

Definition of Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage as an Outcome Event in Clinical Trials and Observational Studies

Proposal of a Multidisciplinary Research Group

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Background and Purpose—In clinical trials and observational studies there is considerable inconsistency in the use of definitions to describe delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage. A major cause for this inconsistency is the combining of radiographic evidence of vasospasm with clinical features of cerebral ischemia, although multiple factors may contribute to DCI. The second issue is the variability and overlap of terms used to describe each phenomenon. This makes comparisons among studies difficult.

Methods—An international ad hoc panel of experts involved in subarachnoid hemorrhage research developed and proposed a definition of DCI to be used as an outcome measure in clinical trials and observational studies. We used a consensus-building approach.

Results—It is proposed that in observational studies and clinical trials aiming to investigate strategies to prevent DCI, the 2 main outcome measures should be: (1) cerebral infarction identified on CT or MRI or proven at autopsy, after exclusion of procedure-related infarctions; and (2) functional outcome. Secondary outcome measure should be clinical deterioration caused by DCI, after exclusion of other potential causes of clinical deterioration. Vasospasm on angiography or transcranial Doppler can also be used as an outcome measure to investigate proof of concept but should be interpreted in conjunction with DCI or functional outcome.

Conclusion—The proposed measures reflect the most relevant morphological and clinical features of DCI without regard to pathogenesis to be used as an outcome measure in clinical trials and observational studies. (*Stroke*. 2010;41:2391-2395.)

Key Words: cerebral infarction ■ definition ■ delayed cerebral ischemia ■ subarachnoid hemorrhage ■ vasospasm

Aneurysmal subarachnoid hemorrhage (SAH) is a life-threatening disease. Patients who survive the initial hours after the hemorrhage and have their aneurysms secured by clipping or coiling are still at risk for severe complications, especially within the first 2 weeks after the hemorrhage. One of the most feared complications is cerebral ischemia, which

occurs in ≈30% of patients surviving the initial hemorrhage, mostly between days 4 and 10 after SAH.^{1,2} Clinical features of cerebral ischemia after SAH mostly consist of focal neurological signs, such as aphasia or hemiparesis, or a decrease in the level of consciousness, typically with gradual and often fluctuating onset. Signs of cerebral ischemia are

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In this article, the term “vasospasm” is reserved for the angiographic finding of narrowed cerebral arteries. The term “delayed cerebral ischemia” is used for the clinical signs of ischemia or radiographic (CT/MRI) evidence of ischemia.

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sometimes reversible but may also progress to cerebral infarction, which can cause severe disability or even result in death.^{1,3} Although these clinical deficits often occur in conjunction with angiographic evidence of vessel narrowing, each may occur independently of the other.

In clinical trials and observational studies that have cerebral ischemia as an outcome event, the use of terms and definitions to describe the phenomenon of cerebral ischemia is inconsistent. Because of its delayed onset, this complication is often called delayed cerebral ischemia (DCI).^{2,4} Besides the term “DCI,” many other terms are used in the literature to describe this clinical phenomenon, such as delayed ischemic neurological deficit,^{5–7} delayed ischemic deficit,^{8,9} delayed neurological deficit,^{10,11} secondary cerebral ischemia,^{12,13} vasospasm,^{14,15} clinical vasospasm,^{16,17} symptomatic vasospasm,^{18,19} symptomatic ischemia,²⁰ and cerebral infarction.²¹ The use of so many different terms is problematic, not only because many studies provide incomplete definitions of the terms used, if at all,^{22,23} but also because a variety of definitions are used for the same term. A major cause for the inconsistency in terms and definitions is the combining of radiographic evidence of vasospasm with clinical features of cerebral ischemia, whereas multiple factors may contribute to DCI.^{7,24–27} A second cause is the variability and overlap of terms used to describe each phenomenon. Clinical deterioration attributable to DCI is a diagnosis *per exclusionem* (after exclusion of other causes such as infection, hypotension, hyponatremia, and others), and it is especially difficult to diagnose in patients who are comatose or sedated. Therefore, often surrogates are used that are easier to measure. Because of the association between clinical deterioration from DCI and angiographic vasospasm, arterial narrowing on angiography and increased blood flow velocities on transcranial Doppler ultrasound examination are often used as a surrogate diagnostic tool. This has contributed to the interchangeable use of the terms for DCI and angiographic vasospasm.

