Author's response to reviews

Title: Final 2 year results of the Vascular Imaging of acute Stroke for Identifying predictors of clinical Outcome and recurrent ischemic eveNts (VISION) study.

Authors:

Shelagh B Coutts (scoutts@ucalgary.ca)
Michael D Hill (hillmd@ucalgary.ca)
Misha Eliasziw (eliasziw@ucalgary.ca)
Karyn Fischer (Karyn.Fischer@CalgaryHealthRegion.ca)
Andrew M Demchuk (ademchuk@ucalgary.ca)

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Author's response to reviews: see over
Reviewer 1:

The paper is well written and the discussion is clear and concise. However, this study has two major limitations that should be emphasized in the discussion: 1. Extracranial MR angiography was only possible approximately half of the way through this study. 2. The subgroup of patients with moderate/severe stroke was rather small (n=105). It is possible that the small sample size is the reason for finding no MRI-predictors in this subgroup.

The reviewer is correct. Both of these points have been added as limitations to the discussion.

3. In my opinion, the rate of stroke progression is 0% in TIA patients by definition. For this reason, I suggest to exclude TIA patients for all analyses of stroke progression.

We disagree with the reviewer as the definition of TIA is made at 24 hours if the patient is still neurologically intact. This paper is designed to aid assessment of patients when they first present in the emergency room, not after waiting for 24 hours to see if the patient deteriorates.

4. The authors should give more details on the definition of standard acute and secondary prevention treatments for stroke at the discretion of the treating physician, e.g. was early carotid endarterectomy or stenting performed in patients with symptomatic carotid stenosis.

All patients were treated as directed by the treating physician. The exact treatment regime was not collected for each patient. However this is tertiary referral stroke centre where patients would routinely be treated with antiplatelet agents, statin, antihypertensives. More than 95% of patients with symptomatic severe carotid stenosis are treated within 2 weeks of symptom onset. This has been added to the methods section as per the reviewers suggestion.

Minor comments and questions:

1. The authors should describe how they defined leukoaraiosis.

Leukoaraiosis was simply defined as the presence of any T2 or FLAIR white matter lesion that was not related to the acute infarct. The severity was not rated any further than that. This has been added to the methods section.

2. In my opinion the definition of mismatch MTT>DWI should be more refined. I suggest to define subgroups with small and large mismatch.

We have previously shown that the visual estimation of percentage mismatch is not reliable and so this is why we have chosen to simply define this as present or absent (Stroke. 2003 Jul;34(7):1681-3. Epub 2003 Jun 12). Without automated measurement of lesion volumes this is not possible and would not be available for use in most institutions. This is why we used this very simple definition.
3. Did the authors assess intracranial vessel status before thrombolysis?  
The timing of thrombolysis relative to vessel imaging was variable. Frequently the tPA was infusing at the time of MRI, but this information was not recorded as part of the study.

4. Consensus definition for minor stroke is lacking (Stroke. 2010;41:661.)  
In this study NISSH 0 to 5 was used for definition of minor stroke. Why did the authors use this definition?  
We agree with the reviewer that this is arbitrary. The decision to split the patients in this manner was made a priori. A test for interaction completed prior to completing the analysis and showed there was indeed an interaction based on this grouping of NIHSS. Given that this was our original decision we have elected not to look at other cut points.

5. The authors should explain why p-value for DWI lesions in Table 2 are not significant unlike in the abstract and results. Did the authors test DWI lesions versus no DWI-lesions without indicating this result in Table 2?  
The results presented are a test for interaction. This type of statistical test is notoriously underpowered and most researchers would accept a p value of 0.1 as representing statistical significance with this test. This is described in the methods section. Of more relevance than the p value is the magnitude of the differences in the hazard ratios. We have however changed this table to show simply none versus any DWI lesion as per the suggestions from both reviewers.

6. Why did the authors not assess stroke etiology according to TOAST criteria?  
We do have the information on TOAST criteria available, but have chosen not to present it because the TOAST classification is made after all investigations have been completed including prolonged cardiac monitoring. Thus, this information is not readily available at the time of treatment decision-making. The information presented in this manuscript was designed to include only things that would be available in the first few hours of emergency assessment of the patient.

Reviewer 2:

The main weaknesses of this study are:

1) The lack of statistical power to assess all of the outcomes that have occurred with low frequency (<10%) and therefore the potential for unstable models and random effects. This is further compounded by the necessity to stratify prognosis rather arbitrarily according to baseline NIHSS score into ‘mild’ and ‘moderate’ severe stroke at baseline. I would rather have seen this kept as a continuous measure and adjusted MRI and other imaging data in analyses.

We agree with the reviewer that this is arbitrary. However the decision to
split the patients in this manner was made a priori. A test for interaction was also completed prior to the analysis and showed there was indeed an interaction based on this grouping of NIHSS. Given that this was our original decision we have elected not to look at other cut points. Moreover, the NIHSS is an ordinal scale and therefore the incremental values cannot be assumed to be equally spaced as is required for a continuous measure.

2) Another problem is the lack of standardization of the definition of ‘progression’ over recurrent stroke, which the authors acknowledge, but at least this could have been kept to less than 28 days from onset in which the most controversy exists.

Although the definition that we have used to not have a threshold at which the event cannot be called progression in it, this is implicit within the use of this definition. In this study all progression events were in the first 72 hours and so the use of 28 days is not necessary.

3) Further, as repeat CT or MRI was only undertaken in those with recurrent symptoms, there is no way of assessing new ischaemic lesions that are asymptomatic but still clinically important from a prognostic viewpoint.

As described above this study was designed to look at factors available in the emergency room and how they predict recurrent events. Repeat imaging although of interest would not help with this question. This has been clarified in the introduction.

4) There are very wide confidence intervals around the predictor point estimates, again due to lack of statistical power, which considerably limits the utility and reliability of the results.

We agree that there are limitations in the conclusions that can be drawn however this is the first study of its type and the results are hypothesis generating.

5) Given the lack of interaction between ‘solitary’ and ‘multiple’ DWI lesions, I wonder if it would have been better to have ‘any’ versus ‘none’ DMI lesions.

We agree with the reviewers comments and have changed this in the analysis.

6) It is difficult to interpret the meaning of ‘symptomatic’ ICA stenosis (>50%) when other vascular lesions have not been referred to in the same way.

We chose to look particularly at ICA stenosis greater than 50%, as this is a
condition that a specific treatment exists for (ie carotid revascularization). It is less clear what a 50% vertebral artery stenosis or another arterial lesion means in terms of outcome or treatment. This result has changed our practice in this institution as we are much more aggressive at revascularizing moderate carotid stenosis than we were prior to this work.

• Major Compulsory Revisions The major issues relate to statistical power and interpretation. Given that exposure times vary according to being alive to develop recurrence and progression, it would be better to combine death with these outcomes to 28 days rather than 2 years. The outcome predictors in the first 28 days are likely to be different to those over 2 years.

The power for time-to-event analyses is ‘driven’ by number of events and therefore having longer follow-up for recurrence and death is advantageous. We did not combine outcome events as we specifically wanted to illustrate that different factors predict different outcomes. In regards to statistical power, it is quite remarkable that even with a moderate sample size of 334 patients, we were able to detect clinically important outcome modifications by baseline stroke severity, and therefore we feel we had sufficient power to accomplish our aims of the study.

• Minor Essential Revisions There are minor spelling mistake ‘vone’ instead of ‘none’ in Table 1.

This has been changed.