ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Volume 1, Issue 13 | August 2015

Greetings from Dr. Qureshi, Principal Investigator for ATACH-II

Dear ATACH-II Colleagues:

Thanks to all of you for your continued support of the ATACH-II study. Even though spring and summer months are especially slow for enrollment, 2015 enrollment is better than last year. From March through August 2015 we enrolled 170 subjects compared to 123 subjects from the same period in 2014. We hope to reach our target enrollment of 1280 in the next 12 months. We are counting on your continued support and dedication to achieve this goal.

This newsletter includes a few recent discussion points. I have included a detailed summary of issues regarding the interpretation of the new American Stroke Association (ASA) guidelines for systolic blood pressure following Intracerebral Hemorrhage (ICH). Earlier, this document was sent out to all ATACH-II site investigators and staff. If you have any questions regarding the new guidelines or if you would like to discuss this further, please be in touch with our Clinical Coordinating Center.

We sincerely appreciate your cooperation and hard work for the recent data freeze. Thank you for submitting outstanding data and sending in images.

Hope you all are having a wonderful summer!

Warm regards,

Adnan I. Qureshi

Adnan I. Qureshi, M.D.

Inside this Issue...

- Interpretation of New ASA Guidelines
- 2015 ATACH-II Award Recipients
- Friendly Reminders & Recent Issues
- Recent DSMB Meetings
- ATACH-II Site Leaderboard
- ATACH-II Country Leaderboard
- Imaging Procedure
- Contact Information

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UNIVERSITY OF MINNESOTA

Summary of Issues Regarding the Interpretation of the New ASA Guidelines for Systolic Blood Pressure Following Intracerebral Hemorrhage: by Adnan I. Qureshi, M.D.

Re: Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH, Scott PA, Selim MH, Woo D; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology. Stroke. 2015 Jul;46(7):2032-60.

There has been a question regarding the interpretation of guidelines pertaining to acute blood pressure reduction in patients with intracerebral hemorrhage (ICH). The statements are provided below. It is important to note that both Class II a and Class II b recommendations explicitly are recommendations with emphasis on need for additional studies. The current guidelines do not use terms like "should," "is recommended" or "is indicated" to avoid providing the impression that the current evidence is complete and no further studies are required. Therefore, the current guidelines are really supportive of continuing to randomize eligible subjects in the Antihypertensive Treatment of Acute Cerebral Hemorrhage II trial. The guidelines are providing reasonable steps to undertake in patients who are not included in clinical trials.

For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe *(Class I; Level of Evidence A)* and can be effective for improving functional outcome *(Class IIa; Level of Evidence B)*. Class II recommendations are based on conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a treatment. Class IIa is defined by additional studies with focused objectives needed. It is reasonable to administer treatment. For ICH patients presenting with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring *(Class IIb; Level of Evidence C)*. Class II b is defined by additional studies with broad objectives needed. Treatment may be considered.

Following is the reference to an article that describes in detail issues relevant to interpretation of Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT II).

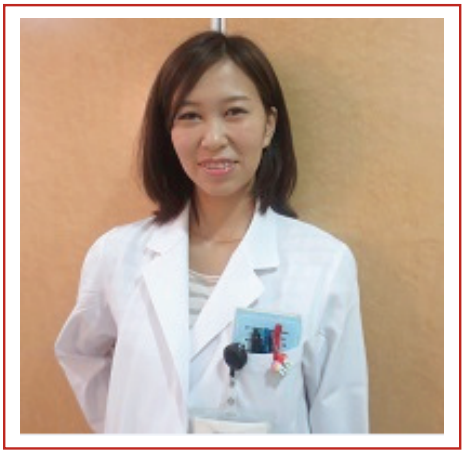
Qureshi AI[1], Palesch YY[1], Martin R[1], Toyoda K[1], Yamamoto H[1], Wang Y[1], Wang Y[1], Hsu CY[1], Yoon BW[1], Steiner T[1], Butcher K[1], Hanley DF[1], Suarez JI[1]. Interpretation and Implementation of Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT II). J Vasc Interv Neurol. 2014 Jun;7(2):34-40.

2015 ATACH-II Award Recipients from Japan

Ms. Sakina Yoshihira, Kobe City Medical Center General

Category: High Enrollment and Prompt Response for Case Report Form (CRF) Submission and Data Clarification Requests (DCR)

Sakina Yoshihira, Primary Study Coordinator



Do you have any comments or experience with the ATACH-II research that you would like to share with the readers?

I am sincerely honored to have been presented with this award. I must thank our site doctors for their guidance and Japan office for their backup during our studies. This is my third year as a CRC and I am honored to be part of this study from day one. Not only has this project taught me the importance of clinical research, but also improved myself as a healthcare professional. I hope to continue to contribute to ATACH-II for better health.

What is the best advice you've ever received?