The inconsistency in terms and definitions makes it almost impossible to compare the results between studies, understand the true impact of an intervention, aggregate results in meta-analyses,^{28,29} or construct guidelines with a high level of evidence.^{23,30} In the absence of an established biomarker or an easily performed and minimally invasive neuroimaging study with reliable test characteristics, a need exists for a robust and widely acceptable definition of cerebral ischemia after aneurysmal SAH. The aim of the present article was to propose a uniform definition for this complication to be used as outcome measure in future clinical trials and observational studies.

Materials and Methods

An international ad hoc panel of experts involved in SAH research developed and proposed a definition of DCI to be used as an outcome measure in clinical trials and observational studies. We used a consensus-building approach. In the first phase of problem identification, 3 authors (M.D.I.V., M.V., and Y.B.W.E.M.R.) made the plan to write an article to address this issue and to propose a uniform definition. In the second phase of participant identification and recruitment, experts were contacted who were known from previous collaborations. It was decided to have experts from different disci-

plines within the panel (neurology, neurosurgery, interventional neuroradiology, and neurocritical care). These experts were asked for advice to get in contact with other experts. One of the authors (M.D.I.V.) facilitated the complete process of consensus building. All authors were contacted by e-mail with the invitation to participate in the writing of an article to propose a uniform definition of DCI, with the aim to end the inconsistent use of DCI definitions in the literature. Subsequently, a draft manuscript was written by 2 authors (M.D.I.V., Y.B.W.E.M.R.) and sent to all authors. After receiving comments and suggestions of the coauthors, a revised manuscript was written and sent to all authors again. This process was repeated until consensus was reached. The manuscript was submitted for publication after approval was received of all authors.

Considerations for Uniform Terms and Definitions

As long as the precise pathogenesis of DCI remains unknown, no assumptions can be made about which term is preferable. However, the authors agree on the following considerations. Terms such as clinical vasospasm, symptomatic vasospasm, and vasospasm-related ischemia suggest that clinical features of DCI are present in combination with radiologically confirmed arterial narrowing. However, patients with SAH can also have clinical deterioration attributable to DCI in the absence of radiologically confirmed vasospasm,^{4,31} because radiological confirmation is not obtained, it is not obtained when clinical deterioration from DCI develops, or because DCI is caused by other factors. The reverse situation in which patients have angiographic vasospasm but no DCI also frequently occurs.⁴ The use of terms that include vasospasm suggests that patients with clinical deterioration attributable to DCI in the absence of radiological vasospasm are not included in the analysis. Furthermore, the word “vasospasm” by itself is often used for describing clinical deterioration from DCI. By doing so, it is implicitly suggested that DCI is always caused by arterial narrowing of the cerebral arteries, which often is not the case.^{32–35} Therefore, as long as the pathogenesis of DCI is incompletely known, it is preferable to use a term that describes the clinical picture and in which no assumption is made about its pathogenesis. Delayed neurological deficit is a general term, without any assumption about pathogenesis and cause. However, there is a large body of evidence that deterioration after SAH is attributable to ischemia, provided specific other complications have been ruled out (such as re-bleeding, hydrocephalus, and systemic disorders). The term secondary ischemia also refers to a delayed onset, without referring to causality. However, it may incorrectly suggest that clinical deterioration is secondary to an identifiable cause, such as hydrocephalus. The terms delayed cerebral ischemia, delayed ischemic neurological deficit, and delayed ischemic deficit are practically identical, although the word “deficit” might suggest that only clinical deterioration with focal neurological findings should be taken into account. “Cerebral infarction” should preferably be limited to describe findings on either CT or MRI of the brain or found at autopsy that are suggestive of brain tissue that died as a result of ischemia.

