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Outcomes-based assessment of a new reference standard for delayed cerebral ischemia related to vasospasm in aneurysmal subarachnoid hemorrhage

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Abstract

Rationale and Objectives—The purpose is to perform outcomes-based assessment of a new reference standard for delayed cerebral ischemia (DCI) related to vasospasm.

Materials & Methods—Retrospective study was performed with consecutive aneurysmal subarachnoid hemorrhage (A-SAH) patients from January 2002–May 2009. A new reference standard for DCI was applied to the study population incorporating clinical and imaging criteria. Diagnostic accuracy was determined by chart diagnosis. Outcome measures for assessment included: permanent neurologic deficits, infarction, functional disability, treatment, and discharge status. Medical record review was performed by two blinded observers. Chi-square test calculated statistical significance between DCI and no DCI groups.

Results—A total of 137 patients were included; 59%(81/137) classified as DCI and 41%(56/137) as no DCI by the reference standard. Overall accuracy is 96%(95% confidence interval 92–99%) with 100% sensitivity, 92% specificity, 94% positive- and 100% negative predictive values. Patients classified as DCI had 40%(32/81) permanent neurologic deficits and 57%(46/81) infarction compared to 0%(0/56) classified as no DCI. DCI patients had 33%(27/81) functional disability compared to 13%(7/56) classified as no DCI. Ninety-four percent (76/81) DCI patients received treatment compared to 0%(0/56) classified as no DCI. DCI group had 46%(37/81) discharged to rehabilitation facilities and 11%(9/81) mortality compared to 25%(14/56) and 2%(1/56), respectively, in no DCI group. There are statistically significant differences ($p<0.0001$) between DCI and no DCI groups for all outcome measures.

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Conclusion—This new reference standard has high diagnostic accuracy for DCI related to vasospasm. The outcomes-based assessment further supports its accuracy in correctly classifying A-SAH patients.

Keywords

reference standard; outcomes-based assessment; delayed cerebral ischemia

Introduction

Aneurysmal subarachnoid hemorrhage (A-SAH) is a devastating condition resulting in significant morbidity and mortality [1,2]. Delayed cerebral ischemia (DCI) is a serious complication of A-SAH further contributing to the poor clinical outcomes seen in this patient population with sequelae of permanent neurologic deficits, cerebral infarction and death. The pathophysiology of DCI is complex often leading to delayed diagnosis and treatment. Early and accurate identification of DCI is necessary to initiate appropriate treatment in order to prevent functional disability and mortality. On the other hand, accurate classification of patients without DCI is also important to prevent unnecessary patient exposure to serious neurologic and systemic complications associated with its treatment. Thereby, critical assessment of the classification scheme and reference standard for DCI is essential in the management and treatment of A-SAH patients.

Recent consensus opinion from an expert panel recommended that clinical trials define DCI using outcome measures of neurologic function and cerebral infarction that are not attributed to other causes [3]. For simplicity, the term vasospasm is reserved for the presence of arterial narrowing on imaging studies [3]. However, DCI and vasospasm may be related with arterial narrowing resulting in reduced cerebral blood flow leading to clinical deterioration and ischemia. In the past, these terms have been considered interchangeable in clinical practice. The caveat is that not all patients with arterial narrowing on angiography develop DCI [4]. Furthermore, not all patients who experience DCI have angiographic vasospasm, which may be partly attributed to circulatory impairment at the microvascular level. Thereby, incorporating both clinical and imaging criteria in the diagnosis of DCI has been reported as most clinically relevant because it has the strongest association with overall poor outcome, cognitive impairment and reduced quality of life [5]. Thus, efforts have been focused on developing methods to uniformly classify A-SAH patients in clinical trials investigating treatment strategies for DCI.

Several methods are often used in combination to determine DCI and vasospasm in clinical practice, such as clinical examination, angiographic studies with CT angiography (CTA) and digital subtraction angiography (DSA), and transcranial Doppler ultrasound (TCD). Since none of these methods alone are an acceptable reference standard, alternative approaches employing composite criterion have been investigated [6]. In our prior work, we have developed and internally validated a reference standard [7,8] using a composite criterion incorporating the most relevant clinical and imaging criteria for vasospasm. The terminology of DCI and vasospasm is continuously under review by investigators to establish the most appropriate description of ischemia after SAH. The previously published reference standard has been modified in our study to improve its accuracy incorporating both of these terms as these two entities are associated and often used interchangeably in clinical practice. The purpose of this study is to perform an outcomes-based assessment of this new reference standard for DCI related to vasospasm to further evaluate its accuracy in classifying A-SAH patients.

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Materials and Methods

Study population

A retrospective study was performed including consecutive patients admitted to our institution with A-SAH from January 2002 – May 2009. Inclusion criterion was an admission diagnosis of A-SAH documented by noncontrast CT and/or cerebrospinal fluid analysis for SAH and CTA and/or DSA for a ruptured aneurysm. There were no exclusion criteria in this study. Institutional review board approval was obtained and written informed consent was waived.

Review of the medical records was performed for the clinical and demographic characteristics of the study population, including age, gender, aneurysm location and treatment, and Hunt and Hess grades on presentation. All management and treatment decisions were based on evidence of clinical deterioration, TCD and DSA examinations, as per usual standard-of-care.

