A DELPHI consensus statement on antiplatelet management for intracranial stenting due to underlying atherosclerosis in the setting of mechanical thrombectomy

Goyal, M.; Orlov, K.; Jensen, M.E.; Taylor, A.; Majoie, C.; Jayaraman, M.; ... ; Ospel, J.M.

Neuroradiology (2021) 63:627–632
https://doi.org/10.1007/s00234-020-02556-z

INTERVENTIONAL NEURORADIOLOGY

A DELPHI consensus statement on antiplatelet management for intracranial stenting due to underlying atherosclerosis in the setting of mechanical thrombectomy

Mayank Goyal[1] · Kirill Orlov[2] · Mary E. Jensen[3] · Allan Taylor[4] · Charles Majoie[5] · Mahesh Jayaraman[6] · Jianmin Liu[7] · Geneviève Milot[8] · Patrick Brouwer[9,10] · Shinichi Yoshimura[11] · Felipe Albuquerque[12] · Adam Arthur[13] · David Kallmes[14] · Nobuyuki Sakai[15] · Justin F. Fraser[16] · Raul Nogueira[17] · Pengfei Yang[7] · Franziska Dorn[18] · Lucie Thibault[19] · Jens Fiehler[20] · René Chapot[21] · Johanna Maria Ospel[22,23]

Received: 23 June 2020 / Accepted: 10 September 2020 / Published online: 24 September 2020

Abstract

Purpose There is little data and lack of consensus regarding antiplatelet management for intracranial stenting due to underlying intracranial atherosclerosis in the setting of endovascular treatment (EVT). In this DELPHI study, we aimed to assess whether consensus on antiplatelet management in this situation among experienced experts can be achieved, and what this consensus would be.

Methods We used a modified DELPHI approach to address unanswered questions in antiplatelet management for intracranial stenting due to underlying atherosclerosis in the setting of EVT. An expert-panel (19 neurointerventionalists from 8 countries) answered structured, anonymized on-line questionnaires with iterative feedback-loops. Panel-consensus was defined as agreement ≥ 70% for binary closed-ended questions/≥ 50% for closed-ended questions with > 2 response options.

Results Panel members answered a total of 5 survey rounds. They acknowledged that there is insufficient data for evidence-based recommendations in many aspects of antiplatelet management for intracranial stenting due to underlying atherosclerosis in the setting of EVT. They believed that antiplatelet management should follow a standardized regimen, irrespective of imaging findings and reperfusion quality. There was no consensus on the timing of antiplatelet-therapy initiation. Aspirin was the preferred antiplatelet agent for the peri-procedural period, and oral Aspirin in combination with a P2Y12 inhibitor was the favored postprocedural regimen.

Conclusion Data on antiplatelet management for intracranial stenting due to underlying atherosclerosis in the setting of EVT are limited. Panel-members in this study achieved consensus on postprocedural antiplatelet management but did not agree upon a preprocedural and intraprocedural antiplatelet regimen. Further prospective studies to optimize antiplatelet regimens are needed.

Keywords Ischemic stroke · Intracranial atherosclerosis · Angiography · Intracranial stenting

Introduction

There are no large prospective studies on the effect of different antiplatelet regimens on clinical outcomes and complications in patients who undergo endovascular treatment (EVT) and simultaneous intracranial stenting for underlying atherosclerosis. Possible reasons for this are the low prevalence of the condition in regions other than Asia, and the lack of standardization in management protocols across different institutions and even within hospitals. As a result, neurointerventionalists who have decide whether to place an intracranial stent or not in an EVT patient with underlying atherosclerosis face many unknowns. This carries the risk of increased variability in antiplatelet regimens used, some of which might be associated with a high risk of thromboembolic or hemorrhagic complications. Some physicians might even refrain from intracranial stenting because of the prevailing uncertainty with regard to

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00234-020-02556-z) contains supplementary material, which is available to authorized users.

✉ Mayank Goyal
mgoyal@ucalgary.ca

Extended author information available on the last page of the article

peri-procedural antiplatelet management. The situation is not expected to change in the near future, because intracranial atherosclerosis is rare, which makes conducting informative studies on the topic very difficult.

The DELPHI method has its roots in the 1940s, when it was developed to forecast advancements in warfare technology [1]. It relies on a panel of highly informed individuals ("experts") who anonymously answer iteratively structured questionnaires to make consensus-based forecasts in areas in which sufficient evidence is not sufficient to develop data-driven predictions, and when high-level evidence is unlikely to become available in the near future. In medical research, the DELPHI method has been frequently used, for example to develop guidelines for the diagnosis and management of multiple sclerosis (MAGNIMS consensus guidelines [2]).

