ORIGINAL RESEARCH

Systematic Review of Methods for Assessing Leptomeningeal Collateral Flow

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BACKGROUND AND PURPOSE: The importance of LMF in the outcome after acute ischemic stroke is increasingly recognized, but imaging presents a wide range of options for identification of collaterals and there is no single system for grading collateral flow. The aim of this study was to systematically review the literature on the available methods for measuring LMF adequacy.

MATERIALS AND METHODS: We performed a systematic review of Ovid, MEDLINE, and Embase databases for studies in which flow in the leptomeningeal collateral vessels was evaluated. Imaging technique, grading scale, and reliability assessment for collateral flow measurement were recorded.

RESULTS: We found 81 publications describing 63 methods for grading collateral flow on the basis of conventional angiography (n = 41), CT (n = 7), MR imaging (n = 9), and transcranial Doppler (n = 6). Inter- and/or intraobserver agreement was assessed in only 8 publications.

CONCLUSIONS: There is inconsistency in how LMF is graded, with a variety of grading scales and imaging modalities being used. Consistency in evaluating collateral flow at baseline is required for the impact of collateral flow to be fully appreciated.

ABBREVIATIONS: ACA = anterior cerebral artery; ASL = arterial spin-labeling; IA = intra-arterial; LMF = leptomeningeal collateral flow; PCA = posterior cerebral artery; TCD = transcranial Doppler; TIMI = Thrombolysis in Myocardial Infarction

Leptomeningeal collaterals are anastomotic vessels providing alternative routes for blood flow in stroke.[1] In chronic hypoperfusion due to severe carotid stenosis or occlusion, flow via leptomeningeal vessels can maintain cerebral blood flow when primary collateral flow (via the arterial segments of the circle of Willis) is insufficient.[2,3] Better LMF is associated with less infarct growth and better outcome following acute stroke,[4,5] while poor collateralization is associated with hemorrhage after IA thrombolysis.[6] Numerous studies, using several imaging modalities and grading methods, suggest that leptomeningeal collaterals confer a benefit in stroke. Because the influential role of collaterals has been repeatedly reported, we conducted a systematic literature review to investigate the available LMF assessment methods.

Materials and Methods

MEDLINE and Embase were searched from inception to week 32, 2009, by using the Ovid on-line portal for LMF assessments. The search strategy is shown in Appendix 1. The search was supplemented by review of journal electronic tables of contents and by searching the bibliographies of relevant articles; when full text was unavailable, authors were contacted. Studies that graded LMF, published in English and performed on humans, were considered, with assessments on patients with Moyamoya disease excluded. The target population included patients with acute stroke (<24 hours from onset) or patients with known cerebrovascular disease who had collateral flow assessed at later time points. Studies that graded collateral flow and provided a description of the assessment method were included. Terms such as "cortical/pial anastomoses" were judged as being synonymous with leptomeningeal collaterals and were assessed according to the same criteria. Positron-emission tomography and single-photon emission CT examinations, which indirectly evaluated collaterals, were excluded. Included publication dates ranged from January 1965 to October 2010.

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Results

MEDLINE and Embase searches yielded 9456 and 6847 publications, respectively, 195 of which were screened as relevant and had full texts reviewed. After screening, we included 39 articles. A further 42 articles were obtained by handsearching bibliographies and review of electronic tables of contents, providing a total of 81 different publications for inclusion (n = 4686 patients, Table 1). In total, 41 different criteria for grading LMF with conventional angiography (n = 3467 patients), including both acute and nonacute patient groups with collateral assessments in anterior and posterior circulation, were recorded (Table 2).[4,6-62] Reliability assessments were available for 2 of these methods, demonstrating good and very good inter-/intraobserver agreement (n = 172).[6,14,40] Arterial injection sites, when described, included unilateral carotid/MCA (n = 3),[34,54,56] bilateral carotid (n = 3),[24,52,63] a minimum of ipsilateral carotid and vertebral (n = 10),[9,31,36,38,39,45,51,53,55,58] and other combinations (n = 5).[10,11,28,49,50]

Seven grading scales by using CTA were identified, with LMF assessments performed on 593 patients with suspected acute stroke (Table 3).[5,34,64-73] Interobserver agreement was assessed for 5 CTA methods, ranging from moderate to excellent (n = 247). One grading scale used a combination of CTP in addition to CTA to confirm the retrograde direction of true LMF.[5] MR imaging (n = 358 patients) and TCD (n = 268 patients) were used according to 9 and 6 grading methods respectively, with no assessments of interobserver agreement