Study design

All A-SAH patients were applied to this new reference standard in a step-wise manner using a weighted multi-stage hierarchical design with the strongest evidence at the primary level. Figure 1 is a flow diagram illustrating the new reference standard design. At the primary level, DSA is used to determine a diagnosis of DCI related to vasospasm. The angiographic criterion for vasospasm is based on the degree of vessel narrowing compared to the normal parent vessel diameter. Mild vasospasm is defined as less than 50% degree of luminal narrowing; moderate vasospasm as 50–75% narrowing; and severe vasospasm as greater than 75% narrowing. In this new reference standard, patients with no vasospasm on DSA proceed to the secondary level for further evaluation.

The secondary level evaluates patients who do not have DSA performed during hospitalization or have no vasospasm on DSA at the primary level. At the secondary level, the following clinical and imaging outcome measures are used. The clinical criterion for a diagnosis of DCI is presence of a permanent neurologic deficit on physical examination, distinct from the deficit at baseline produced by the initial A-SAH. The imaging criterion for a diagnosis of DCI is delayed cerebral infarction present on follow up computed tomography (CT) or magnetic resonance imaging (MRI). Delayed infarction is defined as a new infarction on CT or MRI, that occurred after day 4, which was not present on imaging within 3 days after onset of A-SAH. This criterion effectively excludes patients with brain damage from the initial hemorrhagic event and post-operative complications [9]. Patients who fit either or both of these criteria are classified as DCI at the secondary level. For patients who do not fit either of the above criteria, then further consideration of medical treatment is warranted. Patients who did not receive treatment with medically induced hypertension, hypervolemia and hemodilution (HHH) therapy and do not meet either of these outcome criteria are classified as no DCI. However, patients who did receive HHH therapy and do not meet either of these outcome criteria, proceed to the tertiary level for further evaluation.

The tertiary level evaluates patients who have received HHH therapy and do not meet the criteria at the primary and secondary levels. At the tertiary level, a response to treatment is assessed. Patients who demonstrate an improvement in symptoms and/or clinical examination after HHH therapy are considered responders to appropriate treatment and are classified as DCI. Patients who do not improve after treatment and have another etiology to explain their symptoms, such as hydrocephalus, re-hemorrhage from aneurysm, postoperative infarction, infection, etc., are classified as no DCI.

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Outcomes-based assessment

Several outcome measures were used to assess appropriate classification of patients by this new reference standard design. To determine the diagnostic accuracy of the new reference standard, the gold standard in this study was the chart diagnosis of DCI and/or vasospasm according to the documentation in the discharge summary and progress notes. Clinical and imaging outcome measures for DCI were also evaluated, including a permanent neurologic deficit determined by physical examination on discharge and delayed cerebral infarction determined by follow-up CT and/or MR imaging. Functional status was used as a clinical outcome measure to assess long-term disability of patients following discharge. Full or incomplete return to baseline status prior to A-SAH was assessed by medical record review of the outpatient clinic notes up to one year following discharge.

Several surrogate outcome measures were also evaluated in this study. Treatment of DCI was used as an outcome measure to assess appropriate classification of patients who require treatment intervention. Due to the serious risks associated with treatment, it is also important to accurately classify patients who do not require treatment to prevent additional morbidity in this patient population. This outcome measure was categorized as medical HHH therapy only, intra-arterial (IA) therapy in patients who did not adequately respond to the initial HHH therapy, and no treatment. Discharge status was also used as a surrogate outcome measure to roughly estimate appropriate classification of patients according to discharge position as another measure to indicate degree of functional disability. This outcome measure was categorized as home, acute rehabilitation facility, long-term skilled nursing facility, and death. The mean length of stay in the hospital was also determined for the study population, DCI and no DCI groups.

Two blinded observers, including a 3rd year Radiology resident and 4th year medical student, performed a retrospective review of the medical records, including the discharge summary, progress notes and outpatient clinic notes for data collection.

Statistical analysis

Measurements of diagnostic accuracy were determined for the new reference standard, including sensitivity, specificity, positive and negative predictive values using 2 x 2 table analysis. Overall accuracy was calculated using the sum of the true positives and true negatives divided by all patients in the study population. The 95% confidence interval (CI) was calculated as a measure of variability using the modified Wald method. The incidence of the outcome measures for the new reference standard and each of its levels was determined by simple frequency calculations. The chi-square test was used to determine statistical significance between the DCI and no DCI groups for each outcome measure. Statistical significance was accepted with two-tailed P value as <0.05. All statistical analysis was performed using GraphPad software (GraphPad software, Inc., La Jolla, CA).

Results

Study popu lation characteristics

A total of 137 consecutive A-SAH patients were included in the statistical analysis. Importantly, no patients were excluded from the study. Clinical and demographic characteristics of the study population are presented in Table 1.

Application of the reference standard design

Applying this new reference standard to the study population, 59% (81/137) of patients were classified as DCI and 41% (56/137) as no DCI. A total of 81 patients were classified as DCI

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with 70% (57/81) at the primary level, 14% (11/81) at the secondary level and 16% (13/81) at the tertiary level. A total of 56 patients were classified as no DCI at the secondary level.

The new reference standard rendered a diagnosis at the primary level in 42% (57/137) of patients, at the secondary level in 49% (67/137) and at the tertiary level in 9% (13/137). At the primary level, 63% (86/137) of patients had DSA performed. Out of these patients, 66% (57/86) had angiographic vasospasm and were classified as DCI related to vasospasm. The remaining 34% (29/86) of patients had no angiographic vasospasm and proceeded to the secondary level for further evaluation. At the secondary level, using defined clinical and imaging criteria, 16% (11/67) of patients were classified as DCI and 84% (56/67) as no DCI. At the tertiary level, using treatment response, all patients (n=13) were classified as DCI.