In this study, we used a modified DELPHI approach to assess whether consensus on antiplatelet management for intracranial stenting due to underlying atherosclerosis in the setting of EVT can be achieved among a panel of experienced experts, and what this consensus would be.

Methods

In this DELPHI study, 19 neurointerventionalists with longstanding expertise in EVT and an additional pharmacology expert were chosen as experts and asked to answer questions regarding preprocedural, intraprocedural, and postprocedural antiplatelet management strategies in the setting of EVT with simultaneous intracranial stenting due to underlying atherosclerosis. The panel members were chosen based on personal and institutional academic collaborations. We aimed to represent as broad a range of geographic regions as possible, keeping in mind that the expert panel group size had to be kept limited, since chances of achieving consensus decrease rapidly with increasing group sizes. Special emphasis was put on including experts from Asia because of the relatively higher prevalence of intracranial atherosclerosis in Asian countries. We did not require a minimum volume of cases/intracranial stenting procedures for experts to participate in this study because a high caseload of intracranial stenting procedures may not necessarily be indicative of the level of experience, especially with regard to antiplatelet management (a high-volume operator strictly following his/her institutional antiplatelet regimen for example is likely to have only limited knowledge on the mechanisms of action of different antiplatelet agents). In order to ensure high content expertise with regard to drug mechanisms of action, a pharmacological expert was included in the panel group, who provided input with regard to the pharmacokinetics and pharmacodynamics of different antiplatelet agents, but did not participate in the actual DELPHI process. For a list of the panel members, and detailed description and flowchart of the DELPHI method as it was used in this study, see Fig. 1 and suppl. material. Panel consensus was defined as agreement ≥ 70% for binary closed-ended questions/≥ 50% for closed-ended questions with > 2 response options. For this type of study, approval from an ethics board is not required since no patient data were used.