Table 1: Number of LMF assessments per imaging modality

Modality	Different Assessment Methods	No. of Publications	Studies with Inter-/Intraobserver Agreement Assessed
Angiography	41	58	2[6,14,40]
CT	7	12	5[5,64,69,71,72]
MR imaging	9	13	0
TCD	6	7	0

being reported (Tables 4 and 5).[2,13,19,27,31,35,51,74-86] A total of 8 publications compared noninvasive LMF assessments with MR imaging ($n = 5$), CT ($n = 2$), or TCD ($n = 1$) with a reference standard by using DSA; in each, a different grading scale for the criterion standard was used.[13,19,27,31,34-36,51]

Discussion

The quality of LMF is reported to be an independent predictor of outcome after acute ischemic stroke, after adjustment for other known prognostic factors such as age, clinical stroke severity, baseline imaging characteristics, occlusion site, treatment, and recanalization/reperfusion[4,5,43,63,65,69,72] and suggests that, as a minimum, there is a need to account for its influence on outcomes after stroke. Good collateral flow is assumed to be associated with favorable outcome as a consequence of maintaining the ischemic penumbra for longer until reperfusion occurs, though the effect of collaterals appears to be independent of conventional indices of penumbra such as arterial recanalization/reperfusion.[5,65]

It is unclear whether the collateral grade represents an inherent characteristic of individual subjects or a potential therapeutic target. Collateral flow grades on CTA are reportedly better in patients who undergo imaging later after symptom onset, while better collateral flow grades on conventional angiography have been reported in patients treated with statins before stroke,[18] suggesting that collateral flow is dynamic and could potentially be modified.

The fact that LMF is not accounted for in occlusion classifications may be important in defining arterial occlusions at the entry to a clinical trial and adoption of scoring systems from coronary artery disease; notably, the TIMI[87] system or minor modifications of such systems (eg, thrombolysis in cerebral ischemia) ignore fundamental differences in the acquisition of images and the anatomy of the different vascular beds. For example, when applied to the cerebral circulation, a "good" TIMI score on CTA (eg, TIMI 2) could actually represent a complete arterial occlusion (no anterograde flow) with extensive retrograde flow via collaterals. A consistent method for assessment and grading is required to investigate collaterals in acute stroke. Our review revealed wide variation in the methods for grading LMF, few of which are supported even by measurement of observer agreement.

Conventional angiography, considered the criterion standard for assessing cerebrovascular anatomy, can reveal retrograde collateral perfusion in a dynamic fashion and has been used for LMF assessments in the largest number of patients. The most frequently used scale was proposed by the American Society of Interventional and Therapeutic Neuroradiology in an effort to homogenize grading with angiography[16], but an assessment of interobserver agreement has not yet been reported. Good intraobserver agreement has been demonstrated with angiography when LMF was graded according to the anatomic extent of retrograde flow ($\kappa = 0.81$).[6,14] The Qureshi scale also demonstrates good interobserver agreement but does not focus on LMF independently. One collateral grading scale quantified collateral flow according to the time taken for contrast to travel from the ICA to the M2 segment of the MCA via collaterals but described flow through primary collaterals of the circle of Willis rather than through cortical anastomoses.[88] Although not truly grading LMF, it provides a quantitative time-based measurement that could potentially be used for collateral assessments. Because LMF is derived from neighboring arterial territories, its quality may only be fully evaluated when the contribution of all potential inflow sources is assessed. Descriptions of arterial injection sites are infrequently provided, and even when available, the contribution of the whole cerebral circulation is seldom evaluated. Conventional angiography is invasive and is usually performed when a patient is being considered for IA therapy which, in general, is reserved for those with contraindications to intravenous treatment (eg, presentation beyond 4.5 hours with favorable appearances on CT), meaning that angiographic LMF assessments are predominantly restricted to this group. Because multimodal CT and MR imaging are increasingly used in clinical practice and before entry to clinical trials, they offer a larger potential population in which LMF can be assessed noninvasively.

