Imaging of the Vulnerable Carotid Plaque –

Current Role of Imaging Techniques and a Research Agenda

Brief title: The vulnerable carotid plaque

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ONLINE SUPPLEMENT

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METHODS

SEARCH STRATEGY

We performed a comprehensive search of the literature in English using the PubMed, EMBASE and Cochrane libraries databases, where search terms (text words) included: “stroke”; OR “transient ischemic attack” OR “TIA”; AND “carotid plaque”; OR “predictors”; OR “high-risk plaque” OR “vulnerable plaque” OR “unstable plaque” OR “culprit plaque”; OR “imaging”; OR “biomarkers”. Because vulnerable plaque is an emerging concept, no specific Medical Subject Headings (MeSH) are available. Since we focused on the current thinking about the vulnerable plaque concept, we limited the search from 2000 to present. Literature thus scanned included clinical and interventional studies, pathology studies, observational studies, meta-analyses, systematic and narrative reviews, editorials, clinical guidelines or statements or recommendations. We also performed a manual cross-referencing, reviewing selected papers from the pertinent reference lists. The search was limited to studies conducted in humans, and performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [1, 2].

Search outcomes

Figure e-2 reports results of the literature search (PRISMA Flow Diagram of Systematic Searches and Selection Process). From an initial search covering 515 papers in English, we excluded the “primary” coronary literature (except for reviews, editorials or statements/recommendations/guidelines). We identified abstracts of studies dealing with the broad concept of carotid vulnerable plaque (i.e., studies with the aim of examining plaque features related to the susceptibility of an atherosclerotic plaque to cause a clinical event). These features included histopathologic, bio-humoral and imaging findings. We included primary studies that were conducted in living humans, or cross-sectional studies validating autoptic plaque findings with imaging techniques. We also evaluated narrative and systematic reviews, meta-analyses, guidelines/statements/recommendations and editorials on the concept of the vulnerable plaque.

We extracted information about study design (cross-sectional or longitudinal follow-up, or prospective or retrospective collections of data), predictors of interest (imaging characteristics, histopathology, biomarkers, and others) and outcomes (clinical, or imaging). Exclusion criteria were:

- articles referring to combined stroke and other vascular disease (e.g., ischemic heart disease) outcomes;
- articles referring to biomarkers or imaging techniques during the acute stroke phase;
- articles relating biomarkers or imaging techniques to stroke type or severity;
- articles primarily dealing with therapeutic implications (pharmacological trials or interventions).

We eventually included 100 papers.

LEGEND TO ONLINE FIGURES

Figure e-1: Silent brain infarction, defined as focal T2 hyperintensities >3 mm with correlative T1 hypointensities at magnetic resonance imaging (MRI). In panel **a**, on the left, diffusion-weighted imaging (DWI) shows an ischemic lesion (on the left side, in a nucleo-capsular position, in white, see the red box). The same lesion is identified in the Apparent Diffusion Coefficient (ADC) acquisition (panel **b**, on the right, in black, see the red box). The examination was performed in a 70 years old male patient with initial cognitive impairment.

Figure e-2: PRISMA Flow Diagram of Systematic Searches and Selection Process.

Figure e-3: Single-photon emission tomography (SPECT) images of carotid artery lesions after the injection of autologous platelets labeled with ^{111}Indium. The figure shows the correspondence with histopathology of a scintigraphically silent carotid lesion (panel A) and a lesion with significant ^{111}In uptake (panel B; see the region marked by the arrows). Panels C and D show the corresponding histologic appearance after endarterectomy. The plaque in A and C is from a 65-years old male patient, with an angiographically diagnosed 75% stenosis on the right internal carotid artery. The plaques in panels B and D is from a 48-years old female patient with a quantitatively similar 75% stenosis on the right internal carotid artery. Authors' own data, reproduced from [3] (with permission).

Table e-1: Relationship between clinical presentation and plaque types

	Asymptomatic (220 patients)	TIA (119 patients)	Stroke (118 patients)	Total (457 patients)
Thrombotic plaques—n (%)	**59 (26.8)**	**43 (36.1)**	**79 (66.9)**	**181**
Rupture:	54(24.5)	36(31.0)	73(63.6)	163
Ulceration	30(13.6)	18(15.1)	38(32.2)	86
Luminal thrombus	10 (4.5)	8(6.7)	18(15.3)	36
Organizing thrombus	14 (6.4)	11 (9.2)	19(16.1)	44
Erosion	0	0	1(0.8)	1
Calcified nodule	5(2.3)	6(5.1)	3(2.5)	14
Non-thrombotic plaques—n (%)	**161 (73.2)**	**76 (63.9)**	**39 (33.1)**	**276**
Stable	122 (55.5)	53(44.6)	29(24.6)	204
Fibrocalcific	86(39.1)	38(31.9)	13(11.0)	137
Healed rupture	36(16.4)	15(12.7)	16(13.6)	67
Vulnerable	39(17.7)	23(19.3)	10 (8.5)	72

* Statistical analysis—thrombotic vs. non-thrombotic plaques: asymptomatic vs. TIA (Transient Ischemic Attack): $p = 0.05$; asymptomatics vs. stroke: $p < 0.001$; TIA vs. stroke: $p < 0.001$. From [4]

Table e-2: Summary of histopathological features of atheromatous plaques

AHA Plaque Type	Histopathological Findings
Type I	Deposition of macrophages and foam cells (isolated)
Type II	Fatty streak lesion with mainly intracellular lipid accumulation.
Type III	Deposition of intracellular lipids within the plaque.
Type IV	Dense accumulation of extracellular lipid. Inflammatory cells infiltration. No fibrous tissue formation. No surface defects or thrombosis.
Type V	Fibrous cap overlying necrotic lipid core. Inflammation within plaque and in the vasa vasorum of the artery wall. Prone to hematoma, thrombus formation, and fissuring.
Type VI	Fissuring and ulceration of plaque. Necrotic lipid core. Intra-plaque hemorrhage and thrombus. Inflammation within the plaque.