The overall accuracy (95% CI) of this new reference standard as determined by chart diagnosis is 96% (92–99%). The test characteristics (95% CI) of the new reference standard are 100% (94–100%) sensitivity, 92% (82–97%) specificity, 94% (86–98%) positive predictive value and 100% (92–100%) negative predictive value. Further analysis was performed to determine the diagnostic accuracy (95% CI) at each level in the new reference standard. The primary level had the highest accuracy of 98% (90–100%), followed by the secondary level at 96% (87–99%) and the tertiary level at 92% (65–100%).

Outcomes-based assessment of the new reference standard

The classification of patients by the new reference standard was correlated with the most relevant clinical and imaging outcome measures of DCI, including permanent neurologic deficits and cerebral infarction. In this study population, 23% (32/137) of patients had permanent neurologic deficits and 34% (46/137) had cerebral infarction. For patients classified as DCI, 40% (32/81) had permanent neurologic deficits and 57% (46/81) had cerebral infarction. Patients classified as no DCI had 0% (0/56) of permanent neurologic deficits and infarction. There are statistically significant differences between the DCI and no DCI groups for both permanent neurologic deficits ($p < 0.0001$) and cerebral infarction ($p < 0.0001$). Table 2 demonstrates the distribution of these clinical and imaging outcomes for each level in the new reference standard.

Functional status on follow-up visits was assessed to determine full return to baseline prior to the A-SAH event. In this study population, 60% (82/137) of patients' functional status returned to baseline and 25% (34/137) did not have full recovery. In 15% (21/137) of patients, the functional status could not be determined due to missing data. For patients classified as DCI, 48% (39/81) had functional status return to baseline, 33% (27/81) did not and 19% (15/81) were unknown. For patients classified as no DCI, 77% (43/56) had functional status return to baseline, 13% (7/56) did not and 11% (6/56) were unknown. There is a statistically significant difference in the functional status between the DCI and no DCI groups ($p < 0.0001$). Table 3 demonstrates the distribution of this data for each level in the new reference standard.

Treatment received for DCI was used as a surrogate outcome measure. In this study population, 22% (30/137) of patients received HHH therapy, 34% (46/137) underwent IA-therapy (intra-arterial therapy with vasodilatory agents and/or angioplasty) and 45% (61/137) received no treatment. For patients classified as DCI, 37% (30/81) received HHH, 57% (46/81) underwent IA-therapy and 6% (5/81) did not receive treatment. None of the patients classified as no DCI received HHH nor IA-therapy. There is a statistically significant difference in the treatment received between the DCI and no DCI groups ($p < 0.0001$). Table 4 demonstrates the distribution of treatment for each level in the new reference standard.

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Discharge status was also used as a surrogate outcome measure. In this study population, 50% (68/137) of patients were discharged home, 26% (36/137) acute rehabilitation acility, 11% (15/137) long-term skilled nursing facility and 7% (10/137) died during hospitalization. The discharge status was not recorded in 6% (8/137) of patients due to missing data. For patients classified as DCI, 37% (30/81) were discharged home, 32% (26/81) acute rehabilitation facility, 14% (11/81) long-term skilled nursing facility, 11% (9/81) death and 6% (5/81) unknown. For patients classified as no DCI, 68% (38/56) were discharged home, 18% (10/56) acute rehabilitation, 7% (4/56) long-term skilled nursing facility, 2% (1/56) death and 5% (3/56) unknown. There is a statistically significant difference in the discharge status between the DCI and no DCI groups ($p < 0.0001$). Table 5 demonstrates the distribution of the discharge status for each level in the new reference standard.

The mean length of stay (LOS) in the hospital was 24 days with a range of 3–63 days. The mean LOS (range) was 21 (10–63) days for patients classified as DCI and 19 (3–46) days for no DCI. The mean LOS (range) for patients diagnosed at the primary level with DCI was 28 (10–63) days, at the secondary level with DCI was 27 (12–44) days, at the secondary level with no DCI was 19 (3–46) days and at the tertiary level with DCI was 25 (14–62) days.

Discussion

It is well recognized that a perfect reference standard for DCI does not exist, however, the challenge remains to apply the best criteria in order to accurately classify patients in both clinical practice and research studies. DCI related to vasospasm following A-SAH is a complex entity involving delayed narrowing of the intracranial arteries that may lead to neurologic deterioration, cerebral infarction and death. A review of the literature reveals that inconsistent terminology has been used to describe this entity in clinical trials and observational studies. The association between clinical deterioration from DCI and angiographic vasospasm has led to imaging studies often being used as surrogate diagnostic tools [9]. This has also contributed to the interchangeable use of the terms for DCI and vasospasm. This variability in the classification of patients may affect outcomes by altering management and treatment decisions. With this understanding, our study is focused on further evaluating the accuracy of a new reference standard for DCI related to vasospasm using outcomes-based assessment.

This new reference standard has a high overall accuracy of 96% as determined by chart diagnosis. Evaluation of each level individually reveals that the primary level has the highest accuracy (98%), followed by the secondary (96%) and tertiary (92%) levels supporting its design as weighted multi-stage hierarchical levels. In addition, the high accuracy of each individual level also indicates that the most relevant criteria for determining DCI related to vasospasm have been appropriately incorporated in its design. Specifically, at the primary level, DSA remains a valuable imaging criteria in defining DCI related to vasospasm. Figure 2 demonstrates the clinical significance of using DSA to prospectively classify patients for treatment prior to development of permanent neurologic deficits and cerebral infarction.