The clinical diagnosis of clinical deterioration attributable to DCI is difficult for several reasons. First, the clinical spectrum of DCI is wide. Typical clinical features of DCI are neurological deficits (such as hemiparesis, aphasia, apraxia, and neglect) as a result of focal cerebral ischemia, or a decrease in the level of consciousness as a result of global cerebral ischemia. However, some studies also included neck stiffness, fever, and mutism in the definition of DCI, although it is unknown whether these signs truly reflect DCI.^{2,36,37} Second, clinical deterioration from DCI is a diagnosis *per exclusionem*. Clinical deterioration after SAH can have multiple causes other than DCI, such as seizures, hypoxia, hypotension, fever, heart failure, and the effect of sedatives. Third, because a proportion of SAH patients are comatose or sedated, a definition of DCI that is purely based on clinical features will underestimate the true incidence of DCI.³⁸

The clinical features of DCI may resolve spontaneously or after treatment. However, infarction on CT or MRI demonstrates the ultimate outcome of the ischemic event and thus may be the most appropriate outcome measure for clinical trials and observational

studies. In a recent large cohort study, DCI (defined as a new focal neurological deficit or decrease in level of consciousness, a new infarct revealed by follow-up CT imaging, or both) was independently associated with death or severe disability at 3 months only when CT results were included in the definition of DCI.³⁹ Cerebral infarction alone had equally strong correlations with 3-month functional outcome (measured with either Glasgow Outcome Scale or modified Rankin Scale) as the combination of clinical deterioration attributable to DCI with cerebral infarction on neuroimaging.⁴⁰ In the same cohort, it was shown in a multivariate analysis that patients with asymptomatic infarction, who were mostly comatose patients, more often had a poorer outcome (death and moderate to severe disability) than patients with symptomatic DCI.³⁸ Cerebral infarction on CT imaging was also the primary outcome measure in the largest trial that investigated the efficacy of nimodipine, which is the only drug with class I evidence of a beneficial effect in the prevention of DCI.^{21,41}

Given these considerations, the authors have a preference, which is partly based on subjective judgments, for the use of the following terms: “clinical deterioration caused by delayed cerebral ischemia” for clinical features; “cerebral infarction” for CT, MRI, or autopsy results; and “vasospasm” or “arterial narrowing” for the results of angiography.

Clinical Deterioration Caused by DCI

Typical features of clinical deterioration caused by DCI are the development of focal neurological signs, such as aphasia or hemiparesis, and a decrease in the level of consciousness. Obviously, to detect new focal neurological signs or a decreased level of consciousness, frequent neurological examinations are required. For the detection of a decrease in the level of consciousness, we recommend the use of the Glasgow Coma Scale.^{5,12} Although this scale was initially developed for patients with traumatic brain injury, this scale is widely used in (neuro)critical care units for the monitoring of patients with SAH, because it is easy and fast. Besides, it is the basis of the World Federation of Neurosurgical Societies scale for grading the severity of SAH on admission.⁴² Because patients with SAH often have spontaneous mild fluctuations in the level of consciousness, a decrease of 2 points in the Glasgow Coma Score (either on the total score or on one of its components [eye, motor on either side, verbal]) will be more appropriate for detecting a decreased level of consciousness as a clinical feature of DCI than a decrease of a single point. The number of false-negative events ascribed to DCI will further decrease by adding a minimal duration of the neurological deterioration in the definition. There is some recent experience with the National Institutes of Health Stroke Scale in patients with aneurysmal SAH,^{5,43} but this scale is quite extensive and can only be applied by qualified persons. Future studies are needed to investigate if the National Institutes of Health Stroke Scale is an adequate tool to detect clinical deterioration caused by DCI.

Laboratory investigations are required to exclude metabolic causes of deterioration, such as hyponatremia. A search for infection should be performed, especially in patients with a decrease in the level of consciousness. Cerebral imaging should be performed to exclude re-bleeding, edema, and hydrocephalus. Because these other factors can be found in mild degrees, it is difficult to know when clinical deteriorations can be truly attributed to DCI. As long as the pathogenesis of DCI remains unknown and no adequate biomarker or easily performed neuroimaging study with reliable characteristics is available, there is no gold standard and these diagnostic decisions are subject to bias. For example, it is unknown what the cut-off values are at which hyponatremia, hyperthermia, and hypotension can be accepted as a cause of clinical deterioration. Also it is not generally feasible to reverse the effects of sedative medications. Although, to our knowledge, no studies have been performed to test interobserver agreement rates for the diagnosis of clinical deterioration from DCI, we suspect that they are fairly low for these reasons.

