Avoidance of OAC for 4-8 weeks, in patients without mechanical heart valves, might decrease the risk of ICH recurrence.
Use of Statins

Number of prescriptions of statins is rapidly rising ~ by 500,000 a month!

Number of people taking atorvastatin alone increased from 25 to 56 million after the recent ACC/AHA 2013 lipid management guidelines!

“We found a bunch of these clogging your arteries. They’re cholesterol pills.”
Resumption of statins after ICH

- Should we?
- When?
- What agent?
- Under what circumstances?
  - Patient characteristics
  - ICH characteristics (location/etiology)

- No consensus
- No data from RCTs
- Various opinions based on a combination of observational data, small studies, pathophysiological considerations, and competing benefit/risk assessment
Balancing the risks…

- Increased risk of ICH recurrence
- Concern about increased risk of cognitive decline from accumulating microbleeds
- Decreased risk of MACCE
- Pleotropic effects leading to enhancement of recovery
o Overall incidence of ICH was 1.8%, BUT
  o ICH was significantly higher in the atorvastatin group vs. the placebo group (2.3% vs. 1.4%)
  o Relative risk of ICH on statin = 1.68 (95% CI: 1.09-2.59), compared with placebo
  o Statins treatment, increasing age, male sex, and having ICH as the qualifying stroke to be enrolled in the study were associated with increased risk for ICH

o 93 out of 4,731 (2%) of subjects enrolled in SPARCL had ICH as the index event (45 received atorvastatin and 48 placebo). These patients did not seem to benefit from atorvastatin:
  o Stroke or TIA occurred in 14.6% of placebo-treated patients vs. 24.4% of atorvastatin-treated patients
  o Major cardiovascular events occurred in 12.5% vs. 24.4%; and death in 10.4% vs. 15.6%

o The risk for ICH was independent of the effects of statin therapy cholesterol levels
• Statin use in survivors of lobar ICH increases the rate of ICH recurrence from 14% to 22% per year (relative risk increase of 1.57)

• This small increase in ICH risk was sufficient to offset any potential benefits for both primary and secondary cardiovascular prevention over a wide range of stipulated event rates

• In sensitivity analyses, avoiding statins remained the preferred option over a wide range of values for statins-associated relative risk for ICH, including the lower limit of the 95% CI of the relative risk for ICH reported in SPARCL, and stipulated MACCE rates
Statin Use and Microbleeds in Patients With Spontaneous Intracerebral Hemorrhage

Diono C. Haussen, MD; Nils Henninger, MD; Sandeep Kumar, MD; Magdy Selim, MD, PhD

Background and Purpose—Statin use has been associated with increased risk of intracerebral hemorrhage (ICH), particularly in elderly patients with previous ICH. Recurrent ICH in the elderly is often related to cerebral amyloid angiopathy. Therefore, we investigated whether statin use is associated with increased prevalence and severity of microbleeds (MB), particularly cortico-subcortical microbleeds (cMB), which are frequently observed in cerebral amyloid angiopathy.

Methods—We studied 165 consecutive patients with spontaneous ICH who underwent magnetic resonance imaging within 30 days of presentation. We retrieved clinical information and analyzed magnetic resonance imaging for the presence, location, and number of MB, which were divided into cMB or other (other MB). We performed group comparisons stratified by statin use and by the presence vs absence of any MB (cMB and/or other MB) or cMB alone.

Results—Sixty-four percent had prior ICH. Overall, 35% had microbleeds and 39% had cMB. Statin users were older, had significantly lower cholesterol and low-density lipoprotein levels, and higher prevalence of hypertension, diabetes, dyslipidemia, and antplatelet use. The prevalence and number of other MB were similar in statin-treated and statin-untreated individuals. However, more statin-treated patients had cMB (57% vs 33%; P=0.007), with almost twice as many lesions (46±11.3 vs 24±8.0, P=0.007) compared with untreated patients. Age and statin use were independently associated with both the presence and increased number of MB (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.00–1.05; P=0.01 and OR, 2.72; 95% CI, 1.02–7.22; P=0.04, respectively) and cMB (OR, 1.03; 95% CI, 1.00–1.06; P=0.01 and OR, 4.35; 95% CI, 1.54–11.20; P<0.01) in multivariate analyses.

