PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial Protocol
AUTHORS	Dawley, Troy; Claus, Chad; Tong, Doris; Rajamand, Sina; Sigler, Diana; Bahoura, Matthew; Garmo, Lucas; Soo, Teck; Kelkar, Prashant; Richards, Boyd

VERSION 1 – REVIEW

REVIEWER	Walter van den bergh UMCG, The Netherlands
REVIEW RETURNED	12-Dec-2019

GENERAL COMMENTS	The authors describe a study protocol for a phase II RCT studying the effect and safety of cilostazol as add on to nimodipine for prevention of DCI after aSAH. The study is funded by the Ascension Providence Hospital Institutional research grant, so I assume there has been some review of the study protocol by that institute and therefore major changes to the study methodology are impossible. Nonetheless I have some comments on the protocol. • Why only anterior circulation aneurysms? • Nimodipine has no effect on vasospasm, but it prevents DCI. • In view of the results of the CONSCIOUS studies I would suggest to remove all endpoints regarding vasospasm as it is not relevant for functional outcome. • The primary outcome is defined as low-density areas on CT (or MRI) at one week or one month after SAH. Any low-density areas? I would suggest including only DCI associated infarcts one month after SAH. • Symptomatic vasospasm is defined as the common definition of DCI in presence of vasospasm. Why not use DCI whether or not vasospasm is present (as is the case in one-third of the DCI patients)? • The power calculation is unrealistic. Please recalculate with an effect size of 10% or less. As this is a phase II study superiority does not have to be proven in this study. Also, the incidence of DCI is not 60%. The incidence of vasospasm may be 60% (depending on definition), but is irrelevant. Please recalculate with an incidence of 25-30%. Please bear in mind that the endpoint of a subsequent phase III has to be functional outcome. • As this is a phase II study and thus studying safety, only one interim analyses hallway seems little • In figure 1, please fill in estimated numbers

REVIEWER	Rajat Dhar Washington University in St. Louis
REVIEW RETURNED	14-Mar-2020

GENERAL COMMENTS	This protocol for a randomized comparative trial compares standard-of-care nimodipine in aneurysmal subarachnoid hemorrhage to the combination of nimodipine and cilostazol. Cilostazol has been demonstrated to reduce complications of SAH such as angiographic and symptomatic vasospasm in prior studies but has not been tested in combination with nimodipine (as already used to improve outcomes in North America and Europe). This is a reasonable and well-outlined study protocol. All major aspects of study design are reasonable and described here. A few comments on study design may be warranted: 1. The primary outcome is delayed cerebral ischemia (DCI) which is an important intermediate endpoint (complication). Studies of cilostazol have suggested benefit for this endpoint. However, DCI is defined as "low-density areas on CT or signal changes on MRI performed at 1-week and 1-month." The sensitivity (and implications) of finding a lesion on CT vs. MRI is very different but these two are combined into a single endpoint. Further, it is not clear which patients will receive CT vs. MRI. This may depend on clinical circumstances beyond the control of trial investigators. Nonetheless, if more subjects receive MRI in one group, this could bias ascertainment of "DCI" an lead to imbalances not due to the drug. It would be preferable to use a standard measure (whether CT or MRI defined). Secondly, new lesion is vague - presumably this represents new from time of clipping or coiling to exclude post-surgical lesions. Additionally, does this only include ischemic appearing lesions (delayed infarction) and how is this determined - to exclude other hypodensities - such as those from surgery, ventriculostomy, etc. 2. DCI is generally defined as either clinical deterioration (ischemic deficits) and/or infarction - but in this study they are only applying the latter (infarction). While they will collect data on deterioration (under symptomatic vasospasm) it is unclear why they applied this selective definition of DCI. Secondly, they quote a local rate of DCI at 60% which is extremely high if this excludes peri-procedural and early injury and only focuses on infarcts (see #1). This also impacts the power calculation which is based on this very high rate of baseline DCI. 3. Posterior circulation aneurysms are excluded. Rationale for this is not provided. Although these represent only 10% or less of aSAH, they could have been included.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Walter van den Bergh

• Why only anterior circulation aneurysms?