Outcomes-based assessment was also performed to further evaluate the accuracy of this new reference standard in classifying patients. Permanent neurologic deficits and cerebral infarction occurred significantly more often in patients classified as DCI compared with patients classified as no DCI. It is not surprising that the new reference standard correlated well with these clinical and imaging outcome measures as these are the most relevant outcomes criteria for DCI that have been incorporated at the secondary level. However, classification of DCI at the primary level also correlated well with these outcome measures confirming that DSA is a relevant imaging criteria in this new reference standard design.

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Please note that the tertiary level had no patients with permanent neurologic deficits and infarction because only patients who did not meet these outcome measures proceeded to the tertiary level to assess treatment response from HHH therapy. Functional status on follow-up outpatient visits was also assessed as an indicator of long-term clinical outcomes (Table 3). There is statistically significant increased functional disability in the patients classified as DCI by the new reference standard compared to the no DCI group. However, there is similar frequency of functional disability for patients classified as DCI at the primary and secondary levels suggesting that the different criteria at these levels both provide valuable information regarding long-term clinical outcomes.

Treatment received during hospitalization was used as a surrogate outcome measure to assess appropriate classification of patients for treatment intervention (Table 4). Since this is a retrospective study, this new reference standard was not utilized in determining treatment decisions in the study population. For patients classified as DCI, significantly more patients received HHH and IA-therapy compared to patients classified as no DCI. These findings support that the new reference standard appropriately classifies patients with DCI who require treatment, and importantly patients without DCI who do not need treatment and can avoid its unnecessary serious risks.

Discharge status was also used as a surrogate outcome measure to estimate appropriate classification of patients according to discharge position reflecting patients' long-term functional disability (Table 5). There is a statistically significant difference between patients classified as DCI compared to no DCI with almost twice as many patients discharged to rehabilitation facilities (acute and long-term) in the DCI group. There is also statistically significant increased mortality during hospitalization in the patients classified as DCI. Furthermore, the patients classified as DCI at the primary level had the highest discharge status to rehabilitation facilities and mortality compared to the DCI patients classified at the secondary level. The patients classified as DCI at the tertiary level had the most favorable discharge status with significantly less patients discharged to rehabilitation facilities and lower mortality.

The main strength of this new reference standard is its widespread applicability to all patients in the A-SAH population, including complex patients with limited clinical examination and patients with discrepancies between clinical findings, TCD, CTA and CT perfusion exams. This new reference standard can be applied to both research and clinical settings potentially improving translation of research into clinical practice. Using the most relevant outcome measures of DCI alone in a reference standard may limit its usefulness in clinical practice as the goal is to identify these patients for treatment in order to prevent its devastating outcomes of permanent neurologic deficits and cerebral infarction. Thereby, a comprehensive approach including surrogate outcome measures, such as angiographic vasospasm, has remained a valuable component in this new reference standard as it also has an association with patient outcomes. However, patients with no angiographic vasospasm at the primary level proceed to the secondary level for further evaluation using clinical and imaging criteria of DCI. This modification strengthens the new reference standard design by addressing the ongoing concern that DSA alone has a low sensitivity of 80% for the detection of vasospasm [10] and patients with DSA-negative exams may have other causes attributing to DCI, such as microvascular vasospasm. Figure 3 illustrates the significance in accurately classifying patients with DSA-negative exams. Another unique feature of this new reference standard is that incorporates treatment response in determining DCI. Considering the effects of treatment is rarely included in a reference standard because most patients who are treated for the disease have already been diagnosed. However, in this patient population prophylactic treatment measures may be used and can also add diagnostic value in determining DCI at the tertiary level.

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A careful and thoughtful review of the new reference standard was also performed to consider the potential limitations at each level. At the primary level, the criterion for angiographic vasospasm does not include symptomatology for classifying patients as DCI related to vasospasm. There is potential for asymptomatic patients with angiographic vasospasm to be classified as DCI. According to clinical practice at our institution, DSA is typically performed in patients with clinical symptoms or findings suspicious of DCI due to its associated procedural risks, including vascular injury, intracranial hemorrhage, cerebral infarction and death. Thereby, most asymptomatic patients with no clinical symptoms or findings of DCI will be classified at the secondary and tertiary levels in the new reference standard.

At the secondary level, using clinical or imaging criteria, the potential limitation is that patients classified as no DCI could, in fact, have DCI related to vasospasm that has gone unrecognized by objective and subjective reference criteria. This small subgroup classified incorrectly as no DCI is considered an acceptable limitation because the objective is to classify patients with clinically significant DCI for initiating treatment. This subgroup with non-clinically significant DCI, who have not received treatment, did not manifest the outcome measures of DCI. Therefore, the classification as no DCI is preferred to avoid exposing these patients to unnecessary serious risks associated with treatment.

At the tertiary level, using treatment response may potentially introduce misclassification bias because symptom improvement may possibly be due to other etiologic factors. However, it is standard-of-care at our institution that prior to starting HHH therapy, all other etiologic factors to explain symptom onset are considered, specifically including but not limited to hydrocephalus, re-hemorrhage from the aneurysm, post-operative infarction or contusion, infection or sepsis, and metabolic disturbances. Following a thorough investigation and exclusion of these other treatable etiologies, then HHH therapy is started. The frequency of other “undetected” etiologies resulting in symptom improvement without dedicated treatment is considered very low in this patient population. On the other hand, it is possible that patients with DCI who receive HHH therapy do not manifest a symptom response because the treatment is not effective and will be misclassified as no DCI. However, at our institution standard management of A-SAH patients with symptoms of DCI who do not respond to HHH therapy and no other etiologic factors are identified will undergo DSA for further diagnostic testing and possibly intra-arterial treatment. These patients would then be classified at the primary or secondary levels.