Although lacking dynamic information, CTA permits visualization of the extent of LMF. The independent predictive value of collaterals has been confirmed with different CTA methods, and interobserver agreement within different grading scales has been assessed.[64,69,71,72] Retrograde flow relative to a proximal arterial occlusion provides a measurement of LMF adequacy, but grading LMF this way for more distal occlusions may be more difficult. A collateral scoring system based on contrast enhancement in defined regions of interest provides a scale not dependant on a specific occlusion, which could potentially be applied in a larger patient population.[64] The addition of CT perfusion to CTA adds important dynamic information to confirm that collateral flow is truly retrograde and demonstrates excellent interobserver agreement.[5] New multidetector scanners that enable simultaneous acquisition of both CTA and CTP allow dynamic collateral flow assessment with CT.[89]

LMF assessments with MR imaging use different imaging characteristics to infer the presence of collaterals. FLAIR vascular hyperintensities due to retrograde flow in leptomeningeal vessels have been associated with larger mismatch volumes and smaller subacute infarct volumes, while abnormal vessels on T2* imaging may be due to deoxygenated blood in collaterals and are associated with smaller infarct volumes.[80,81] ASL, by using different criteria, has also been used to grade collateral flow with MR imaging.[13,51,78] These and other LMF assessments with MR imaging have not been replicated nor has interobserver reliability been graded, and it remains to be seen if they represent robust means of assessing collateral flow.

Relative blood flow velocity and vessel pulsatility have been used as surrogate markers for leptomeningeal collateral flow by using TCD in a small number of studies, but the criteria for defining LMF varied among publications (Table 5). The lack of an agreed definition for LMF on TCD, absence of direct

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Table 2: Catheter angiography collateral scoring methods[a]