Posterior circulation aSAH represents only 10% of aSAH. Posterior circulation aSAH are also *known to have lower risk for developing symptomatic vasospasm. We only included anterior circulation aSAH in our trial for the following reasons:*

- *To increase the internal validity of the trial by having a more homogenous study population*
- *To increase the specificity of our results when applied to anterior circulation aSAH which has a significantly higher risk of vasospasm and its complications*
- *With the higher incidence of vasospasm in aSAH, we will need a smaller sample size to reach a well-powered result*

Our rationales were added on page 6, second paragraph, lines 154-6.

*Hirashima Y, Kurimoto M, Hori E, et al. Lower incidence of symptomatic vasospasm after subarachnoid hemorrhage owing to ruptured vertebrobasilar aneurysms. Neurosurgery 2005;**57**:1110–6; discussion 1110-1116.*

• Nimodipine has no effect on vasospasm, but it prevents DCI.

We replaced 'vasospasm' with 'DCI". This change is reflected in our introduction on page 4, line 103.

• In view of the results of the CONSCIOUS studies, I would suggest removing all endpoints regarding vasospasm as it is not relevant for functional outcome.

The CONSCIOUS studies evaluated the use of Clazosentan, an endothelin receptor antagonist, for the prevention of angiographic vasospasm. While it improved the rate of vasospasm, it was found to have no effect on vasospasm-related mortality and morbidity endpoints in CONSCIOUS -1 and no effect on functional outcome in CONSCIOUS-2 and 3.

Please note our responses as follows:

- *The CONSCIOUS study evaluated Claszosentan which has a different pharmacological action than both Nimodipine and Cilostazol.*
- *The evidence associating vasospasm and functional outcomes is still inconclusive.*
- *The PRIMARY outcome of our study is DCI with vasospasm as a SECONDARY outcome. We believe by including both DCI and vasospasm as endpoints, we will contribute more evidence in this area.*

Senbokuya N, Kinouchi H, Kanemaru K, et al. Effects of cilostazol on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a multicenter prospective, randomized, open-label blinded endpoint trial. J Neurosurg 2013;118:121–30. doi:10.3171/2012.9.JNS12492

Budohoski KP, Guilfoyle M, Helmy A, *et al.* The pathophysiology and treatment of delayed cerebral ischaemia following subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 2014;**85**:1343–53. doi:10.1136/jnnp-2014-307711

Francoeur CL, Mayer SA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. *Crit Care Lond Engl* 2016;**20**:277. doi:10.1186/s13054-016-1447-6

• The primary outcome is defined as low-density areas on CT (or MRI) at one week or one month after

SAH. Any low-density areas? I would suggest including only DCI associated infarcts one month after SAH.

The primary outcome is defined as DCI with comparison of 24-hour post-intervention and 1 month CT to evaluate ischemic changes during the vasospasm window. This comparison of ischemic changes exclude changes on CT from intervention (such as ventriculostomy, hematoma if present, etc). We removed the use of MRI as an evaluation method. We are only using CT for the evaluation of ischemic changes.

This was changed to reflect your recommendation on page 7, lines 184-8.

• Symptomatic vasospasm is defined as the common definition of DCI in presence of vasospasm. Why not use DCI whether or not vasospasm is present (as is the case in one-third of the DCI patients)?

Our primary outcome, DCI, is defined radiographically and does not have to correlate with vasospasm. It is in agreement with your comment.

• The power calculation is unrealistic. Please recalculate with an effect size of 10% or less. As this is a phase II study superiority does not have to be proven in this study. Also, the incidence of DCI is not 60%. The incidence of vasospasm may be 60% (depending on definition), but is irrelevant. Please recalculate with an incidence of 25-30%. Please bear in mind that the endpoint of a subsequent phase III has to be a functional outcome.

Incidence of secondary delayed ischemia with clinical deterioration is variable throughout the literature with rates from 18% to 56%. We recalculated the sample size using a baseline DCI incidence of 50% aiming for a relative effect size of 25% and an absolute effect size of 16%. Our total population required is 126 and we would be screening 160 with the goal to randomize 138.

This was changed to reflect your recommendation on page 8, 210-13.

Crowley RW, Medel R, Kassell NF, Dumont AS. New insights into the causes and therapy of cerebral vasospasm following subarachnoid hemorrhage. Drug Discov Today. 2008; 13:254–60. 10.1016/j.drudis.2007.11.010

Abla AA, Wilson DA, Williamson RW, Nakaji P, McDougall CG, Zabramski JM, Albuquerque FC, Spetzler RF. The relationship between ruptured aneurysm location, subarachnoid hemorrhage clot thickness, and incidence of radiographic or symptomatic vasospasm in patients enrolled in a prospective randomized controlled trial. J Neurosurg. 2014; 120:391–97. 10.3171/2013.10.JNS13419

• As this is a phase II study and thus studying safety, only one interim analyses hallway seems little

Thank you for the suggestion. We agree that we can perform more interim analyses to ensure safety and efficacy. We have revised our protocol to include interim analyses every quarter.