The major limitation of this study is its retrospective study design relying on medical record review for data collection. There was variability in the chart documentation of the outcome measures resulting in missing data, particularly assessing the functional status and discharge status. Another limitation of the study is the small sample size, particularly at the tertiary level. A larger prospective study is needed to further support these findings.

In summary, this new reference standard for DCI related to vasospasm has a high overall accuracy for classifying A-SAH patients. The composite criterion method used to incorporate the most relevant clinical and imaging criteria of DCI in a weighted multi-stage hierarchical design is an appropriate classification scheme. The outcomes-based assessment of the new reference standard substantiates its accurate classification of patients with and without DCI according to patient outcomes. Specifically, at the primary level, DSA remains a valuable imaging criteria in defining DCI related to vasospasm given its high accuracy and association with clinically important outcome measures. The future implications of this new reference standard with widespread applicability in this patient population includes its uniform use in research studies investigating imaging and treatment options of DCI. Furthermore, this new reference standard design may be adapted in clinical practice to

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include additional surrogate imaging, such as perfusion techniques using CT and MR imaging to support a diagnosis of DCI related to vasospasm. An external validation process is the next step to determine the generalizability of the new reference standard to other target populations by assessing its precision and reproducibility. Importantly, evaluation of the clinical effectiveness of the new reference standard and its implications for treatment decisions is recommended in the final steps of the validation process.

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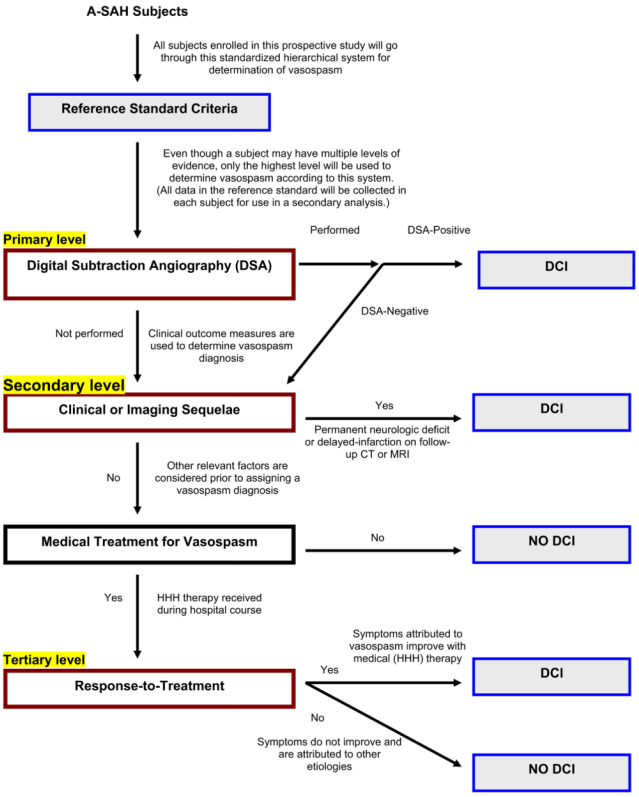

Figure 1.
Flow chart for the new reference standard to determine DCI related to vasospasm.

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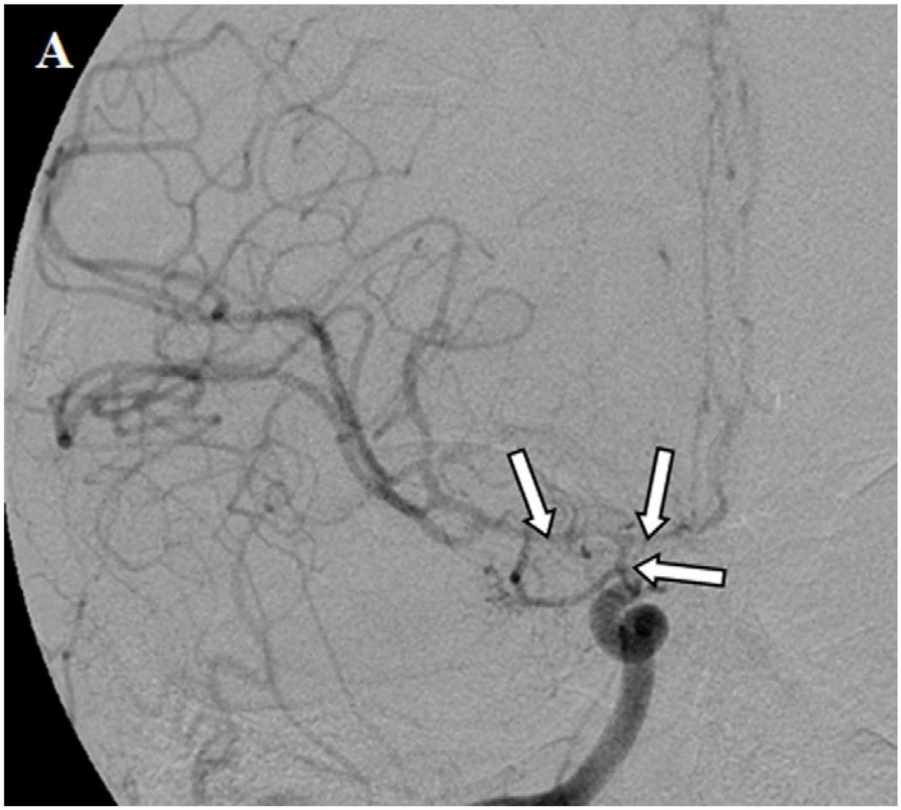