Neuroimaging

For a uniform definition of cerebral infarction, we suggest including the use of CT or MRI. The advantages of CT over MRI are the wider

availability of CT scans, it is less time-consuming, and the logistics are easier in intensive care patients. However, if serial MRI can be performed, it is the preferred method because MRI is more sensitive and autopsy studies have strongly suggested that small cortical lesions have an important effect on outcome after SAH.^{33,44} Within a given study, either CT or MRI should be serially performed to allow detection of changes with the same imaging modality. We suggest that the best time to perform the follow-up neuroimaging procedure to detect cerebral infarction is within 6 weeks after SAH, after the time window in which DCI occurs, and when most SAH patients are in a stable clinical condition. Because surgical or endovascular occlusion of the aneurysm may cause edema and infarction, we suggest that between 24 and 48 hours after each procedure for aneurysm occlusion a CT or MR scan should be performed to rule this out.⁴⁵ In sedated patients, these iatrogenic lesions may have been erroneously attributed to DCI.

We also considered whether a neuroimaging definition should include any of the techniques that are available for measuring cerebral perfusion, such as perfusion CT imaging, xenon CT, and positron emission tomography.^{4,27,31,46,47} Access to quantitative cerebral blood flow information within a critical care environment has been problematic but is potentially available via invasive and noninvasive technologies. The feasibility of radioactive and stable xenon to provide relevant quantitative cerebral blood flow information has been extensively reported.⁴⁶ The role of perfusion CT imaging is presently undergoing intensive investigation.^{4,31} However, because cerebral perfusion techniques have not yet been optimized and perfusion changes after SAH are highly unstable,²⁶ we feel that these modalities cannot be used in the neuroimaging definition at this time. Furthermore, cerebral blood flow may be difficult to interpret without information on cerebral metabolism. Nevertheless, they might become a promising tool for detecting DCI in the future, not only in comatose and sedated patients but also in patients who are more alert.^{4,31,48}

Proposed Definitions

We conclude that uniform definitions of “clinical deterioration caused by delayed cerebral ischemia” and “cerebral infarction” should capture the most relevant elements in terms of morphological and clinical characteristics, without assumptions about its pathogenesis. Because cerebral infarction on CT/MRI is strongly correlated with functional outcome 3 months after SAH, and given its expected high interobserver agreement rate, its ability to detect DCI in sedated and comatose patients, and its objective quantification of the consequences of DCI, cerebral infarction on neuroimaging might be a better outcome measure than clinical deterioration caused by DCI alone. Although previous definitions of DCI often combined clinical features of DCI with either angiography/transcranial Doppler findings or cerebral infarction on neuroimaging or autopsy, we suggest that these should be separately reported.

To obtain high interobserver agreement rates, phase II and III clinical trials aiming to reduce DCI should include the occurrence of cerebral infarction on CT or MRI as well as functional outcome as main end points. We suggest that clinical deterioration caused by DCI should be not more than a secondary measure of outcome, because of suspected lower interobserver agreement rates.

The proposed definition of clinical deterioration caused by DCI is: “The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies.”

Because no strict criteria can be given for factors that exclude the presence of DCI, especially when factors other than DCI occur in combination, the decision whether a clinical deterioration can be attributed to the occurrence of DCI will be fairly subjective.

The proposed definition of cerebral infarction is: “The presence of cerebral infarction on CT or MR scan of the brain within 6 weeks after SAH, or on the latest CT or MR scan made before death within 6 weeks, or proven at autopsy, not present on the CT or MR scan between 24 and 48 hours after early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment. Hypodensities on CT imaging resulting from ventricular catheter or intraparenchymal hematoma should not be regarded as cerebral infarctions from DCI.”

We strongly recommend to restrict the use of the words “vasospasm” or “arterial narrowing” to descriptions of a radiological test (either CT angiography, MRA, or digital subtraction angiography), and we recommend not applying this term to clinical manifestations of DCI. Vasospasm on angiography can also be used as an outcome measure to investigate proof of concept but should not be used as a surrogate outcome measure. Transcranial Doppler has a lower sensitivity and specificity to diagnose angiographic arterial narrowing;⁴⁹ therefore, it is not adequate to investigate proof of concept.