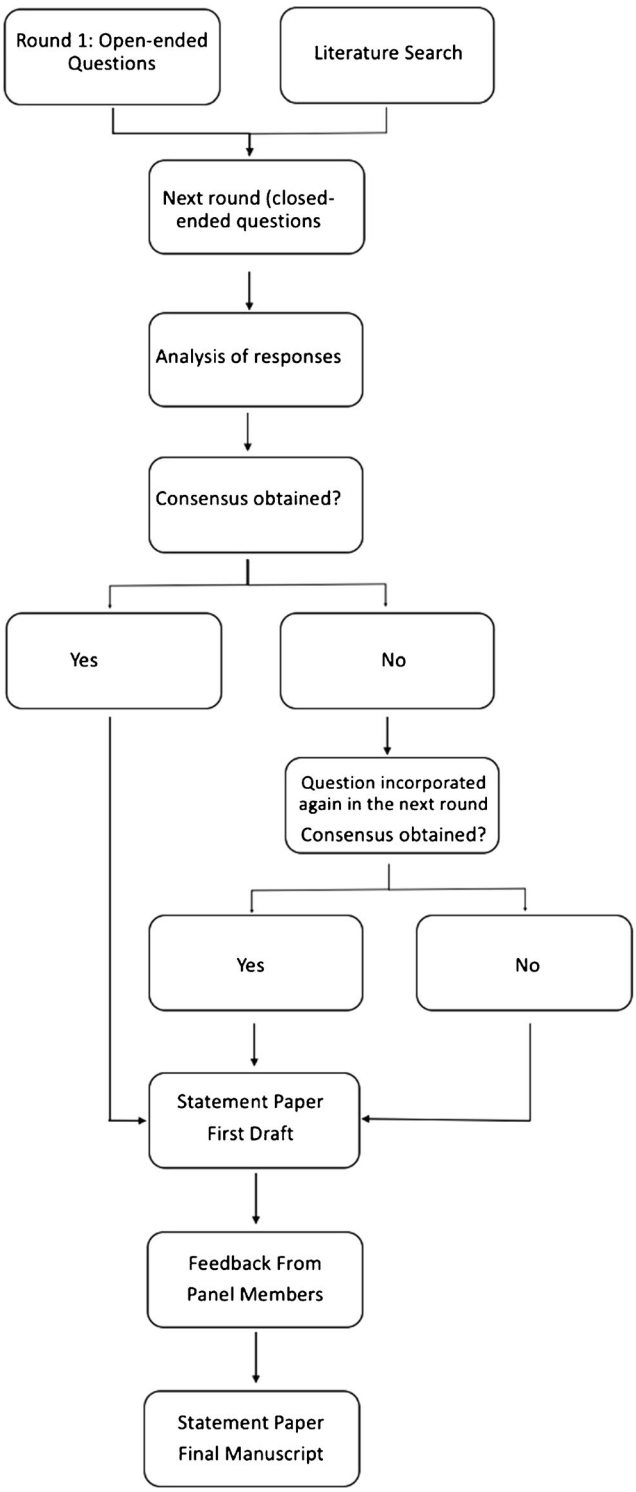

Fig 1 DELPHI methodology as it was used in this manuscript

All participants gave their consent prior to answering the survey questions.

Results

Panel consensus

All 19 invited experts agreed to participate in the study, and there were no drop-outs during the course of the study. The 19 panel members in this study achieved consensus that the antiplatelet management for intracranial stenting due to intracranial atherosclerosis in the setting of EVT should be standardized, i.e., the regimen should not be changed based on Alberta Stroke Program Early CT Score (ASPECTS)/ischemic "core" on CT/MR perfusion, final reperfusion result (expanded Treatment in Cerebral Infarction (TICI) score), or treatment with intravenous alteplase. They also believed that Heparin, other than small doses in the infusion, might not be necessary. The panel did not achieve consensus on whether antiplatelet management should be initiated prior to the procedure if the neurointereventionalist perceives the likelihood of an intracranial stent being needed to be high. Confronted with the lack of consensus, the investigators took a pragmatic approach and decided to address both options in the following rounds, i.e., experts were asked about their opinion regarding antiplatelet regimen in two distinct scenarios: (1) antiplatelet therapy is initiated prior to the procedure, and (2) antiplatelet therapy is initiated during the procedure. The panel agreed that, if an operator perceives the likelihood of an intracranial stent being placed so high that she/he decides to initiate antiplatelet therapy prior to the procedure, Aspirin (preferred route of administration if available: Intravenous application of 500 mg should be the first choice, with rectal Aspirin as a second choice [3] . If antiplatelet therapy is initiated during the procedure (rather than before), the panel consensus was to proceed with intravenous Aspirin (500 mg bolus), or if intravenous Aspirin is not available, a GPIIbIIIa inhibitor as a single antiplatelet agent (either Tirofiban, Eptifibatide, or Abciximab loading dose followed by a maintenance dose over 12–24 h if necessary, see suppl. Table I for dose suggestions). Panel members agreed that the intravenous antiplatelet regimen can be converted to a dual oral regimen within 24 h, whereby Aspirin (70–100 mg) and a P2Y12 inhibitor (either Clopidogrel, Prasugrel, or Ticagrelor, see suppl. Table II for dose suggestions) was the combination choice. Table 1 summarizes the DELPHI consensus results.

Unanswered questions

There was no consensus on whether antiplatelet management should be initiated prior to the procedure. If an operator chooses to do so, the panel achieved consensus on Aspirin as the first-line preprocedural agent (see previous paragraph), but there was no consensus whether a second antiplatelet agent should be administered intraprocedurally in such cases and what this agent would be. Panel members also disagreed on whether platelet function testing should be used to guide postprocedural antiplatelet therapy. Table 2 summarizes unanswered questions, i.e., aspects of antiplatelet management for which no consensus could be achieved in this study.

Table 1 DELPHI consensus recommendations on antiplatelet management for intracranial stenting due to underlying atherosclerosis in the setting of EVT

Intraprocedural antiplatelet management
Standard antiplatelet regimen irrespective of baseline imaging findings, reperfusion result, thrombolytics
Intraprocedural Heparin (other than small doses in the infusion) might not be necessary
Scenario 1: Antiplatelet therapy initiated **prior** to the procedure
Preprocedural first-line agent of choice: intravenous, rectal, or oral Aspirin*
Scenario 2: Antiplatelet therapy initiated **during** the procedure
Intraprocedural single first-line agent of choice: intravenous Aspirin, alternative agent: GPIIbIIIa inhibitor**
Postprocedural antiplatelet management
Postprocedural regimen: oral Aspirin (70–100 mg) plus oral P2Y12 inhibitor+