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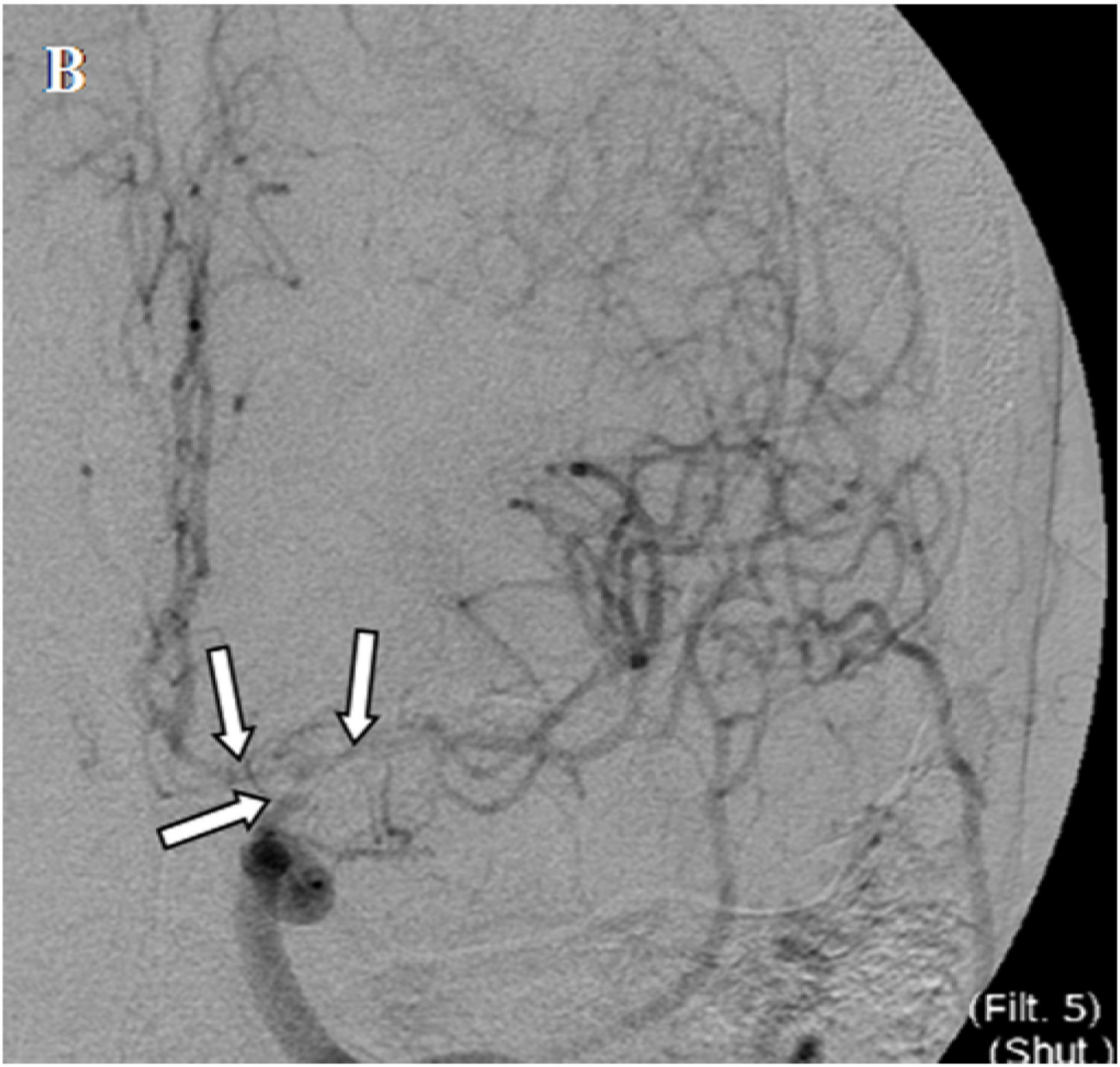

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Figure 2.

35 year-old female presents with aneurysmal subarachnoid hemorrhage from a ruptured right middle cerebral artery bifurcation aneurysm. Patient presented as a Hunt and Hess grade 3 and developed symptoms of DCI on day 7. DSA was performed with anteroposterior views during injection of the right (**A**) and left (**B**) internal carotid arteries. There is severe vasospasm of the internal carotid, anterior and middle cerebral arteries bilaterally (arrows). Patient received treatment with intra-arterial verapamil therapy. Follow-up non-contrast CT (**C**) performed on day 18 shows no evidence of cerebral infarction.

