ON-LINE APPENDIX

Panel Members (in Alphabetical Order)

Felipe Albuquerque, MD

Department of Neurosurgery

Barrow Neurological Institute

Phoenix, Arizona

Adam Arthur, MD

Department of Neurosurgery

Semmes-Murphey Clinic/University of Tennessee

Memphis, Tennessee

Patrick Brouwer, MD

Department of Interventional Neuroradiology

Karolinksa Hospital

Stockholm, Sweden

University NeuroVascular Center

Leiden University Medical Center

Haaglanden Medical Center

Leiden, the Netherlands

Franziska Dorn, MD

Department of Neuroradiology

University Hospital Bonn, Bonn, Germany

Jens Fiehler, MD

Department of Diagnostic and Interventional Neuroradiology

University Medical Center Hamburg-Eppendorf

Hamburg, Germany

Justin Fraser, MD

Departments of Neurosurgery, Neurology, Radiology, and

Neuroscience

University of Kentucky

Lexington, Kentucky

Mahesh Jayaraman, MD

Departments of Diagnostic Imaging, Neurology, and

Neurosurgery

Warren Alpert School of Medicine at Brown University

Rhode Island Hospital

Providence, Rhode Island

Mary E. Jensen, MD

Departments of Neurologic Surgery, Radiology, and Medical

Imaging

University of Virginia Health

Charlottesville, Virginia

David Kallmes, MD

Department of Radiology

Mayo Clinic

Rochester, Minnesota

Jianmin Liu, MD

Department of Neurosurgery

Changhai Hospital Naval Medical University

Shanghai, China

Charles Majoie, MD

Department of Radiology

Academic Medical Center

Amsterdam, the Netherlands

Raul Nogueira, MD

Department of Neurology

Emory University School of Medicine

Atlanta, Georgia

Kirill Orlov, MD

Meshalkin Novosibirsk Research Institute of Circulation

Pathology

Novosibirsk, Russian Federation

Nobuyuki Sakai, MD

Department of Neurosurgery

Kobe City Medical Center General Hospital

Hyogo, Japan

Allan Taylor, MD

Groote Schuur Hospital

University of Cape Town

Cape Town, South Africa

Additional Experts

René Chapot, MD

Department of Neuroradiology

Alfred Krupp Krankenhaus Essen

Essen, Germany

Lucie Thibault, PharmD

Member of the Scientific Committee World Federation of

Interventional and Therapeutic Neuroradiology

Consensus Definition

Consensus was predefined as an agreement of 70% for a particular answer option in case of dichotomous questions and 50% for questions with \geq 2 answer options. If consensus for a particular question was not achieved, this question was included in the next survey round. Each question was asked a maximum of 2 times.

Literature Search. Our MEDLINE literature search showed that the number of publications focusing on stent-assisted coiling/ flow diversion for ruptured intracranial aneurysms increased substantially from 2006 to 2019 (On-line Fig 1). However, literature on antiplatelet management for these cases was mostly limited to small retrospective studies. ¹⁻⁷

REFERENCES

- Li C, Li Y. Stent-assisted coiling of ruptured wide-necked intracranial aneurysms. Interv Neuroradiol 2013;19:283–88 CrossRef Medline
- Yang P, Zhao K, Zhou Y, et al. Stent-assisted coil placement for the treatm ent of 211 acutely ruptured wide-necked intracranial aneurysms: a single-center 11-year experience. Radiology 2015;276: 545–52 CrossRef Medline
- Liu P, Lv X, Li Y, et al. Stent-assisted coiling of ruptured widenecked intracranial aneurysms: A single-center experience of 218 consecutive patients. Neurol India 2016;64(Suppl):S70-77 CrossRef Medline
- Madaelil TP, Moran CJ, Cross DT, et al. Flow diversion in ruptured intracranial aneurysms: a meta-analysis. AJNR Am J Neuroradiol 2017;38:590–95 CrossRef Medline
- Bhogal P, Henkes E, Schob S, et al. The use of flow diverters to treat small (</=5 mm) ruptured, saccular aneurysms. Surg Neurol Int 2018;9:216 CrossRef Medline
- 6. Zuo Q, Yang P, Lv N, et al. Safety of coiling with stent placement for the treatment of ruptured wide-necked intracranial aneurysms: a contemporary cohort study in a high-volume center after