This was changed to reflect your recommendation on page 9, lines 254-6.

• In figure 1, please fill in estimated numbers

Figure 1 was filled in to represent estimated numbers.

Reviewer: 2
Reviewer Name
Rajat Dhar

1. The primary outcome is delayed cerebral ischemia (DCI) which is an important intermediate endpoint (complication). Studies of cilostazol have suggested benefits for this endpoint. However, DCI is defined as "low-density areas on CT or signal changes on MRI performed at 1-week and 1-month." The sensitivity (and implications) of finding a lesion on CT vs. MRI is very different but these two are combined into a single endpoint. Further, it is not clear which patients will receive CT vs. MRI. This may depend on clinical circumstances beyond the control of trial investigators. Nonetheless, if more subjects receive MRI in one group, this could bias ascertainment of "DCI" and lead to imbalances not due to the drug. It would be preferable to use a standard measure (whether CT or MRI defined). Secondly, ‘new lesion’ is vague - presumably this represents new from time of clipping or coiling to exclude post-surgical lesions. Additionally, does this only include ischemic appearing lesions (delayed infarction) and how is this determined - to exclude other hypodensities - such as those from surgery, ventriculostomy, etc.

We removed the use of MRI as an evaluation method. We are only using CT for the evaluation of ischemic changes.

We also updated our description to reflect the evaluation of ischemic changes as compared to the 24-hour post-intervention CT in order to exclude patients with imaging changes due to intervention (such as ventriculostomy) or initial hemorrhage (such as hematoma, if present).

This was changed to reflect your recommendation on page 7, lines 184-9.

2. DCI is generally defined as either clinical deterioration (ischemic deficits) and/or infarction - but in this study, they are only applying the latter (infarction). While they will collect data on deterioration (under symptomatic vasospasm) it is unclear why they applied this selective definition of DCI. Secondly, they quote a local rate of DCI at 60% which is extremely high if this excludes peri-procedural and early injury and only focuses on infarcts (see #1). This also impacts the power calculation which is based on this very high rate of baseline DCI.

Although previous definitions of DCI include both clinical and radiographic features, the authors defined DCI based on an objective radiographic outcome with high interobserver agreement as suggested by Vergouwen et al. It is suggested that clinical deterioration caused by DCI should not be more than a secondary outcome as done in our study.

Vergouwen MD., et al. 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. Stroke. 2010;41:2391-2395

Incidence of secondary delayed ischemia with clinical deterioration is variable throughout the literature with rates from 18% to 56%. We recalculated the sample size using a baseline DCI

incidence of 50% aiming for a relative effect size of 25% and an absolute effect size of 16%. Our total population required is 126 and we would be screening 160 with the goal to randomize 138.

This was changed to reflect your recommendation on page 8, 210-13.

Crowley RW, Medel R, Kassell NF, Dumont AS. New insights into the causes and therapy of cerebral vasospasm following subarachnoid hemorrhage. Drug Discov Today. 2008; 13:254–60. 10.1016/j.drudis.2007.11.010

Abla AA, Wilson DA, Williamson RW, Nakaji P, McDougall CG, Zabramski JM, Albuquerque FC, Spetzler RF. The relationship between ruptured aneurysm location, subarachnoid hemorrhage clot thickness, and incidence of radiographic or symptomatic vasospasm in patients enrolled in a prospective randomized controlled trial. J Neurosurg. 2014; 120:391–97. 10.3171/2013.10.JNS13419

3. Posterior circulation aneurysms are excluded. Rationale for this is not provided. Although these represent only 10% or less of aSAH, they could have been included.

Posterior circulation aSAH represents only 10% of aSAH. Posterior circulation aSAH are also *known to have lower risk for developing symptomatic vasospasm. We only included anterior circulation aSAH in our trial for the following reasons:*

- *To increase the internal validity of the trial by having a more homogenous study population*
- *To increase the specificity of our results when applied to anterior circulation aSAH which has a significantly higher risk of vasospasm and its complications*
- *With the higher incidence of vasospasm in aSAH, we will need a smaller sample size to reach a well-powered result*

Our rationales were added on page 6, second paragraph, lines 154-6.