Description	Grading	Author (No.)	Acute (<24 hr from Symptom Onset)/ Non-Acute	Reliability Assessed?	Prognostic Significance of Good Collateral Flow Grade in Acute Stroke
Extent of anterograde and retrograde vessel filling	0–3	Brandt[7] (20) Arnold et al[8] (40)	Acute	No	Beneficial[7,8]
No. and rapidity of collateral vessel filling	0–2	von Kummer[9] (53)	Acute	No	Beneficial
No. and rapidity of collateral vessel filling	N/A	Bozzao et al[10] (36) Bozzao et al[11] (36) Toni et al[63] (80)	Acute	No	NS[10] NS[11], beneficial[63]
Filling extent of main and distal vessels via collaterals	0–3	Wu et al[13] (51)	Nonacute	No	N/A
Reconstitution of vessel relative to occlusion	1–5	Christoforidis et al[6] (104) Christoforidis et al[14] (53)	Acute	Yes, κ = 0.81[6,14]	Beneficial[6,14]
Retrograde MCA flow to insula	Present, absent, indeterminate	Derdeyn et al[15] (117)	Nonacute	No	N/A
Rapidity and extent of retrograde collateral flow	0–4	Bang et al[4] (44) Higashida et al[16] (0)[a] Bang et al[17] (119) Ovbiagele et al[18] (95) Sanossian et al[19] (74) Liebeskind[20] (120) Liebeskind[21] (120) Liebeskind[22] (50) Liebeskind[23] (66)	Acute	No	Beneficial[4,17,20] N/A[16] No effect[18] NS[19,21-23]
Flow extent across cortical surface	N/A	Powers et al[24] (19)	Nonacute	No	N/A
Visual inspection	N/A	Klijn et al[25] (76)	Nonacute	No	N/A
Delayed contrast washout	N/A	Essig et al[26] (30)	Nonacute	No	N/A
Visualization of slow flow	N/A	Kamran et al[27] (8)	Acute	No	NS
Visualization of flow pattern	Grade 4 = leptomeningeal flow	Ozgur et al[28] (27)	Nonacute	No	N/A
Cortical branches from contralateral ACA/PCA	N/A	Rutgers et al[29] (112)	Nonacute	No	N/A
Visualization of pial vessels	N/A	Zappe et al[30] (86)	Unclear	No	NS
Visualization of anastomoses from adjacent vascular territories	N/A	Noguchi et al[31] (5)	Acute	No	NS
Visualization of arteriogram	N/A	Grubb et al[32] (81)	Nonacute	No	N/A
Cortical arteries from PCA	N/A	Fukuyama et al[33] (3)	Nonacute	No	N/A
No. and rapidity of vessel filling	0–2	Lee et al[34] (8)	Acute	No	NS
Distal MCA branches filling through ACA or PCA	N/A	Kim et al[35] (51)	Acute	No	NS
Retrograde vessel filling	N/A	Kinoshita et al[36] (10)	Unclear	No	NS
Cortical branches from PCA to MCA	N/A	van Laar et al[37] (23)	Nonacute	No	N/A
Retrograde filling of MCA branches	N/A	Yamauchi et al[38] (42)	Nonacute	No	N/A
Extent and no. of vessels filling via collateral flow	Absent, mild, or prominent	Uemura et al[39] (25)	Combination	No	NS
Combination of occlusion site and extent of collateral flow	0–5	Qureshi[40] (15) Mohammad et al[41] (57) Mohammad et al[42] (55)	Acute	Yes, κ = 0.73[40]	Beneficial[40-42]
Extent of retrograde flow in MCA	Good, poor	Kucinski et al[43] (111) Gasparotti et al[44] (27)	Acute	No	Beneficial
Capillary blush in MCA	Grade 4 = leptomeningeal flow	Russell et al[45] (14)	Nonacute	No	N/A
MCA/PCA filling from posterior circulation	N/A	Bischopps et al[46] (68)	Nonacute	No	N/A
Opacification of basilar artery by collaterals	Distal vs distal and proximal	Cross et al[47] (24)	Acute	No	Beneficial
Cortical branches filling MCA/ACA from PCA	N/A	Bokkers et al[48] (17)	Nonacute	No	N/A
Pial collateral flow from ACA and PCA	N/A	Derdeyn et al[49] (10)	Nonacute	No	N/A
Flow via anastomotic channels on brain surface	N/A	Smith et al[50] (18)	Nonacute	No	N/A
Collateral flow assessment based on ASPECTS (13 areas)	0–3 in corresponding anatomic locations	Chng et al[51] (18)	Nonacute	No	N/A
No. and rapidity of vessel filling from ACA	Good or scarce	von Kummer et al[52] (77)	Acute	No	No effect
No. and rapidity of vessel filling from ACA and PCA	0–2	von Kummer et al[53] (32)	Acute	No	Beneficial
Filling extent of at risk territory	1–3	Roberts et al[54] (180)	Acute	No	Beneficial
Collateral flow assessment based on ASPECTS (15 areas)	0–3 in corresponding anatomic locations	Kim et al[55] (44)	Acute	No	Beneficial
MCA branch filling in early venous phase	Good, moderate, poor	Ringelstein et al[56] (34)	Acute	No	Beneficial
Retrograde arterioles visualized in capillary phase	N/A	Weidner et al[57] (4)	Unclear	No	NS[57]
Presence of superficial PCA/ACA cortical branches	N/A	Hoffmeijer et al[58] (70)	Nonacute	No	N/A
Extent of leptomeningeal anastomoses in occluded territory	Poor, good	Arnold et al[59] (98) Meier et al[60] (311)	Acute	No	No effect[59] Beneficial[60]
Presence of collaterals in affected territory	None/minimal, moderate/max	Gonner et al[61] (43) Brekenfeld et al[62] (294)	Acute	No	No effect[61] Beneficial[62]

Note:—NS indicates not stated; N/A, not applicable; ASPECTS, Alberta Stroke Program Early CT Score; max., maximal; PCA, posterior cerebral artery.
[a] Proposal on working group on collateral grading.

Table 3: CT-based collateral scoring methods

Modality	Description	Grading	Author (No.)	Acute (<24 hr from Symptom Onset)/ Non-Acute	Reliability Assessed?	Prognostic Significance of Good Collateral Flow Grade in Acute Stroke
Axial CTA-SI	Extent of perilesional vessel filling	None, moderate, good, excellent	Liebeskind[64] (36)	Acute	Yes, ICC = 0.81	NS
CTA-SI	Comparison of Sylvian collaterals with contralateral hemisphere	Absent, less, equal to, greater than contralateral hemisphere, exuberant	Rosenthal et al[65] (44)	Acute	No	Beneficial[65-67]
			Maas et al[66] (135)			
			Lima et al[67] (196)			
CTA-SI and MPR	Extent of perilesional enhancement	Good, poor	Schramm et al[68] (20)	Acute	Yes, κ = 0.494	Beneficial[68,69]
			Tan et al[69] (113)			
CTA-SI and reconstructions	MCA filling in Sylvian fissure	Good, moderate, absent	Wildermuth et al[70] (40)	Acute	Yes	Beneficial[70,71]
			Knauth et al[71] (21)		88% agreement between 2 raters[71]	
CTA MIP	Extent of filling in territory of occluded vessel	0–3	Tan et al[69] (113)	Acute	Yes	Beneficial[69.72,73]
			Tan et al[72] (85)		κ = 0.669[69], ICC 0.87[72]	
			Soares et al[73] (22)			
CTA, MIP, CTP	Retrograde filling of MCA	Good, moderate, poor	Miteff et al[5] (92)	Acute	Yes	Beneficial
					κ = 0.93	
(TCTP)	Extent of perfusion deficit on TCTP	Severe, moderate	Lee et al[34]	Acute	No	NS