Conclusion

We conclude that the proposed definitions capture the most relevant elements of cerebral ischemia after SAH. We recommend using these definitions in future clinical trials and observational studies that have DCI as an outcome event until more accurate, reliable, and sensitive tests are developed to measure DCI. For studies investigating the efficacy of strategies to reverse DCI once it occurs (in which DCI is an entry event rather than an outcome event), the described definition is probably too strict. The occurrence of clinical deterioration caused by DCI should be described separately from the results of angiography. The term “vasospasm” should be reserved for angiographic arterial narrowing. Implementation of the proposed definitions will facilitate the identification of robust, evidence-based treatments for patients with aneurysmal SAH. Future investigations should be performed to clarify the full spectrum of clinical features of DCI, and to evaluate the operational characteristics of ancillary investigations and proposed definitions. To achieve this aim, we suggest intensive clinical monitoring in combination with serial MRI (including diffusion-weighted imaging, MRA, and MR perfusion), CT (including CT angiography and perfusion), transcranial Doppler, and digital subtraction angiography.

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Special Report

脳動脈瘤によるくも膜下出血後の遅発性脳虚血：臨床試験と観察研究の評価項目としての定義

— 集学的研究グループの提案

Definition of Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage as an Outcome Event in Clinical Trials and Observational Studies

— Proposal of a Multidisciplinary Research Group

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背景および目的：臨床試験や観察研究では、脳動脈瘤性くも膜下出血後の遅発性脳虚血 (DCI) に関して一貫した定義が用いられていない。その原因にはさまざまな要因が関与していると考えられるが、主な原因は放射線検査による血管攣縮の存在と脳虚血の臨床的特徴が併用されていることにある。もう1つの問題は、それぞれの現象を記述するのにさまざまな用語が用いられたり用語の重複がみられることであり、それが研究間の比較を困難にしている。

方法：くも膜下出血研究の専門家によって構成された国際特別委員会において、臨床試験や観察研究で転帰として評価されるDCIの定義を作成・提案した。作業はコンセンサスを形成する形で進められた。

結果：DCI 予防戦略を目的とする観察研究や臨床試験では、主要評価項目を (1) CT もしくは MRI で確認されるか、または剖

検で証明された脳梗塞 (手技に伴う梗塞は除く)、および (2) 機能的転帰とすることを提案する。副次評価項目は、DCI によって生じた臨床的な悪化 (他の考えられる原因によるものを除く) にすべきである。概念実証 (proof of concept) 研究の場合は、血管造影または経頭蓋超音波ドプラ検査で認められた血管攣縮を評価項目として用いてもよいが、解釈には DCI または機能的転帰を併用することが必要である。

結論：上記の評価基準案には、臨床試験や観察研究における転帰の評価項目として、病因は考慮に入れず、最も関連の深い DCI の形態的・臨床的特徴が反映されている。

※ この Special Report には図表が掲載されていないため抄録のみを掲載する。

編集後記：2010年を振り返って

Stroke 日本語版は創刊後5年が過ぎ、ひとつの節目を迎えました。この間出版にご尽力いただいたワイリー・ブラックウェル社、教育助成基金でご支援をいただいた大塚製薬株式会社、および本誌を読んでいただいた読者の皆様方に深謝致します。英文 Stroke 誌は2010年7月から Editor-in-Chief が Dr. Marc Fisher に交代しましたが、その後も順調に出版が続けられています。例年日本語版に掲載しています Advances in Stroke は Stroke 誌の電子版だけの掲載となりましたが、内容の重要性を考慮して日本語版には引き続き要訳を掲載しています。一方、年度末にまとめて掲載してきた Cochrane Corner は電子版になったことと臨床的に有用な報告が少ないことから、今年度は掲載を見合わせました。また AHA/ASA Guideline は脳内出血の管理に関するものが1篇と、Scientific Statement は脳卒中後の看護と集学的リハビリテーションに関するものが1篇の掲載に止まりましたが、脳卒中の二次予防に関するガイドラインが10月の Stroke 電子版と2011年1月の Stroke 誌に掲載されたため、特集としてこの日本語版 Vol.5, No.4 の分冊に要約と推奨文を刊行します。日本の脳卒中医療は経静脈 t-PA 療法に続き機械的血栓除去術も一部認可され、MRI もいよいよ 7-Tesla の時代に入りつつあり、血液モニタリングの必要がない経口抗凝固薬も導入されようとしています。このような脳卒中医療の進歩に対応して、私達も2011年にはさらに充実した Stroke 日本語版を、大塚製薬株式会社からの教育助成基金とワイリー・ブラックウェル社のご協力のもとに出版したいと考えていますので、読者の皆様方のご支援ご鞭撻を宜しくお願い致します。

編集委員 一同