*Hirashima Y, Kurimoto M, Hori E, et al. Lower incidence of symptomatic vasospasm after subarachnoid hemorrhage owing to ruptured vertebrobasilar aneurysms. Neurosurgery 2005;**57**:1110–6; discussion 1110-1116.*

VERSION 2 – REVIEW

REVIEWER	Walter M. van den Bergh UMCG The Netherlands
REVIEW RETURNED	15-Apr-2020

GENERAL COMMENTS	Assuming a baseline DCI incidence of 50% is unprecedented with this definition of DCI (new ischemic lesion) and should be 20-25%. Furthermore, assuming a relative effect size of 25% is also unrealistic. With this power calculation there is no doubt this trial will have a negative results.

REVIEWER	Rajat Dhar Washington University in St. Loius
REVIEW RETURNED	The authors have responded to the feedback. There are no significant outstanding issues.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Walter van den Bergh

Assuming a baseline DCI incidence of 50% is unprecedented with this definition of DCI (new ischemic lesion) and should be 20-25%. Furthermore, assuming a relative effect size of 25% is also unrealistic. With this power calculation there is no doubt this trial will have a negative results.

In the initial literature search, we found that the historical incidence of secondary delayed ischemia with clinical deterioration after endovascular intervention in aSAH is variable with rates ranging from 18% to 56%. Therefore, we conducted a feasibility study in 2018 to determine the institutional rate of symptomatic Cerebral Vasospasm (sVS) and Delayed Cerebral Ischemia (DCI) post acute Aneurysmal Subarachnoid Hemorrhage (aSAH) - see below. We found that our institutional rate of DCI was 59.4%. As a result of our feasibility study, we used a DCI incidence of 50% as a baseline to calculate our sample size.

Title: Institutional Rate of Symptomatic Cerebral Vasospasm (sVS) and Delayed Cerebral Ischemia (DCI) Post Acute Aneurysmal Subarachnoid Hemorrhage (aSAH): Feasibility Study of 112 Consecutive Patients
Final Abstract Number: 506

Crowley RW, Medel R, Kassell NF, Dumont AS. New insights into the causes and therapy of cerebral vasospasm following subarachnoid hemorrhage. Drug Discov Today. 2008; 13:254–60. 10.1016/j.drudis.2007.11.010

Abla AA, Wilson DA, Williamson RW, Nakaji P, McDougall CG,Zabramski JM, Albuquerque FC, Spetzler RF. The relationship between ruptured aneurysm location, subarachnoid hemorrhage clot thickness, and incidence of radiographic or symptomatic vasospasm in patients enrolled in a prospective randomized controlled trial. J Neurosurg. 2014; 120:391–97.10.3171/2013.10.JNS13419

Regarding the effect size, we have recalculated the sample size with a more conservative relative effect size of 15%. Assuming a baseline incidence rate of 0.5, with a power of 0.8 and alpha of 0.05, the new sample size is 349. In anticipation of any unforeseen events and those who are lost to follow up, we will enroll 390 patients. This change was made on page 8, line 205.

VERSION 3 – REVIEW

REVIEWER	Walter M. van den Bergh UMCG The Netherlands
REVIEW RETURNED	16-Jun-2020

GENERAL COMMENTS	I can't imagine that in the author's institution the incidence of new ischemic lesions caused by DCI is over 50%. That would be the largest incidence worldwide and even if true, the study can't be repeated in other centers with a lower incidence.

VERSION 3 – AUTHOR RESPONSE

Replies to Reviewer 1:

I can't imagine that in the author's institution, the incidence of new ischemic lesions caused by DCI is over 50%. That would be the largest incidence worldwide, and even if true, the study can't be repeated in other centers with a lower incidence.

In our last reply, we stated, 'Incidence of secondary delayed ischemia with clinical deterioration is variable throughout the literature with rates from 18% to 56%.'. The institutional rate of (50%) we used to calculate our sample size is at the higher end of the range. To further study the prevailing reported DCI rate, we have reviewed the **Saber (2018)** meta-analysis and the **Shan (2019)** meta-analysis.
In both meta-analyses, we used the forest plots data to present the DCI incidence in the control group and the relative reduction of DCI incidence with the use of Cilostazol. The control DCI incidence ranged from 10.8% to 38.2%, with an average of around 25%. The relative reduction of DCI with the use of Cilostazol was about 50%.