Be confident, be humble

What is one of your favorite hobbies?

Volleyball, Classical ballet

Ms. Mihoko Matsukami, Toranomon Hospital

Category: High Enrollment and Prompt Response for CRF submission and DCR Response

Mihoko Matsukami, Primary Study Coordinator

Do you have any comments or experience with the ATACH-II research that you would like to share with the readers?

I feel very much honored that I was able to win such a big prize. I am most grateful to the all the staff members of the coordinating center in USA and Japan. This award is not mine alone. I appreciate the support of my study team members including doctors, nurses, and paramedics in Toranomon Hospital. I'll continue to do my best for ATACH-II trial.

What is the best advice you've ever received?

Taizen-jijyaku (Be imperturbable)

What is one of your favorite hobbies?

Cooking

Mr. Ryo Fujii, Nakamura Memorial Hospital

Category: Dedicated in Screening for Potential Candidates

Ryo Fujii, Primary Study Coordinator

Do you have any comments or experience with the ATACH-II research that you would like to share with the readers?
I am so honored to receive this award. While recording the screen failure log, I found that although the patients were enrolled only in the day time in our hospital, there are as many study candidates visited in off hours as in day time. This may be one of the factors to consider for us, but we will keep doing our best for enrolling candidates smoothly.

What is one of your favorite hobbies?
Reading books

2015 ATACH-II Award Recipients from Taiwan

National Taiwan University Hospital (NTUH) Stroke Team

Category: Highest Enrolling Site in Taiwan

"Principal Investigator Dr. Jeng, has the highest enrolling site in Taiwan. All stroke team members including the primary study coordinator, Yu-Ting, support ATACH2. Even though Dr. Tsai and Ms. Huang are not ATACH2 members, they inform the principal investigator, Co-Investigator or the PSC if they find any eligible subjects. This flexible communication is done under the leadership of Dr. Jeng and Yu-Ting which enables NTUH to be the highest enrolling site in Taiwan."

Jiann-Shing Jeng M.D., Ph.D. Principal Investigator

Yu-Ting Wang Primary Study Coordinator

National Taiwan University Hospital (NTUH) Stroke Team

NTUH Stroke Team

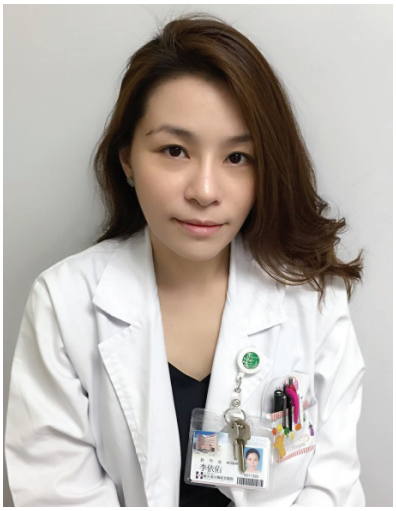
From Left: Yu-Ting Wang (Primary Study Coordinator), Sung-Chun Tang, M.D. (Co-Investigator), Jiann-Shing Jeng, M.D., Ph.D.(Principal Investigator), Ming-Ju Hsieh, M.D., LLD.(Co-Investigator), Li-Kai Tsai, M.D., Ph.D., Kuang-Yu Huang

Ms. I-Yu Lee, Shin-Kong Wu Ho-Su Memorial Hospital (SKMH)

Category: Prompt Data Entry and Response to Data Clarification Requests

"Under the leadership of the principal investigator, Dr. Lien, Ms. Lee is very diligent and responsible to correct data and respond to DCRs. Her performance is the top in all Taiwan sites."

Li-Ming Lien, M.D., Ph.D.
Principal Investigator



I-Yu Lee
Primary Study Coordinator

2015 ATACH-II Award Recipients from Germany

Dr. Azize Bostöm from the University of Bonn

Category: High Recruitment and Prompt Response

Azize Bostöm, M.D.
Primary Study Coordinator

"University of Bonn is a very good recruiting site and Dr. Bostöm is very responsive and always helpful etc. Dr. Bostöm is a neurosurgeon (consultant) and is the primary study coordinator."

Dear ATACH-II readers,

First of all, on behalf of my team-members, thanks to everybody for the nomination for our outstanding contribution. And many thanks to my colleagues and our chair Prof. Hartmut Vatter, for their support and encouragement. ATACH-II is a very well designed and organised study with so many kind people, giving us support in randomising patients for the study.

I remember a little anecdote in the past, when we were waiting in the ER for an ICH-patient who was being transferred from another hospital to us – a possible candidate for ATACH-II. It was one of our first cases and we were still excited that everything runs well in randomising and enrolling the patient. Therefore, we had prepared everything: informed consent form for the patient, lab tubes and so on. As well, we opened Web-DCU but right at that time no online randomisation was available! So, we searched for the emergency phone numbers in the US and finally we got a call back from Kathy. She gave us her private mobile phone number to avoid any additional delay and assured that she will be available for randomising at any time we think the patient meets the inclusion criteria. Finally and unfortunately, the patient did not meet the inclusion criteria (use of dabigatran), but now we have Kathy`s mobile number for the next time ☺.