Note:—NS indicates not stated; ICC, intraclass correlation coefficient; CTA-SI, CT angiography source images; MPR, multiplanar reconstruction; MIP, maximum intensity projection; TPCT, triphasic CTP.

Table 4: MR imaging-based grading methods

Modality	Description	Author (No.)	Acute (<24 hr from Symptom Onset)/ Nonacute	Reliability Assessed?	Prognostic Significance of Good Collateral Flow Grade in Acute Stroke
FADS	Late FADS implies collateral flow	Martel et al[84] (22)	Acute	No	NS
QMRA	Increased flow ipsilateral to steno-occlusive disease	Ruland et al[83] (16)	Nonacute	No	N/A
Phase-contrast MRA	Flow from posterior to anterior circulation	Schomer et al[82] (29)	Nonacute	No	N/A
FLAIR	FLAIR hyperintensities as a marker of collateral flow	Liebeskind[85] (91)	Acute	No	NS[85,19,27,31,81]
		Kamran et al[27] (8)			
		Noguchi et al[31] (5)			
		Sanossian et al[19] (74)			
		Lee et al[81] (52)			
T2*-weighted MRI	Abnormal visualization of leptomeningeal vessels	Hermier et al[80] (48)	Acute	No	NS
PWI	Delayed perfusion sign visualized on PWI	Hermier et al[79] (29)	Acute	No	NS
ASL	Quantitative distal collateral flow measurement	Wu et al[13] (51)	Nonacute	No	N/A
TASL	Collateral flow assessment based on ASPECTS	Chng et al[51] (18)	Nonacute	No	N/A
CASL	Collateral flow inferred from delayed arterial flow	Chalela et al[78] (15)	Acute	No	NS

Note:—NS indicates not stated; N/A, not applicable; FADS, factor analysis of dynamic structures; QMRA, quantitative MRA; TASL, territorial arterial spin labelling; CASL, continuous arterial spin-labeled/labeling; ASPECTS, Alberta Stroke Program Early CT Score.

collateral visualization, and difficulty in finding acoustic windows are limitations of TCD, though these are offset by the lack of radiation and contrast requirements.[90] Flow diversion on TCD, defined as increased flow velocity in ipsilateral ACA/

Table 5: TCD-based grading methods				
Description	**Author (No.)**	**Acute (<24 hr from Symptom Onset)/Nonacute**	**Reliability Assessed?**	**Prognostic Significance of Good Collateral Flow Grade in Acute Stroke**
Asymmetry of flow in ipsilateral ACA and PCA	Zanette et al[77] (56)	Acute	No	NS
Asymmetric P2 flow and reduced pulsatility	Reinhard et al[76] (30) Reinhard et al[75] (111)	Nonacute	No	N/A
Asymmetric mean blood velocity in proximal ACA or P2 segment of ACA	Muller and Schimrigk[2] (48)	Nonacute	No	N/A
Accelerated flow in A1 segment of ACA	Kaps et al[74] (23)	Acute	No	NS
Flow direction relative to Doppler probe	Hennerici et al[86,a]	Unclear	No	NS
Asymmetric flow velocity and pulsatility index	Kim et al[35] (51)	Acute	No	NS

Note:—NS indicates not stated; N/A, not applicable.
[a] Number not stated.