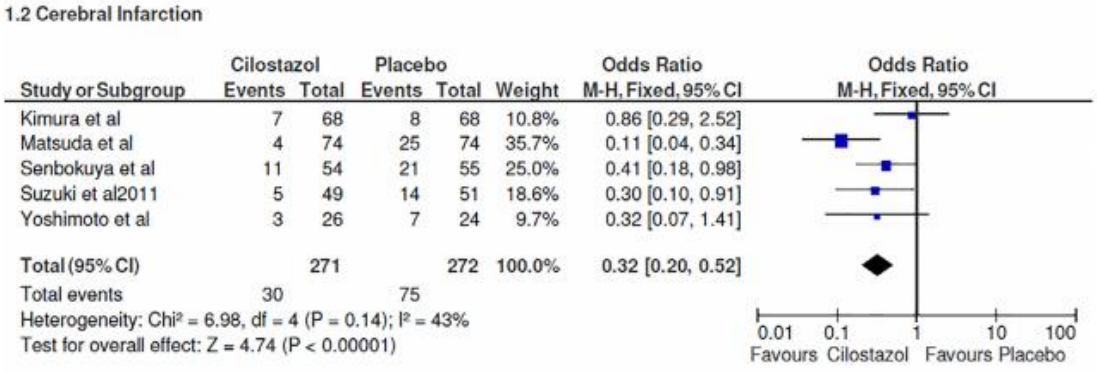
Efficacy of Cilostazol in Prevention of Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Meta-Analysis

Saber H, Desai A, Palla M, Mohamed W, Seraji-Bozorgzad N, Ibrahim M. Efficacy of Cilostazol in Prevention of Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Meta-Analysis. *J Stroke Cerebrovasc Dis*. 2018;27(11):2979-2985. doi:10.1016/j.jstrokecerebrovasdis.2018.06.027

Table 1. Saber - DCI Incidences and Relative Reduction by the Cilostazol Intervention

Reference table in Saber

	Cilostazol			Control				
	Events	Total	%	Events	Total	%	% Absolute Reduction	**% Relative Reduction**
Kimura et al	7	68	10.3%	8	68	11.8%	1.5%	12.8%
Matsuda et al	4	74	5.4%	25	74	33.8%	28.4%	84.0%
Senbokuya et al	11	54	20.4%	21	55	38.2%	17.8%	46.6%
Suzuki et al	5	49	10.2%	14	51	27.5%	17.3%	62.9%
Yoshimoto et al	3	26	11.5%	7	24	29.2%	17.7%	60.6%
Average			**11.6%**			**28.1%**		**53.4%**



Effectiveness and feasibility of Cilostazol in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis

Shan T, Zhang T, Qian W, et al. Effectiveness and feasibility of Cilostazol in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *J Neurol*. 2020;267(6):1577-1584. doi:10.1007/s00415-019-09198-z

Table 2. Shan - DCI Incidences and Relative Reduction by the Cilostazol Intervention

	Cilostazol			Control				
	Events	Total	%	Events	Total	%	% Absolute Reduction	**% Relative Reduction**
Randomized Control Study								
Matsuda 2016	4	74	5.4%	8	74	10.8%	5.4%	50.0%
Senbokuya 2013	6	54	11.1%	16	55	29.1%	18.0%	61.9%

Suzuki 2011	5	49	10.2%	14	51	27.5%	17.3%	62.9%
Average			**8.9%**			**22.5%**		**58.3%**
Observational Study								
Kimura 2015	7	62	11.3%	25	68	36.8%	15.5%	69.3%
Nakatsuka 2016 P	3	33	9.1%	1	5	20.0%	10.9%	16.5%
Nakatsuka 2016 R	8	51	15.7%	10	36	27.8%	12.1%	43.5%
Yoshimoto 2009	3	26	11.5%	7	24	29.2%	17.7%	60.6%
Average			**11.9%**			**28.5%**		**47.5%**