Conclusions—Statin use in patients with ICH is independently associated with MB, especially cMB. Future studies are needed to confirm our findings and to investigate whether cMB can serve as a surrogate marker for ICH risk in statin-treated patients. (Stroke. 2012;43:2777-2781.)

Key Words: amyloid angiopathy ■ brain imaging ■ hemosiderin ■ intracerebral hemorrhage ■ intracranial hemorrhage ■ microbleed ■ statin

Table 4. Multivariate Logistic Regression Analysis for Presence of Cortico-Subcortical Microbleed

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.00–1.06</td>
<td>0.012*</td>
</tr>
<tr>
<td>Male</td>
<td>0.66</td>
<td>0.33–1.31</td>
<td>0.240</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.91</td>
<td>0.42–1.94</td>
<td>0.812</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.42</td>
<td>0.15–1.14</td>
<td>0.090</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.72</td>
<td>0.29–1.75</td>
<td>0.471</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.97</td>
<td>0.35–2.69</td>
<td>0.965</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>0.75</td>
<td>0.33–1.69</td>
<td>0.496</td>
</tr>
<tr>
<td>Statin use</td>
<td>4.15</td>
<td>1.54–11.20</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio.
Apolipoprotein E, Statins and Risk of Intracerebral Hemorrhage

Daniel Woo, MD, MS, Ranjan Deka, PhD, Guido J. Falcone, MD, MPH, Matthew L. Flaherty, MD, Mary Harverbusch, RN, BSN, Sharyl R. Martini, MD, PhD, Steven M. Greenberg, MD, PhD, Alison M. Ayres, BA, Laura Sauserbeck, RN, MS, Brett M. Kissel, MD, MS, Dawn Q. Kleindorfer, MD, Charles J. Moomaw, PhD, Christopher D. Anderson, MD, Joseph P. Broderick, MD, Jonathan Rosand, MD, MS, Carl D. Langeeld, PhD, and Jessica G. Woo, PhD, MHS.

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Center for Human Genetic Research, Division of Neurocritical Care and Emergency Neurology, Massachusetts General Hospital

Hemorrhagic Stroke Research Group, Massachusetts General Hospital

Program in Medical and Population Genetics, Broad Institute

Wake Forest University, Department of Biostatistical Sciences

Cincinnati Children’s Hospital Medical Center, Division of Biostatistics and Epidemiology

Abstract

Background and Purpose—Apolipoprotein E (ApoE) genotypes have been associated with lobar intracerebral hemorrhage (ICH). Although HMG-CoA reductase inhibitors (statins) have been associated with an increased risk of ICH, meta-analyses have not consistently shown a statin-induced risk of ICH. Here, we test whether hypercholesterolemia and ApoE polymorphisms affect the risk with statin use.

Methods—The Genetic and Environmental Risk Factors for Hemorrhagic Stroke study is a prospective, demographically-matched case-control study of ICH. A similar study of ICH, Genetic Risks for Medication-Related Hemorrhagic Stroke study, was used as a replication cohort. Subjects were classified as normocholesterolemia (NC), hypercholesterolemia without statin (HC-NS), and hypercholesterolemia with statin use (HC-S). Statistical comparisons were performed using Fisher’s Exact Test, chi-square tests, and the Breslow-Day test.

Results—The discovery cohort consisted of 558 ICH cases and 1,444 controls, and the replication cohort consisted of 1,030 cases and 882 controls. The association of lower risk for hypercholesterolemia was not attenuated by statin use. Statin use was observed to confer a higher risk for lobar ICH in those carriers ApoE2/E4 and ApoE2/E3 genotypes in both discovery and replication cohorts and combined, showed a trend towards significance (p=0.11 for Statin vs. ApoE4/E4).

Table 3. Risk of Lobar ICH by ApoE Carrier Status and Hypercholesterolemia vs No Hypercholesterolemia

<table>
<thead>
<tr>
<th></th>
<th>Discovery Sample</th>
<th>Replication Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case</td>
<td>Control</td>
</tr>
<tr>
<td>ApoE2 carriers vs E3/E3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normocholesterolia</td>
<td>33 (39%)</td>
<td>53 (24%)</td>
</tr>
<tr>
<td>Hypercholesterolia</td>
<td>28 (46%)</td>
<td>27 (18%)</td>
</tr>
<tr>
<td>ApoE4 carriers vs E3/E3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normocholesterolia</td>
<td>42 (45%)</td>
<td>73 (30%)</td>
</tr>
<tr>
<td>Hypercholesterolia</td>
<td>33 (50%)</td>
<td>73 (37%)</td>
</tr>
</tbody>
</table>

ApoE indicates apolipoprotein E; CI, confidence interval; ICH, intracerebral hemorrhage; and OR, odds ratio.
Compared 3492 consecutive patients having ICH with 3492 age and sex-matched stroke-free control subjects in a case-control analysis, as part of the Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy).