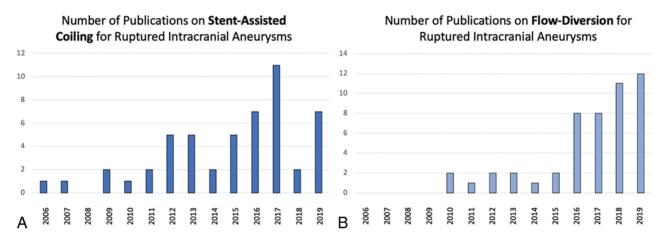
- **improvement of skills and strategy**. *J Neurosurg* 2019;131:435–41 CrossRef Medline
- Howard BM, Frerich JM, Madaelil TP, et al. "Plug and pipe" strategy for treatment of ruptured intracranial aneurysms. J Neurointerv Surg 2019;11:43–48 CrossRef Medline
- 8. Kim KS, Fraser JF, Grupke S, et al. Management of antiplatelet therapy in patients undergoing neuroendovascular procedures. *J Neurosurg* 2018;129:890–905 CrossRef Medline
- Pandya DJ, Fitzsimmons BF, Wolfe TJ, et al. Measurement of antiplatelet inhibition during neurointerventional procedures: the effect of antithrombotic duration and loading dose. J Neuroimaging 2010;20:64-69 CrossRef Medline
- 10. Choi HH, Cho YD, Han MH, et al. **Antiplatelet premedication-free stent-assisted coil embolization in acutely ruptured aneurysms**. *World Neurosurg* 2018;114:e1152–60 CrossRef Medline
- 11. Dumont TM, Kan P, Snyder KV, et al. Adjunctive use of eptifibatide for complication management during elective

- **neuroendovascular procedures**. *J Neurointerv Surg* 2013;5:226–30 CrossRef Medline
- Samaniego EA, Gibson E, Nakagawa D, et al. Safety of tirofiban and dual antiplatelet therapy in treating intracranial aneurysms. Stroke Vasc Neurol 2019;4:36–42 CrossRef Medline
- 13. Kang HS, Kwon BJ, Roh HG, et al. Intra-arterial tirofiban infusion for thromboembolism during endovascular treatment of intracranial aneurysms. *Neurosurgery* 2008;63:230–37; discussion 237–38 CrossRef Medline
- 14. Kim S, Choi JH, Kang M, et al. Safety and efficacy of intravenous tirofiban as antiplatelet premedication for stent-assisted coiling in acutely ruptured intracranial aneurysms. AJNR Am J Neuroradiol 2016;37:508–14 CrossRef Medline
- 15. Brinjikji W, Morales-Valero SF, Murad MH, et al. Rescue treatment of thromboembolic complications during endovascular treatment of cerebral aneurysms: a meta-analysis. AJNR Am J Neuroradiol 2015;36:121–25 CrossRef Medline

On-line Table: Key publications that were identified during the literature search and used as a basis for panel consensus on antiplatelet agents and dosage

Author, Year	Publication Type	Number of Patients	Focus
Kim et al, 2018 ⁸	Review	-	Pharmacokinetics and drug-drug interactions of common antiplatelet agents
Pandya et al, 2010 ⁹	Retrospective cohort study	216	Effect of antiplatelet regimen on platelet function testing results
Choi et al, 2018 ¹⁰	Retrospective cohort study	449	Safety of antiplatelet-premedication-free stent-assisted coiling in acutely ruptured intracranial aneurysms
Dumont et al, 2013 ¹¹	Case series	12	Safety and efficacy of eptifibatide in case of thromboembolic complications during elective neurovascular procedures
Samaniego et al, 2019 ¹²	Retrospective cohort study	141	Safety and efficacy of tirofiban and dual antiplatelet therapy for acute and elective endovascular treatment of intracranial aneurysms
Kang et al, 2008 ¹³	Retrospective cohort study	24	Safety and efficacy of tirofiban in case of thromboembolic complications during acute and elective endovascular treatment of intracranial aneurysms
Kim et al, 2016 ¹⁴	Retrospective cohort study	40	Safety and efficacy of intravenous tirofiban for stent-assisted coiling in ruptured intracranial aneurysms
Brinjikji et al, 2015 ¹⁵	Meta-analysis	516	Rescue treatment strategies for thromboembolic complications during acute and elective endovascular treatment of cerebral aneurysms

Note:— – indicates not applicable (review paper).



ON-LINE FIG 1. Number of publications on stent-assisted coiling (A) and flow diversion (B) for ruptured intracranial aneurysms for 2006–2019 (MEDLINE search).

Whether the patient has an external ventricular drain

Risk for hemorrhage in case further procedures/ surgery is required

Cluster: Intraventricular drain etc Balancing therapeutic anti-platelet activity against risk of ICH/EVD-track hemorrhage

Ventriculostomy management Allowing for safe placement of external ventricular drains or shunts when necessary.

Need for gastrostomy or tracheostomy

Is there a role for platelet aggregation studies post administration of oral anti platelet medication

Cluster: Platelet function testing

Monitoring degree of platelet inhibition

Inability (due to emergent nature) to use VerifyNow to confirm response to clopidogrel

Whether to start single or dual anti-platelet therapy

Cluster: SAPT vs. DAPT

I think I addressed two issues in Problem no 2--classification of drug used, number of drugs needed (SAPT vs DAPT) Problem #3 would be method of application (oral vs parenteral vs per-rectum)

The exact duration of time that dual anti platelets are needed to prevent acute stent thrombosis is unknown. Perhaps only a short course (<5d) of dual anti platelets is needed and then patients can transition to aspirin alone?