Reference table in Shan

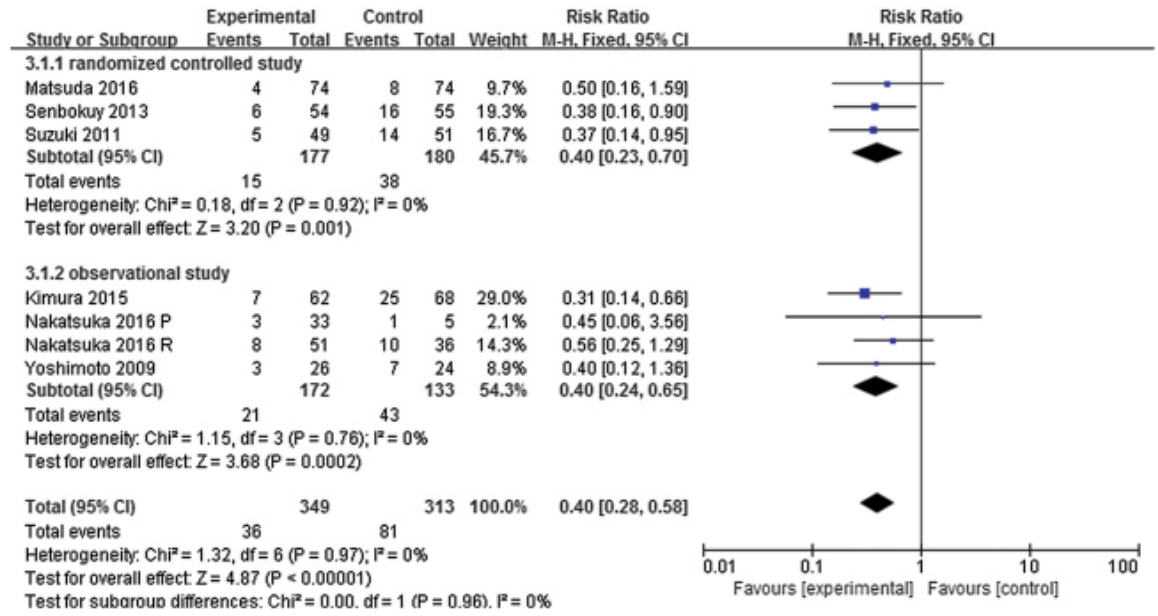
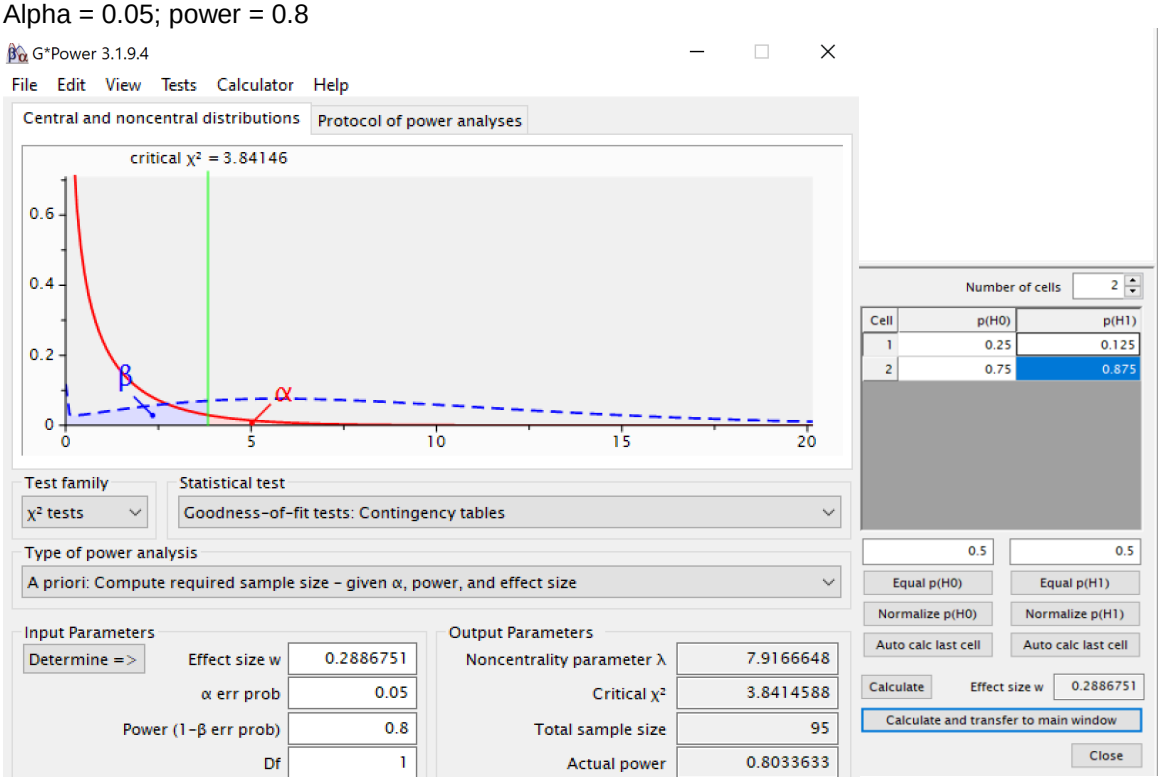