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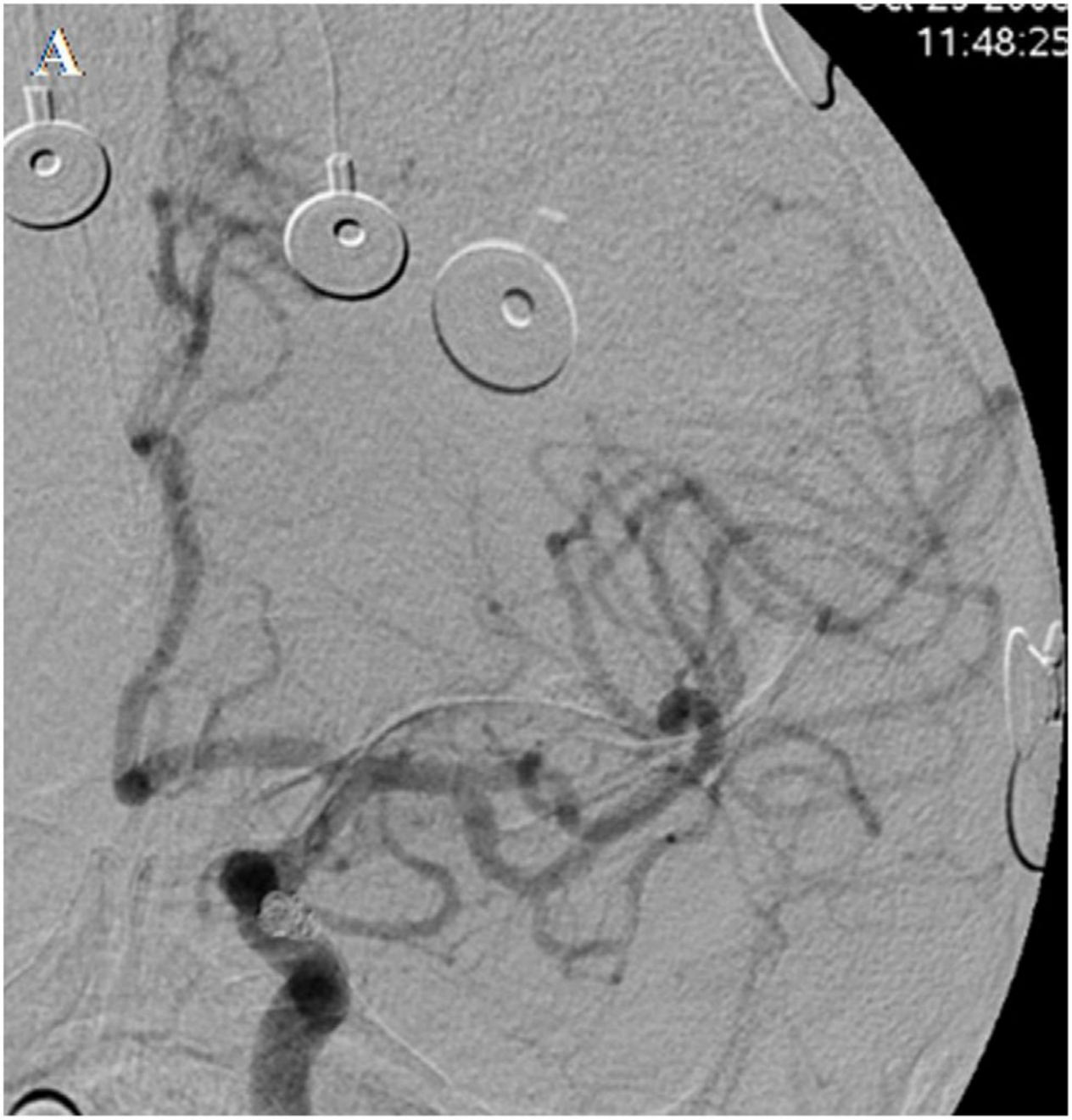

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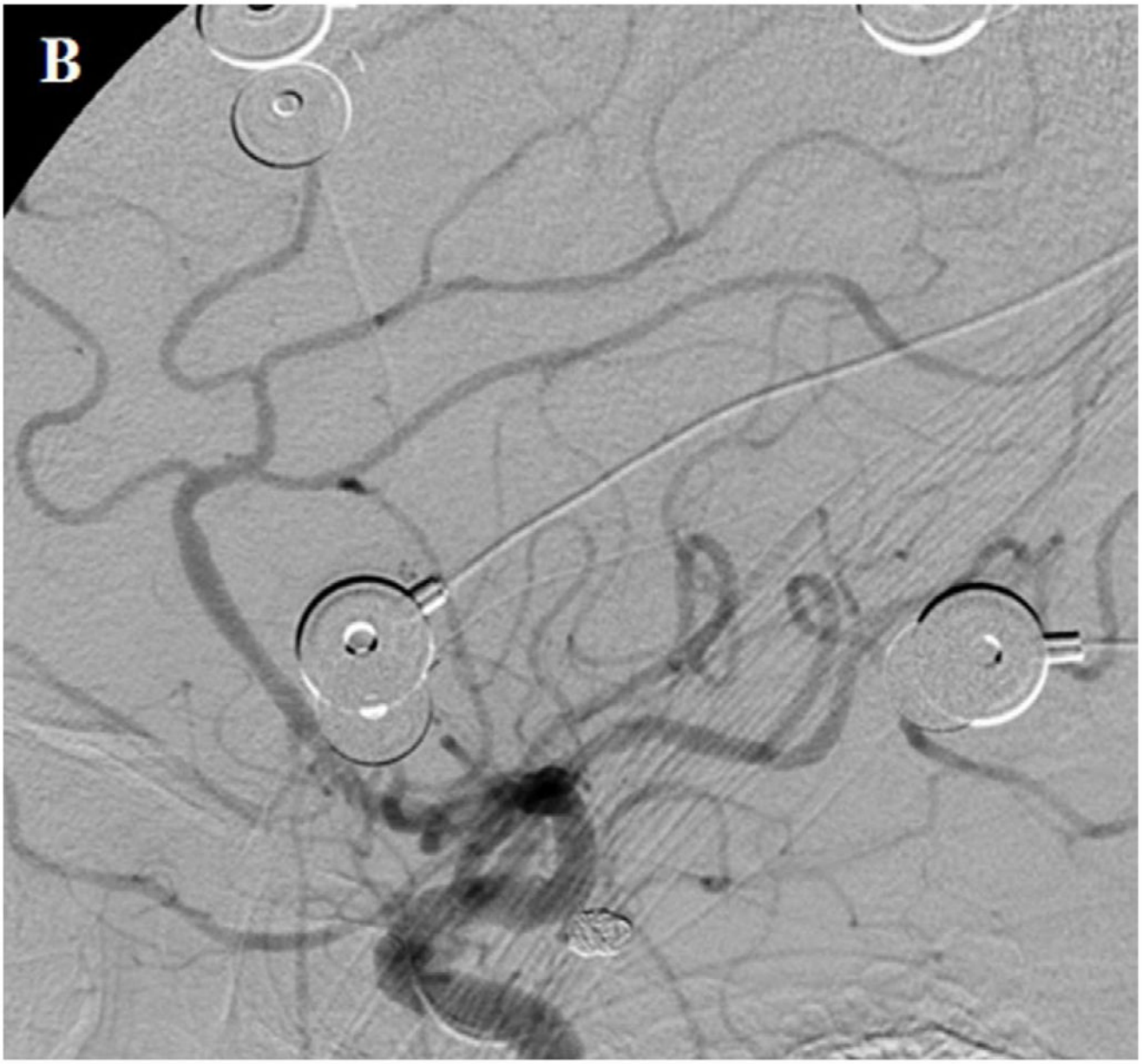