There was an interaction between total serum cholesterol levels and statin use for the risk of ICH (IOR, 1.09; 95% CI 1.05-1.12).

Increasing levels of total serum cholesterol were associated with a decreased risk of ICH within statin strata (OR, 0.87; 95% CI 0.86-0.88 for every increase of 0.26 mmol/l of total serum cholesterol concentrations), while statin use was associated with an increased risk (OR, 1.54; 95% CI 1.31-1.81 of the average level of total serum cholesterol).

The protective effect of serum cholesterol against ICH was reduced by statins in strictly lobar brain regions more than in non-lobar regions.

Meta-analysis of 7 RCTs involving 31099 subjects receiving high-dose statin and 31105 placebo-treated patients to assess the association between higher dose of various statins and risk of ICH among patients with CVD.

A significant risk of ICH was observed in subjects with higher dose of statin (RR 1.53; 95% CI: 1.16-2.01; P = 0.002).

There was no difference in all-cause mortality between the two groups (RR 0.95; 95% CI: 0.86-1.06; P = 0.36).
Statins might increase the propensity for ICH by inhibiting platelets, decreasing thrombus formation, and enhancing fibrinolysis.
• There is insufficient data to recommend restrictions on use of statin agents (Class IIb; Level of Evidence: C).

- Class IIb = Usefulness/efficacy is less well established by evidence or opinion
- Level of Evidence C = Consensus opinion of experts, case studies, or standard of care

AHA/ASA Guideline

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

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, the Congress of Neurological Surgeons, and the Neurocritical Care Society

J. Claude Hemphill III, MD, MAS, FAHA, Chair; Steven M. Greenberg, MD, PhD, Vice-Chair; Craig S. Anderson, MD, PhD; Kyra Becker, MD, FAHA; Bernard R. Bendok, MD, MS, FAHA; Mary Cushman, MD, MSc, FAHA; Gordon L. Fung, MD, MPH, PhD, FAHA; Joshua N. Goldstein, MD, PhD, FAHA; R. Loch Macdonald, MD, PhD, FRCS; Pamela H. Mitchell, RN, PhD, FAHA; Phillip A. Scott, MD, FAHA; Magdy H. Selim, MD, PhD; Daniel Woo, MD, MS; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology

Purpose—The aim of this guideline is to present current and comprehensive recommendations for the diagnosis and treatment of spontaneous intracerebral hemorrhage.

Methods—A formal literature search of PubMed was performed through the end of August 2013. The writing committee met by teleconference to discuss narrative text and recommendations. Recommendations follow the American Heart Association/American Stroke Association methods of classifying the level of certainty of the treatment effect and the class of evidence. Pre-release review of the draft guideline was performed by 6 expert peer reviewers and by the members of the Stroke Council Scientific Oversight Committee and Stroke Council Leadership Committee.

Results—Evidence-based guidelines are presented for the care of patients with acute intracerebral hemorrhage. Topics focused on diagnosis, management of coagulopathy and blood pressure, prevention and control of secondary brain injury and intracranial pressure, the role of surgery, outcome prediction, rehabilitation, secondary prevention, and future considerations. Results of new phase 3 trials were incorporated.

Conclusions—Intracerebral hemorrhage remains a serious condition for which early aggressive care is warranted. These guidelines provide a framework for goal-directed treatment of the patient with intracerebral hemorrhage. (Stroke. 2015;46:2022-2060. DOI: 10.1161/STR.0000000000000609.)

Key Words: AHA Scientific Statements • blood pressure • coagulopathy • diagnosis • intracerebral hemorrhage • intraventricular hemorrhage • surgery • treatment
My Thoughts..

- Avoid high dose statins
- Reserve for compelling indications, especially in patients with suspected CAA
- Minimize use with APLs!
- Avoid in those with recurrent lobar ICHs despite cessation of APLs and adequate BP control

Coming soon …
Thank You