ON-LINE FIG 2. Affinity diagram (round 1). EVD indicates external ventricular drain; ICH, intracerebral hemorrhage; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; FD, flow diverter; PO, per os; NG, nasogastric; IM, intramuscular; ASA, acetylsalicylic acid; 5d, 5 days; AP, antiplatelet; per peg, percutaneous endoscopic gastrostomy; SQ, subcutaneous.

optimal dosage

Is it safe to use a loading dose of antiplatelets drugs before surgery? Cluster: Dosage Is the same duration and intensity of dual antiplatelet needed for aneurysm neck bridging stents (Enterprise, Neuroform Atlas) as for a flow diverter?

What drugs in what doses for planned cases?

The safety of IIb/IIIa antagonist (tirofiban is only available in China) using and the specific dosage

regimen of antithrombotic medicine, which? how much?

How to deal with patient with SAH and stents and/or FDs (Gp IIb/IIIa)?

What agent to take in order to avoid resistance or interaction with other drugs.

The comparison between Clopidogrel and Ticagrelor

There is only one anti platelet which can be administered Per Rectum in the US - Aspirin. Availability of additional agents with a method of delivery other than IV or PO/NG would be helpful. ? IM/SQ injection?

regimen of anti-thrombotic medicine, which? how much?

I think I addressed two issues in Problem no 2--classification of drug used, number of drugs needed (SAPT vs DAPT) Problem #3 would be method of application (oral vs parenteral vs per-rectum) Cluster: Choice of drugs

The second problem is which medication(s) to use? Do you just give one to start and add a second later? Should it be a medication that can be measured, such as ASA or P2Y12 inhibitors? Should a drug be used that is known to work on everyone, e.g. Brilinta vs Plavix. Should the drug used be reversible, e.g. Reopro vs Integrilin?

ON-LINE FIG 2. Continued.

Is the same duration and intensity of dual anti-platelet needed for aneurysm neck bridging stents (Enterprise, Neuroform Atlas) as for a flow diverter?

The overlapping time of IIb/IIIa antagonist and dual-antiplatelet medication, and the proper sequence of administration

Cluster: Timing/Duration of antiplatelet therapy

When using IIbIIIa inhibitors what is the optimal time to administer the loading dose.

When to stop double antiaggregation?

when we need to give antithrombotic medicine, just before/several hours (need

to wait procedure)/1-2 days (need to wait procedure)

The exact duration of time that dual anti platelets are needed to prevent acute stent thrombosis is unknown. Perhaps only a short course (<5d) of dual anti platelets is needed and then patients can transition to aspirin alone?

There is no good literature on the timing of anti-platelet administration. I think we all agree if a flow diverter or stent is placed in a patient with SAH, the patient needs AP protection. But when is it given? prior to placement, after placement during the procedure, after the procedure. Actually, does it have to be anti-platelet agents? Could it be just full heparinization to start with transition to AP agents? The questions we are answering are also applicable to placement of a stent in an acute stroke patient who is undergoing thrombectomy. It would be great if we could answer the question for both groups of patients. In the stroke scenario we would also have to address patients who have received tPA vs those who have not.

When using IIbIIIa inhibitors for how long should the maintenance infusion be continued after administration of oral anti platelet medication

> Delayed or incomplete aneurysm protection

Cluster: Insufficient aneurysm protection

Potential limitation for further treatment in case of incomplete/ late occlusion of the ruptured aneurysm

Patients that already use coumadin, noax or have coagulation disorders will pose a problem in deciding where to go next.

Cluster: Pre existing medication

if patient already received anticoagulant (DOAC, Warfarin), how regimen need to change or no need

Co-administration with anticoagulants

> What is the patient's history pertaining to medications

ON-LINE FIG 2. Continued.

Cluster: Application form

Insufficient resorption if administered over gastric tube

There is only one anti platelet which can be administered Per Rectum in the US - Aspirin. Availability of additional agents with a method of delivery other than IV or PO/NG would be helpful. ? IM/SQ injection?

Intra-arterial local anti-platelet versus oral/per peg/per rectum administration in acute setting

I think I addressed two issues in Problem no 2--classification of drug used, number of drugs needed (SAPT vs DAPT) Problem #3 would be method of application (oral vs parenteral vs per-rectum)

Minimizing the chance of thromboembolic problems while also protecting against rebleeding.

Cluster:

Thrombotic and hemorrhagic complications/other adverse events

increased rebleed risk

how the stent with antiplatelets and cerebral vasospasm interact in acute period of SAH?

occlusion

If you want to use the more reliable drugs you are often forced to give them twice daily which means that the compliance may suffer in certain groups of patients or in case of eg.vomiting.

Ensuring homogenous responses when some medications do not create the same effect in all

patients.

Can we use flow diverters in the acute period of SAH?

Cluster: Miscellaneous

Rapid reversal of anti platelet effect

ON-LINE FIG 2. Continued.