SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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VERSION 2.0 (DECEMBER 2014)

Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Relevance of animal models to human cerebral amyloid angiopathy and microbleeds (preliminary title)	
2.	Authors (names, affiliations, contributions)	L. Jäkel [1,2]; D.J. Werring [3]; W. E. van Nostrand [4]; M.M. Verbeek [1,2] [1] Department of Neurology and Donders Institute for Brain, Cognition and Behaviour; Radboud University Medical Center [2] Department of Laboratory Medicine; Radboud University Medical Center [3] UCL London [4] Stony Brook University	
3.	Other contributors (names, affiliations, contributions)	-	
4.	Contact person + e-mail address	M.M. Verbeek (Marcel.Verbeek@radboudumc.nl)	
5.	Funding sources/sponsors	-	
6.	Conflicts of interest	-	
7.	Date and location of protocol registration		
8.	Registration number (if applicable)		
9.	Stage of review at time of registration	Planned	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Cerebral amyloid angiopathy (CAA) is the accumulation of amyloid in cerebral blood vessels, which poses a significant risk factor for hemorrhagic stroke. It occurs as a sporadic disorder in elderly, but also in ±80% of Alzheimer's disease patients and as a rare genetic condition. The pathogenesis of CAA is yet poorly understood and there are no available interventions. Over the past decades, several animal models have been developed to study CAA. We aim to provide the first systematic review about available animal models of CAA.	
	Research question		
11.	Specify the disease/health problem of interest	Cerebral Amyloid Angiopathy (CAA)	
12.	Specify the population/species	All non-human animals	

	studied		
13.	Specify the intervention/exposure	Any (spontaneous or induced development of CAA).	
14.	Specify the control population	All non-human animals	
15.	Specify the outcome measures	Any	
16.	State your research question (based on items 11-15)	Which animal models for CAA are available? Subquestion: What are the strengths and weaknesses of these models? (Anatomical and physiological features → relevance to human CAA)?	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	X MEDLINE via PubMed X EMBASE	
18.	Define electronic search strategies (*e.g.* use the step by step search guide[15] and animal search filters[20, 21])	Provided below.	
19.	Identify other sources for study identification	X Reference lists of included studies X Reference lists of relevant reviews	
20.	Define search strategy for these other sources	Available reviews will be screened full-text. If models are mentioned that are not otherwise included, the cited papers will be retrieved and analyzed.	
	Study selection		
21.	Define screening phases (e.g. pre-screening based on title/abstract, full text screening, both)	1. Exclusion of duplicate papers 2. Examination of titles for relevance 3. Screening of abstracts for relevance 4. Assessment of full papers for relevance	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	1. Exclusion of duplicate papers → 1 reviewer 2. Examination of titles for relevance → 1 reviewer 3. Screening of abstracts for relevance → 2 reviewers 4. Assessment of full papers for relevance → 2 reviewers	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: • Publications are included if they describe an animal model that displays CAA Exclusion criteria: • Not in English • Journal not peer-reviewed • Clinical studies, reviews, book chapters etc • Non-related animal disease models • Non-animal research • Articles citing the use of previously described	

		model that does not contain new information.	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: any animal Exclusion criteria: non-animal	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: NA Exclusion criteria: NA	
26.	Outcome measures	Inclusion criteria: Any Exclusion criteria: -	
27.	Language restrictions	Inclusion criteria: English language Exclusion criteria: Non-English language	
28.	Publication date restrictions	Inclusion criteria: Any Exclusion criteria: Non	
29.	Other	Inclusion criteria: - Exclusion criteria: -	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase 1: • Duplicate papers Selection phase 2 (title): • Not in English • Non-animal research • Clinical studies, reviews, book chapter, conference abstract etc • Non-related animal disease models Selection phase 3 (abstract): • Not in English • Non-animal research • Clinical studies, reviews, book chapter, conference abstract etc • Non-related animal disease models • Articles citing the use of previously described model that does not contain new information. Selection phase 4 (full-text): • Non-animal research • Clinical studies, reviews, book chapter, conference abstract etc • Non-related animal disease models • Journal not peer-reviewed • Articles citing the use of previously described model that does not contain new information.	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	• 1st author • Year • Title • Journal	
32.	Study design characteristics (*e.g.* experimental groups, number of	• Total number of animals • Quantification CAA (method: histology/MRI/....)	