DELPHI consensus recommendations are statements for which consensus (defined as at least 70% of respondents favoring one answer option in binary closed-ended questions/at least 50% of respondents favoring one answer option in closed-ended questions with > 2 response options) was achieved either the first or second time the question was asked. Questions were asked a maximum number of two times

*Intravenous or rectal Aspirin preferred

**See supp. Table I for dosage suggestions

+ See supp. Table II for dosage suggestions

Table 2 Unanswered questions in antiplatelet management for intracranial stenting due to underlying atherosclerosis in the setting of EVT (aspects on which consensus could not be achieved in this study)

Intraprocedural antiplatelet management
Should antiplatelet therapy be initiated prior to the procedure if the perceived likelihood of an intracranial stent being needed is high?
Should a second antiplatelet agent be given during the procedure and what should this agent be if antiplatelet therapy is initiated prior to the procedure (scenario 1)?
Which GPIIbIIIa inhibitor should be chosen as an alternative if antiplatelet therapy is initiated during the procedure (scenario 2)?
Postprocedural antiplatelet management
Which P2Y12 inhibitor should be chosen in the postprocedural period?
Should platelet function testing guides the postprocedural antiplatelet regimen?

Discussion

This DELPHI study shows that there is a wide variety of opinions regarding antiplatelet management regimens for intracranial stenting due to underlying atherosclerosis in the setting of EVT, most likely because too few data are available to allow for data-driven antiplatelet management decisions. The high variability in reported antiplatelet management strategies in the literature makes evidence-based recommendations hard, if not impossible. Commonly reported regimens range from intravenous GPIIbIIIa inhibition to oral Aspirin and Clopidogrel, and the timing of antiplatelet agent administration is not standardized and varies between studies [4–7]. As a result, the DELPHI panel did not reach to a consensus in several questions that were addressed in the survey: while there was consensus on postprocedural antiplatelet management, panel members could not agree on a particular preprocedural and intraprocedural antiplatelet regimen.

They did agree that antiplatelet therapy should follow a standard approach, irrespective of ASPECTS/ischemic "core" on CT/MR perfusion, final reperfusion result, and treatment with intravenous alteplase. This is a somewhat surprising and controversial result, since the above-mentioned factors are all known to influence the risk of hemorrhage, and it may seem intuitively logical to alter the antiplatelet regimen to account for these risk differences. One possible explanation for this result could be that by not taking these factors into account, one could simplify and standardize antiplatelet regimens, and thereby reduce variability and confusion that often comes along with it, which might be particularly useful for junior neurointerventionalists or those who are not too familiar with the various antiplatelet agents. If such a standardized approach constitutes an oversimplification or not should be addressed in future studies. The panel preferred intravenous Aspirin as first-line agent (or rectal Aspirin if intravenous Aspirin is not available), irrespective whether antiplatelet therapy is initiated prior or during the procedure, probably because of its reliable and fast platelet inhibition: an intravenous dose of 500 mg Aspirin effectively inhibits platelet function within 30 s after administration, while 500 mg oral Aspirin takes over an hour to sufficiently inhibit platelet function [3]. In the postprocedural period, oral Aspirin, which has been used for many years by neurointerventionalists for platelet inhibition after elective endovascular procedures [8, 9], was the preferred first-line agent. No consensus was achieved on whether antiplatelet therapy should be initiated prior to the procedure if the likelihood of an intracranial stent being needed is high, and if one were to do this, whether a second antiplatelet agent should be administered during the procedure and what this agent would be. The lack of agreement among panel members with regard to these questions mirrors the wide variability of antiplatelet regimens, both with in terms of the choice of agents and the timing of their administration. In theory, platelet function testing could be used to guide the choice of postprocedural antiplatelet agents, and some centers routinely do so in the elective setting [10]. But published data on the utility of platelet function testing to guide antiplatelet management after neurovascular procedures is non-conclusive, and one meta-analysis even suggested that platelet function testing prior to elective aneurysm treatment with flow diversion might be associated with worse clinical outcomes, possibly due to lacking consensus on how to interpret the test results and haphazard medication switching [11]. Currently published evidence seems to be inconclusive, and this was reflected in the panel members' responses as well, who could not agree upon the role of platelet function testing for postprocedural antiplatelet management.