When I am not in the hospital, my husband and both my kids are in the center of my life. We are doing excursions or gardening at home, which is my relaxation and inspiration.

Azize Boström, M.D.

Neurosurgeon of Bonn University hospital/Germany

2015 ATACH-II Award Recipients from China

Prof. Zhimin Wang, The First People's Hospital of Taizhou

Category: Prompt Data Entry and Response to Data Clarification Requests

Prof. Zhimin Wang
Principal Investigator

Dr. Zeyu Ding, Beijing Tiantan Hospital

Category: Highest Enrolling Site in China

Zeyu Ding, M.D.
Primary Study Coordinator

Friendly Reminders & Recent Issues: by Kathryn France, BA, RN, PHN, CCRC, CCRA

A. What do we do if our pharmacy reports a temperature excursion in the ATACH-II study Nicardipine storage area?

- The USP definition of *"Controlled room temperature"* indicates a temperature maintained thermostatically that encompasses the usual customary working environment of 20°C to 25° C (68° F to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15°C and 30° C (59°F and 86°F) that are experienced in pharmacies, hospitals, and warehouses. This is how nicardipine is to be stored.
  If a temperature excursion in the storage area occurs that could potentially bring nicardipine stability into question, please don't try to calculate the gravity of excursion yourself. Just have your pharmacist send an email with storage area temperature graphs attached, showing time from a few weeks before the excursion and then also a stable return to normal temperatures afterward to the atachstudydrug@gmail.com email address.
- Please include in your email whether hospital or other study supply is available for use, or whether enrollment is on hold until a decision is received.
- Remember that nicardipine also requires protection from light. Any nicardipine that has been dispensed (i.e., has had the outer packaging opened or has been outside of controlled storage) should be used within 24 hours.

B. Do the new AHA guidelines for ICH management affect enrollment in ATACH-II?

- After INTERACT-2 results were first released in May 2013, which is to the largest degree, what the new AHA guidelines are based on, ATACH-II experienced increased enrollment as people became more aware of how important the results of ATACH-II will be in providing answers about SBP management in ICH patients. Here are some key points to keep in mind about meeting challenges to enrollment:
  - The significant proportion of ICH patients who present with marked hypertension (SBP > 220 mmHg) are especially important to gather data about, as you can see from the way the new guidelines are worded. In general, enrollment of these subjects is uncomplicated. Please remember to titrate nicardipine per protocol (which also follows manufacturer's recommendations for nicardipine use) and use secondary agents as indicated. These subjects are especially vulnerable to having primary treatment failure (the failure to control SBP to the assigned range within 2 hours of randomization).
  - Subject candidates that arrive with SBP that is > 140 mmHg, but < 180 mmHg, who are treated very rapidly to lower SBP before it ever reaches >180 mmHg and meets ATACH-II eligibility criteria may now be ineligible for the trial. A small proportion of screen failures occur because of SBP never reaching 180 mmHg. This will stay the same, but any subjects who have not reached SBP > 180 mmHg upon arrival, but might do so later, are now less

likely to achieve eligibility if there are earlier orders for SBP to be lowered to < 140 mmHg. This is expected to be a low number of overall subject candidates in light of what seems to be typical ICH presentation.

- If initial orders are entered to lower SBP to < 140 mmHg based on the new recommendation, an otherwise eligible population who did not have SBP very much over 180 mmHg may be **more challenging** to enroll, as teams may need to work faster to achieve randomization. Towards this goal, some helpful strategies are as follows:
    - Build awareness for the trial among ED staff and early responders to calls for ICH and/or stroke, and whenever possible have people physically near or among ED staff trained as study team members who can ***consent*** and ***randomize***.
    - Keep posters, pocket cards, study contact information, and needed enrollment materials available in ED areas and make sure that study team members are being called as early as possible when potential candidates arrive.
    - Consider use of remote and emergency randomization where this may be necessary.
    - Use teamwork to best achieve rapid randomization and still be able to check inclusion/exclusion criteria adequately.
- Study team members are encouraged to be prepared to discuss the new guideline, the ongoing relevance of ATACH-II study results, and how hospital staff and study team members can work together to help complete enrollment in ATACH-II regardless of whether their standard of care will change with respect to the prescribed SBP range for ICH patients. Key information about SBP management in ICH is still missing and the results of the ATACH-II trial are eagerly anticipated. Please contact the University of Minnesota Clinical Coordinating Center if you are experiencing difficulty with this issue or if supporting references are sought.