Fig. 4 Forest plot of studies researched on the event of new cerebral infarction with risk ratio and 95% confidence interval

Using the above new data, we repeated our sample size calculation.
Baseline DCI – 0.25; expected DCI with the use of Cilostazol – 0.125
Effect size w = 0.29
Alpha = 0.05; power = 0.8



Our estimated sample size will be 100. In anticipation of any unforeseen events and those who are lost to follow up, we will enroll 120 to randomize 100 patients in total.

References for Table One

Kimura H, Okamura Y, Chiba Y, et al. Cilostazol Administration with Combination Enteral and Parenteral Nutrition Therapy Remarkably Improves Outcome After Subarachnoid Hemorrhage. *Neurovascular Events After Subarachnoid Hemorrhage*. Springer International Publishing; 2015:147-152. doi:10.1007/978-3-319-04981-6_25

Matsuda N, Naraoka M, Ohkuma H, et al. Effect of Cilostazol on Cerebral Vasospasm and Outcome in Patients with Aneurysmal Subarachnoid Hemorrhage: A Randomized, Double-Blind, Placebo-Controlled Trial. Cerebrovasc Dis 2016;42:97-105.

Senbokuya N, Kinouchi H, Kanemaru K, et al. Effects of Cilostazol on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a multicenter prospective, randomized, open-label blinded end point trial. J Neurosurg 2013;118:121-130.

Suzuki S, Sayama T, Nakamura T, et al. Cilostazol Improves Outcome after Subarachnoid Hemorrhage: A Preliminary Report. Cerebrovasc Dis 2011;32:89-93.

Yoshimoto T, Shirasaka T, Fujimoto S, et al. Cilostazol May Prevent Cerebral Vasospasm Following Subarachnoid Hemorrhage. *Neurol Med Chir (Tokyo)*. 2009;49(6):235-241. doi:10.2176/nmc.49.235

References for Table Two

Matsuda N, Naraoka M, Ohkuma H, Shimamura N, Ito K, Asano K, Hasegawa S, Takemura A (2016) Effect of Cilostazol on cerebral vasospasm and outcome in patients with aneurysmal subarachnoid hemorrhage: a randomized, double-blind, placebo-controlled trial. Cerebrovasc Dis 42:97–105.

Suzuki S, Sayama T, Nakamura T, Nishimura H, Ohta M, Inoue T, Mannoji H, Takeshita I (2011) Cilostazol improves outcome after subarachnoid hemorrhage: a preliminary report. Cerebrovasc Dis 32:89–93

Senbokuya N, Kinouchi H, Kanemaru K, et al. Effects of Cilostazol on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a multicenter prospective, randomized, open-label blinded end point trial. J Neurosurg 2013;118:121-130.

Kimura H, Okamura Y, Chiba Y, Shigeru M, Ishii T, Hori T, Shiomi R, Yamamoto Y, Fujimoto Y, Maeyama M, Kohmura E (2015) Cilostazol administration with combination enteral and parenteral nutrition therapy remarkably improves outcome after subarachnoid hemorrhage. Acta Neurochir Suppl 120:147–152.

Nakatsuka Y, Kawakita F, Yasuda R, Umeda Y, Toma N, Sakaida H, Suzuki H (2016) Preventive effects of Cilostazol against the development of shunt-dependent hydrocephalus after subarachnoid hemorrhage. J Neurosurg 127:319–326

Yoshimoto T, Shirasaka T, Fujimoto S, Yoshidumi T, Yamauchi T, Tokuda K, Kaneko S, Kashiwaba T (2009) Cilostazol may prevent cerebral vasospasm following subarachnoid hemorrhage. Neurol Med Chir 49:235–240.