	animals)	and quantification methods.	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	• Animal species • Animal strain • Animal supplier • Animal age • Animal sex • Animal weight • Methods to induce CAA • Time between induction until (full-blown) development CAA	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	NA	
35.	Outcome measures	- Is CAA primary or secondary (e.g. secondary to AD) - Relevance to human CAA: • Composition of CAA ○ Amyloid-β peptides ○ Other proteins/molecules • Location/morphology of CAA ○ Anatomic location in brain ○ Blood vessel size (capillary, arteriole, artery, or vein) ○ Anatomic site within blood vessel: restricted to vessel wall or penetrating surrounding parenchyma • Inflammation characteristics (perivascular activation of microglia and astrocytes) • MRI characteristics (microbleeds, macrobleeds, white matter hypointensities)	
36.	Other (*e.g.* drop-outs)	• Mortality and cause of death • Comorbidity	
	Assessment risk of bias (internal validity) or study quality		
37.	Specify (a) the number of reviewers assessing the risk of bias/study quality in each study and (b) how discrepancies will be resolved	1. A random sample of at least 5% of the included papers will be checked by an independent observer for assessing the reporting of study quality.	
38.	Define criteria to assess (a) the internal validity of included studies (*e.g.* selection, performance, detection and attrition bias) and/or (b) other study quality measures (*e.g.* reporting quality, power)	□By use of SYRCLE's Risk of Bias tool[4] □ By use of SYRCLE's Risk of Bias tool, adapted as follows: □By use of CAMARADES' study quality checklist, e.g [22] □By use of CAMARADES' study quality checklist, adapted as follows: X Other criteria, namely: Animal model characteristics will be tabulated. As this is a descriptive model-focussed review, no formal assessment of risk of bias will be performed.	

	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	Qualitative measures, as described 31-36.	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	NA	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	1. A random sample of at least 5% of the included papers will be checked by an independent observer for accuracy of data-extraction	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	A descriptive overview of the various animal models will be provided. Models will be clustered by species, strain and induction method.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	NA	
	If a meta-analysis seems feasible/sensible, specify (for each outcome measure):		
44.	The effect measure to be used (*e.g.* mean difference, standardized mean difference, risk ratio, odds ratio)	NA	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	NA	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	NA	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	NA	
48.	Any sensitivity analyses you propose to perform	NA	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	NA	
50.	The method for assessment of publication bias	NA	

Final approval by (names, affiliations): Date:

Search strategies:

PUBMED:

("Cerebral Amyloid Angiopathy"[Mesh] OR CAA[tiab]OR congophilic angiopathy[tiab] OR congophilic angiopathies[tiab] OR cerebral amyloid angiopathy[tiab] OR cerebral amyloid angiopathies[tiab] OR vascular amyloid[tiab] OR vascular amyloidosis[tiab] OR cerebral vascular amyloid[tiab] OR cerebral vascular amyloidosis[tiab] OR vascular amyloid pathology[tiab] OR vascular amyloid pathologies[tiab] OR vascular amyloid-beta pathology[tiab] OR vascular amyloid-beta pathologies [tiab] OR cerebral hemorrhage with amyloid[tiab] OR cerebral hemorrhages with amyloid[tiab]) AND (Model*[tiab]) AND Syrcle animal filter for Pubmed[1]

EMBASE

(Vascular amyloidosis/ OR CAA.ti,ab,kw.OR congophilic angiopathy.ti,ab,kw. OR congophilic angiopathies.ti,ab,kw. OR cerebral amyloid angiopathy.ti,ab,kw. OR cerebral amyloid angiopathies.ti,ab,kw. OR vascular amyloid.ti,ab,kw. OR vascular amyloidosis.ti,ab,kw. OR cerebral vascular amyloid.ti,ab,kw. OR cerebral vascular amyloidosis.ti,ab,kw. OR vascular amyloid pathology.ti,ab,kw. OR vascular amyloid pathologies.ti,ab,kw. OR vascular amyloid-beta pathology.ti,ab,kw. OR vascular amyloid-beta pathologies.ti,ab,kw. OR cerebral hemorrhage with amyloid.ti,ab,kw. OR cerebral hemorrhages with amyloid.ti,ab,kw.) AND (Model*.ti,ab,kw.) AND Syrcle animal filter for EMBASE[2]

References

1 Hooijmans, C. R., Tillema, A., Leenaars, M. & Ritskes-Hoitinga, M. Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed. *Laboratory animals* **44**, 170-175, doi:10.1258/la.2010.009117 (2010).

2 de Vries, R. B., Hooijmans, C. R., Tillema, A., Leenaars, M. & Ritskes-Hoitinga, M. Updated version of the Embase search filter for animal studies. *Laboratory animals* **48**, 88, doi:10.1177/0023677213494374 (2014).