PCA, did correlate with angiographic collateral grade when methods were compared, suggesting a possible role for TCD to measure LMF.[35]

When collaterals were measured by using DSA, CTA, and MR imaging, CTA compared favorably, but the methods used for grading LMF on CTA were not clearly stated, so this finding must be interpreted with caution.[36]

Conclusions

The presence of flow in leptomeningeal collaterals is linked with positive outcomes after stroke, but there is little consistency in the methods used to grade the efficacy of collateral flow. Although the importance of leptomeningeal collaterals is consistently reported, the inconsistency in imaging methods and grading currently limits the emphasis that can be placed on collaterals. For targeting collateral vessels in stroke therapeutic strategies, consistency in examining their extent at baseline is required to permit further expansion of this area. At present, conventional angiography remains the method that can best measure collateral extent and number, but CT-based techniques, which have demonstrated good interobserver reliability and correlation with clinical outcome, may provide an accessible and reliable assessment method for grading collateral flow in a larger patient population, particularly with the development of dynamic CTA combined with perfusion imaging. MR imaging and TCD have been used less frequently than angiography or CT but can also provide noninvasive measurements of LMF.

Appendix

Search Strategy MEDLINE (1950 to July Week 1 2009) and Embase before 1980 to 2009 Week 32.

1) stroke.mp. or *Stroke/ (112119)

2) acute stroke.mp. or *Stroke/ (34761)

3) *Adult/ or *Aged/ or *Ischemic Attack, Transient/ or *Cerebrovascular Circulation/ or *Cerebrovascular Disorders/ or *Brain/ or *Middle Aged/ or *Brain Ischemia/ or ischemic stroke.mp. or *Cerebral Infarction/ (93464)

4) cerebral infarction.mp. or *Cerebral Infarction/ (13177)

5) occlusion.mp. (91391)

6) stenosis.mp. or Constriction, Pathologic/ (85260)

7) carotid stenosis.mp. or *Carotid Stenosis/ (7417)

8) *Cerebral Arteries/ or *Cerebrovascular Disorders/ or *Aged/ or *Carotid Artery Diseases/ or *Ischemic Attack, Transient/ or *Cerebral Infarction/ or *Arterial Occlusive Diseases/ or intracranial occlusion.mp. or *Stroke/ (70577)

9) middle cerebral artery occlusion.mp. or *Infarction, Middle Cerebral Artery/ (7330)

10) *Thrombosis/ or *Intracranial Thrombosis/ or *Carotid Artery Thrombosis/ or *"Intracranial Embolism and Thrombosis"/ or thrombosis.mp. (116053)

11) clinical outcome.mp. (26854)

12) contrast media.mp. or *Contrast Media/ (11586)

13) tomography, x-ray computed.mp. or *Tomography, X-Ray Computed/ (55062)

14) *Angiography, Digital Subtraction/ or *Angiography/ or Angiography.mp. or *Cerebral Angiography/ or *Magnetic Resonance Angiography/ (113286)

15) CT angiography.mp. (3058)

16) CT angiogram.mp. (148)

17) CT angiography source images.mp. (7)

18) *Brain Ischemia/ or *Brain/ or *Diffusion Magnetic Resonance Imaging/ or *Magnetic Resonance Imaging/ or MR, diffusion weighted.mp. (111259)

19) MR angiography.mp. or *Magnetic Resonance Angiography/ (12630)

20) digital subtraction angiography.mp. or *Angiography, Digital Subtraction/ (8851)

21) angiogram.mp. (5291)

22) *Ultrasonography, Doppler, Transcranial/ or transcranial.mp. (15831)

23) *Cerebrovascular Circulation/ or *Collateral Circulation/ or pial collaterals.mp. or *Cerebral Arteries/ (4354)

24) leptomeningeal collaterals.mp. (35)

25) collateral circulation.mp. or *Collateral Circulation/ (6309)

26) collateral vessels.mp. (1376)

27) collateral flow.mp. (1333)

28) collateral blood supply.mp. (203)

29) CT perfusion.mp. (380)

30) recanalization.mp. (7177)

31) *Thrombolytic Therapy/ or thrombolysis.mp. or *Stroke/ (45637)

32) angiogram.m_titl. (312)

33) angiography.m_titl. (15333)

34) collateral.m_titl. (3356)

35) 33 or 32 or 21 or 17 or 12 or 20 or 15 or 14 or 22 or 34 or 30 or 13 or 16 or 19 (196091)

36) 6 or 11 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 30 or 10 or 5 (460879)

37) 27 or 25 or 28 or 30 or 24 or 26 or 23 (17675)

38) 35, or 29 (196193)

39) 38, and 36 and 37 (9774)

40) limit 39 to humans (8311)

41) limit 40 to English language (6887)

42) from 41 keep 84,96,99,126,143,161,181,241,247,262–263,290,304,311–312,314,400,439,446,489,492,507,532,613,616,623,694,891,949 (29).

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