Limitations

Most importantly, the purpose of the DELPHI method is to formulate temporary consensus recommendations on how to approach a problem if there is insufficient evidence to develop data-driven recommendations. As such, a DELPHI consensus is not in any way intended to replace evidence-based guidelines. On the contrary, the panel members in this study believed that better data are urgently needed. Second, it is also not the intention of this study to encourage or discourage operators to perform intracranial stenting. Third, the relatively small number of neurointerventionalists in the expert panel could have led to biased results, although care was taken to represent a broad spectrum of specialties and geographic regions. In particular, the results of this study might not be generalizable to geographic regions that were not represented by the expert panel. Fourth, the panel consensus is a snapshot in time, whereas intracranial stenting technologies and antiplatelet agents are constantly refined. Thus, the results of this study will have to be updated as new agents and devices, and ideally better evidence, become available.

Conclusion

This DELPHI study shows that there is a wide variety of opinions regarding antiplatelet management for intracranial stenting due to underlying atherosclerosis in the setting of EVT. Panel members in this study achieved consensus on postprocedural antiplatelet management but did not agree upon a preprocedural and intraprocedural antiplatelet regimen. Future, ideally prospective, studies should aim to investigate whether antiplatelet regimens can be standardized, investigate the optimal timing of antiplatelet therapy (preprocedural vs. intraprocedural initiation), compare single vs. dual intraprocedural regimens, and evaluate whether platelet function testing could be used to optimize the choice of postprocedural antiplatelet agents.

Acknowledgments None

Funding There was no funding for this manuscript.

Compliance with ethical standards

Conflict of interest Johanna Ospel is supported by the University of Basel Research Foundation, Julia Bangerter Rhyner Foundation and Freiwillige Akademische Gesellschaft Basel. Mayank Goyal is a consultant for Medtronic, Stryker, Microvention, GE Healthcare, Mentice. The remaining authors have nothing to disclose.

Ethical approval For this type of study, approval from an ethics board is not required since no patient data were used. All participants gave their consent prior to answering the survey questions.

Informed consent Since the study did not involve patients, formal consent from patients is not required.

References

1. C D (2018) How to train your oracle: the Delphi method and its turbulent youth in operations research and the policy sciences. Soc Stud Sci 48:846–868. https://doi.org/10.1177/0306312718798497
2. Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L, Rovira A, Sastre-Garriga J, Tintore M, Frederiksen JL, Gasperini C, Palace J, Reich DS, Banwell B, Montalban X, Barkhof F, Group MS (2016) MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol 15(3): 292–303. https://doi.org/10.1016/S1474-4422(15)00393-2
3. Meves SH, Neubauer H, Overbeck U, Endres HG (2011) Is there an ideal way to initiate antiplatelet therapy with aspirin? A crossover study on healthy volunteers evaluating different dosing schemes with whole blood aggregometry. BMC Res Notes 4:106. https://doi.org/10.1186/1756-0500-4-106
4. Baek JH, Kim BM, Heo JH, Kim DJ, Nam HS, Kim YD (2018) Outcomes of endovascular treatment for acute intracranial atherosclerosis-related large vessel occlusion. Stroke 49(11): 2699–2705. https://doi.org/10.1161/STROKEAHA.118.022327
5. Chang Y, Kim BM, Bang OY, Baek JH, Heo JH, Nam HS, Kim YD, Yoo J, Kim DJ, Jeon P, Baik SK, Suh SH, Lee KY, Kwak HS, Roh HG, Lee YJ, Kim SH, Ryu CW, Ihn YK, Kim B, Jeon HJ, Kim JW, Byun JS, Suh S, Park JJ, Lee WJ, Roh J, Shin BS, Kim JM (2018) Rescue stenting for failed mechanical thrombectomy in acute ischemic stroke: a multicenter experience. Stroke 49(4): 958–964. https://doi.org/10.1161/STROKEAHA.117.020072
6. Nappini S, Limbucci N, Leone G, Rosi A, Renieri L, Consoli A, Laiso A, Valente I, Rosella F, Rosati R, Mangiafico S (2019) Bail-out intracranial stenting with Solitaire AB device after unsuccessful thrombectomy in acute ischemic stroke of anterior circulation. J Neuroradiol 46(2):141–147. https://doi.org/10.1016/j.neurad.2018.05.004
7. Woo HG, Sunwoo L, Jung C, Kim BJ, Han MK, Bae HJ, Bae YJ, Choi BS, Kim JH (2018) Feasibility of permanent stenting with solitaire FR as a rescue treatment for the reperfusion of acute intracranial artery occlusion. AJNR Am J Neuroradiol 39(2):331–336. https://doi.org/10.3174/ajnr.A5477
8. Kim KS, Fraser JF, Grupke S, Cook AM (2018) Management of antiplatelet therapy in patients undergoing neuroendovascular procedures. J Neurosurg 129(4):890–905. https://doi.org/10.3171/2017.5.JNS162307
9. Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES Jr, Duckwiler GR, Harris CC, Howard VJ, Johnston SC, Meyers PM, Molyneux A, Ogilvy CS, Ringer AJ, Torner J, American Heart Association Stroke Council CoC, Stroke N, Council on E, Prevention, American Heart A, American Stroke A (2015) Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 46(8):2368–2400. https://doi.org/10.1161/STR.0000000000000070
10. Adeeb N, Griessenauer CJ, Foreman PM, Moore JM, Shallwani H, Motiei-Langroudi R, Alturki A, Siddiqui AH, Levy EI, Harrigan MR, Ogilvy CS, Thomas AJ (2017) Use of platelet function testing before pipeline embolization device placement: a multicenter cohort study. Stroke 48(5):1322–1330. https://doi.org/10.1161/STROKEAHA.116.015308
11. Brinjikji W, Lanzino G, Cloft HJ, Siddiqui AH, Hanel RA, Kallmes DF (2015) Platelet testing is associated with worse clinical outcomes for patients treated with the pipeline embolization device. AJNR Am J Neuroradiol 36(11):2090–2095. https://doi.org/10.3174/ajnr.A4411