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Figure 3.
66 year-old female presents with aneurysmal subarachnoid hemorrhage from a ruptured left posterior communicating artery aneurysm. Patient presented as Hunt and Hess grade 4 and developed symptoms of vasospasm on day 10. DSA was performed with anteroposterior (**A**) and lateral (**B**) views during injection of the left internal carotid artery. There is no evidence of cerebral vasospasm. Follow-up non-contrast CT (**C**) performed on day 18 demonstrates acute infarction involving the left basal ganglia (arrows).

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Table 1

Clinical and demographic characteristics of the study population

	All (n=137)	DCI (n=81)	No DCI (n=56)
Age (years)			
Median	52	52	52
Range	24–88	28–88	24–83
Gender			
Female	73% (100/137)	69% (56/81)	79% (44/56)
Male	27% (37/137)	31% (25/81)	21% (12/56)
Aneurysm location			
Anterior	93% (127/137)	94% (76/81)	91% (51/56)
Posterior	7% (10/137)	6% (5/81)	9% (5/56)
Aneurysm treatment			
Surgical clipping	54% (74/137)	57% (46/81)	50% (28/56)
Coil embolization	42% (58/137)	38% (31/81)	48% (27/56)
None	4% (5/137)	5% (4/81)	2% (1/56)
Hunt and Hess classification			
Median	2	3	2
Range	1–5	1–5	1–4

Key: DCI – delayed cerebral ischemia

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Table 2

Clinical and imaging outcomes according to the reference standard levels

Reference standard levels	Neurologic deficits	Cerebral infarction by imaging
Primary – classified as DCI (n=57)	44% (25/57)	67% (38/57)
Secondary – classified as DCI (n=11)	64% (7/11)	73% (8/11)
Secondary – classified as no DCI (n=56)	0% (0/56)	0% (0/56)
Tertiary – classified as DCI (n=13)	0% (0/13)	0% (0/13)
TOTAL (n=137)	23% (32/137)	34% (46/137)

Key: DCI – delayed cerebral ischemia

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Table 3

Functional status according to the reference standard levels

Reference standard levels	Functional status returned to baseline		
	Yes	**No**	**Unknown**
Primary – classified as DCI (n=57)	39% (22/57)	37% (21/57)	25% (14/57)
Secondary – classified as DCI (n=11)	55% (6/11)	36% (4/11)	9% (1/11)
Secondary – classified as no DCI (n=56)	77% (43/56)	13% (7/56)	11% (6/56)
Tertiary – classified as DCI (n=13)	85% (11/13)	15% (2/13)	0% (0/13)

Key: DCI – delayed cerebral ischemia

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Table 4

Treatment received according to the reference standard levels

Reference standard levels	Treatment		
	HHH	**IA-therapy**	**None**
Primary – classified as DCI (n=57)	18% (10/57)	34% (46/57)	2% (1/57)
Secondary – classified as DCI (n=11)	64% (7/11)	0% (0/11)	36% (4/11)
Secondary – classified as no DCI (n=56)	0% (0/56)	0% (0/56)	100% (56/56)
Tertiary – classified as DCI (n=13)	100% (13/13)	0% (0/13)	0% (0/13)
TOTAL (n=137)	22% (30/137)	34% (46/137)	45% (61/137)

Key: DCI – delayed cerebral ischemia, HHH - hypertension, hypervolemia and hemodilution, IA-therapy – intra-arterial therapy

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Table 5

Discharge status according to the reference standard levels

Reference standard levels	Discharge status				
	Home	**Acute Rehabilitation**	**Long-term Nursing Facility**	**Death**	**Unknown**
Primary – classified as DCI (n=57)	30% (17/57)	37% (21/57)	14% (8/57)	14% (8/57)	5% (3/57)
Secondary – classified as DCI (n=11)	36% (4/11)	18% (2/11)	18% (2/11)	9% (1/11)	18% (2/11)
Secondary – classified as no DCI (n=56)	68% (38/56)	18% (10/56)	7% (4/56)	2% (1/56)	5% (3/56)
Tertiary – classified as DCI (n=13)	69% (9/13)	23% (3/13)	8% (1/13)	0% (0/13)	0% (0/13)
TOTAL (n=137)	50% (68/137)	26% (36/137)	11% (15/137)	7% (10/137)	6% (8/137)

Key: DCI – delayed cerebral ischemia