Recent DSMB Meetings

The next DSMB meeting will be in September 14, 2015.

February 23, 2015
The DSMB found everything to be satisfactory and recommended that the study proceed as planned.

May 6, 2014
DSMB had no safety concerns and recommended that the study continue as planned.

November 1, 2013
The DSMB recommended to NINDS that Clevidipine not be allowed as an alternative to Nicardipine for the ATACH-II trial.

October 6, 2013
DSMB had no safety concerns and recommended the study continue.

April 22, 2013
DSMB reviewed the safety and overall progress of the trial: found everything to be satisfactory and recommended the study proceed as planned.

ATACH-II Site Leaderboard as of August 31, 2015

Rank	Site Name	Country	No.	Principal Investigator	Primary Study Coordinator
1	National Cerebral and Cardiovascular Center	Japan	78	Toyoda, Kazunori	Hirase, Kanae
2	Beijing Tiantan Hospital	China	72	Wang, Yongjun	Ding, Zeyu
3	Kobe City Medical Center General Hospital	Japan	52	Sakai, Nobuyuki	Okitsu, Miyuki
4	Toranomon Hospital	Japan	38	Hara, Takayuki	Matsukami, Mihoko
5	National Taiwan University Hospital	Taiwan	34	Jeng, Jiann-Shing	Wang, Yu-Ting
6	The First People's Hospital of Taizhou	China	34	Wang, Zhimin	Chen, Jie
7	Columbia University	USA	27	Agarwal, Sachin	Falo, Cristina
8	St. Cloud Hospital	USA	26	Suri, M. Fareed K	Freese, Melissa
9	Abington Memorial Hospital	USA	23	Shah, Qaisar	Jonczak, Karin
10	Kaohsiung Veterans General Hospital	Taiwan	18	Lin, Ching-Huang	Hsu, Yi-Ting
10	New Jersey Neuroscience Institute, JFK Medical Center	USA	18	Kirmani, Jawad	Porbeni, Charles
	Total as of 8-31-15 = 984				

ATACH-II Country Leaderboard as of August 31, 2015

Rank	Country	Enrollments	Sites Released to Enroll
1	United States	419	67
2	Japan	282	12
3	China	134	4
4	Taiwan	92	7
5	Germany	41	8
6	South Korea	16	2

Imaging Procedure

Dear Readers:

Thank you for your cooperation and promptness in sending the images before the data freeze last month. Based on some of the issues I have found with the recent images, following are my friendly reminders:

- Remember to send both baseline and the 24 hour CT scans for ATACH-II
- Additional CTs, CTAs and MRIs are collected for SCORE-IT and these are optional, however; we really appreciate it if you also send these with the ATACH-II images
- All images must be de-identified of information pertaining to the research subject such as name, address, date of birth etc.
- Each CD should contain a label or you can directly write on the CD the following:
    - Subject number
    - Enrollment date
    - Site number and name
    - Image tracking number
- If the 24 hour CT scan was not done within the required time window, submit the CT scan performed closest in time to 24 hours as the 24-hour scan and enter "24 hours" in column D of the imaging CRF and please provide an explanation as to why the image was not obtained within the required time window.
- Put all CDs in one FedEx express envelope after the subject has reached Day 7/Discharge. Please include a copy of the completed imaging CRF from WebDCU with the CDs. Enter image shipping date on the imaging CRF in WebDCU.
- Images have to be in **DICOM** format for our software to be able to read them.

Please send all ATACH-II images to:

Attention: **ATACH-II Research**
Dinnaken Office Building
925 Delaware Street SE, Suite 300
Minneapolis, MN 55414, USA

Sincerely,
Rauf Afzal

The Current Contact Information for ATACH-II

Don't hesitate to reach out to us - we are here to help you!

Need help with an enrollment or other ATACH-II emergency?

Call the Toll Free Hotline at: 1-855-870-7205 *or* 952-225-0779
The hotline service will ensure that you are connected with a core team member who is available to help you immediately.

General Questions? Contact Kathy France at 612-625-6974 or kafrance@umn.edu

Contract or Reimbursement Questions? Contact Norrita Rech at 612-626-1866 or rech@umn.edu

WebDCU Questions? Contact Kristina Hill at 843-792-1453 or hilkri@musc.edu

NETT CCC Questions? Contact 734-232-2142 **or** ATACHII-TRIAL@UMICH.EDU

Study Drug Questions? Please email your questions or requests for additional study drug to atachstudydrug@gmail.com

Project Management Questions? Contact Jessy Thomas at 612-624-2431 or thoma098@musc.edu

Regulatory Questions for International sites? Contact Kristen Clasen: clasen@musc.edu

To randomize: http://dcu.musc.edu/ctms/

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Funded by NIH through grants U01NS062091 and R01NS061861; The content is solely the responsibility of the authors and does not necessarily represent the official views of NINDS or NIH.