Affiliations

Mayank Goyal[1] · Kirill Orlov[2] · Mary E. Jensen[3] · Allan Taylor[4] · Charles Majoie[5] · Mahesh Jayaraman[6] · Jianmin Liu[7] · Geneviève Milot[8] · Patrick Brouwer[9,10] · Shinichi Yoshimura[11] · Felipe Albuquerque[12] · Adam Arthur[13] · David Kallmes[14] · Nobuyuki Sakai[15] · Justin F. Fraser[16] · Raul Nogueira[17] · Pengfei Yang[7] · Franziska Dorn[18] · Lucie Thibault[19] · Jens Fiehler[20] · René Chapot[21] · Johanna Maria Ospel[22,23]

[1] Departments of Radiology and Clinical Neurosciences, Foothills Medical Centre, University of Calgary, 1403 29th St. NW, Calgary, AB T2N2T9, Canada

[2] Meshalkin National Medical Research Center, Novosibirsk, Russian Federation

[3] Departments of Neurological Surgery, Radiology and Medical Imaging, UVA Health, Charlottesville, VA, USA

[4] Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

[5] Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, location AMC, Amsterdam, The Netherlands

[6] Departments of Diagnostic Imaging, Neurology and Neurosurgery Warren Alpert School of Medicine at Brown University, Providence, RI, USA

[7] Department of Neurosurgery, Changhai Hospital Naval Medical University, Shanghai, China

[8] Department of Neurosurgery, CHU de Québec, Quebec City, Canada

[9] Department of Interventional Neuroradiology, Karolinksa Hospital, Stockholm, Sweden

[10] University NeuroVascular Center 'UNVC', Leiden University Medical Center, Haaglanden Medical Center, Leiden, Netherlands

[11] Department of Neurosurgery, Hyogo College of Medicine 1-1 Mukogawa, Nishinomiya, Hyogo, Japan

[12] Department of Neurosurgery, Barrow Neurological Institute, Phoenix, USA

[13] Department of Neurosurgery, Semmes-Murphey Clinic/ University of TN, Memphis, TN, USA

[14] Department of Radiology, Mayo Clinic, Rochester, USA

[15] Department of Neurosurgery, Kobe City Medical Center General Hospital, Kobe, Japan

[16] Departments of Neurosurgery, Neurology, Radiology, and Neuroscience, University of Kentucky, Lexington, KY, USA

[17] Marcus Stroke & Neuroscience Center, Grady Memorial Hospital and Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA

[18] Department of Neuroradiology, University Hospital Bonn, Bonn, Germany

[19] WFITN, Paris, France

[20] Department of Diagnostic and Interventional Neuroradiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[21] Department of Neuroradiology, Alfred Krupp Krankenhaus Essen, Essen, Germany

[22] Department of Clinical Neurosciences, University of Calgary, Calgary, Canada

[23] Department of Neuroradiology, University Hospital of Basel, Basel, Switzerland