From [5]

Table e-3: Differential diagnostic aspects between carotid and coronary vulnerable plaques

Feature	Carotid	Coronary
Cap thickness	+	-
Ulceration	+	-
Plaque rupture with super-imposed thrombosis	+	-
Primary thrombosis	-	+
Erosion	-	+
Calcified nodule	+	-
Calcification (with prognostic predictive role)	+; (uncertain)	?/-; (prognostic)
Healed ruptures and thrombosis	-	+
Chronic total occlusion	-	+
Plaque Healing (necroscopic findings)	+	-
Embolization	+	-
Severe inflammation (macrophages)	+	-

From: [6-10].

e-REFERENCES

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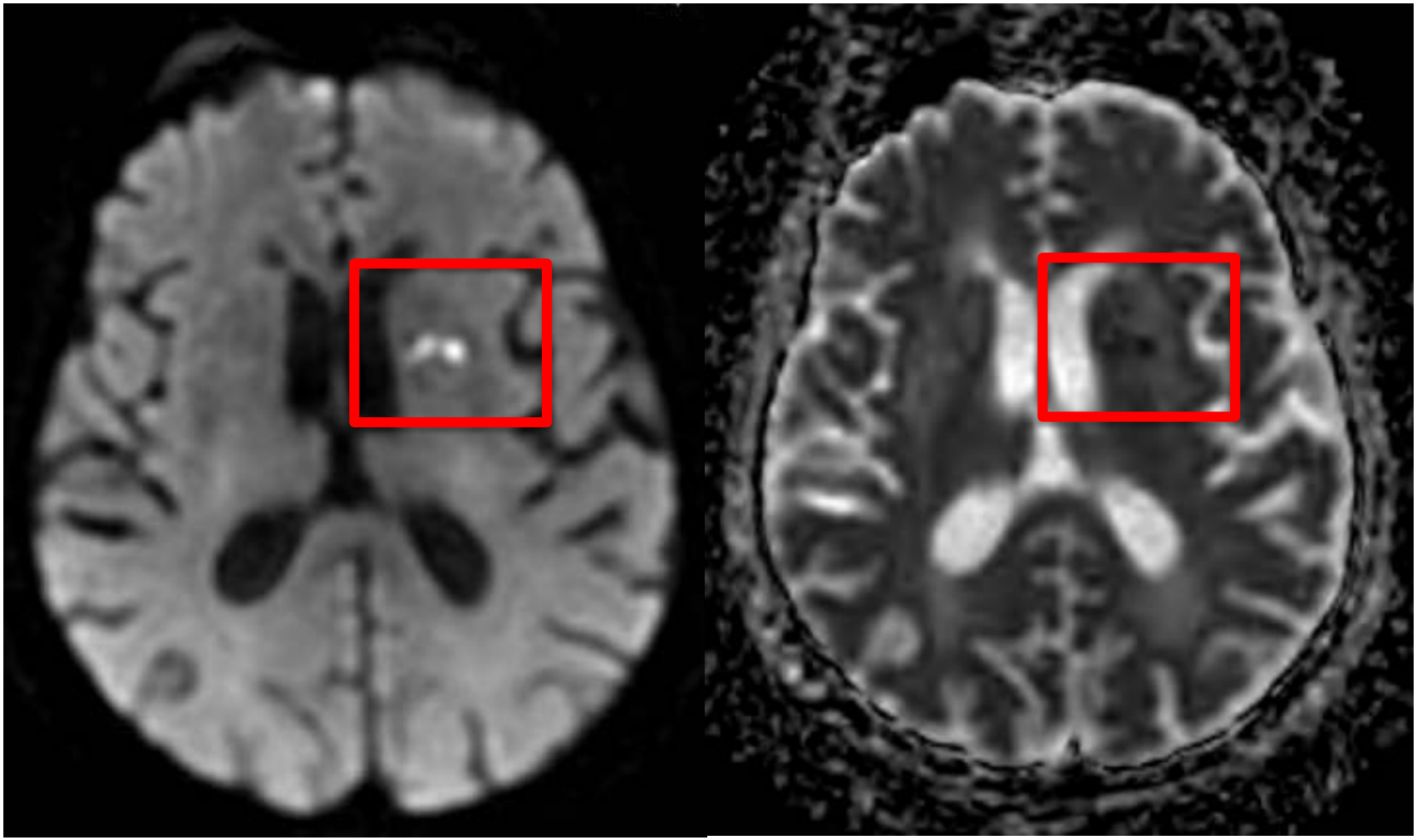

a

b

Figure e-1

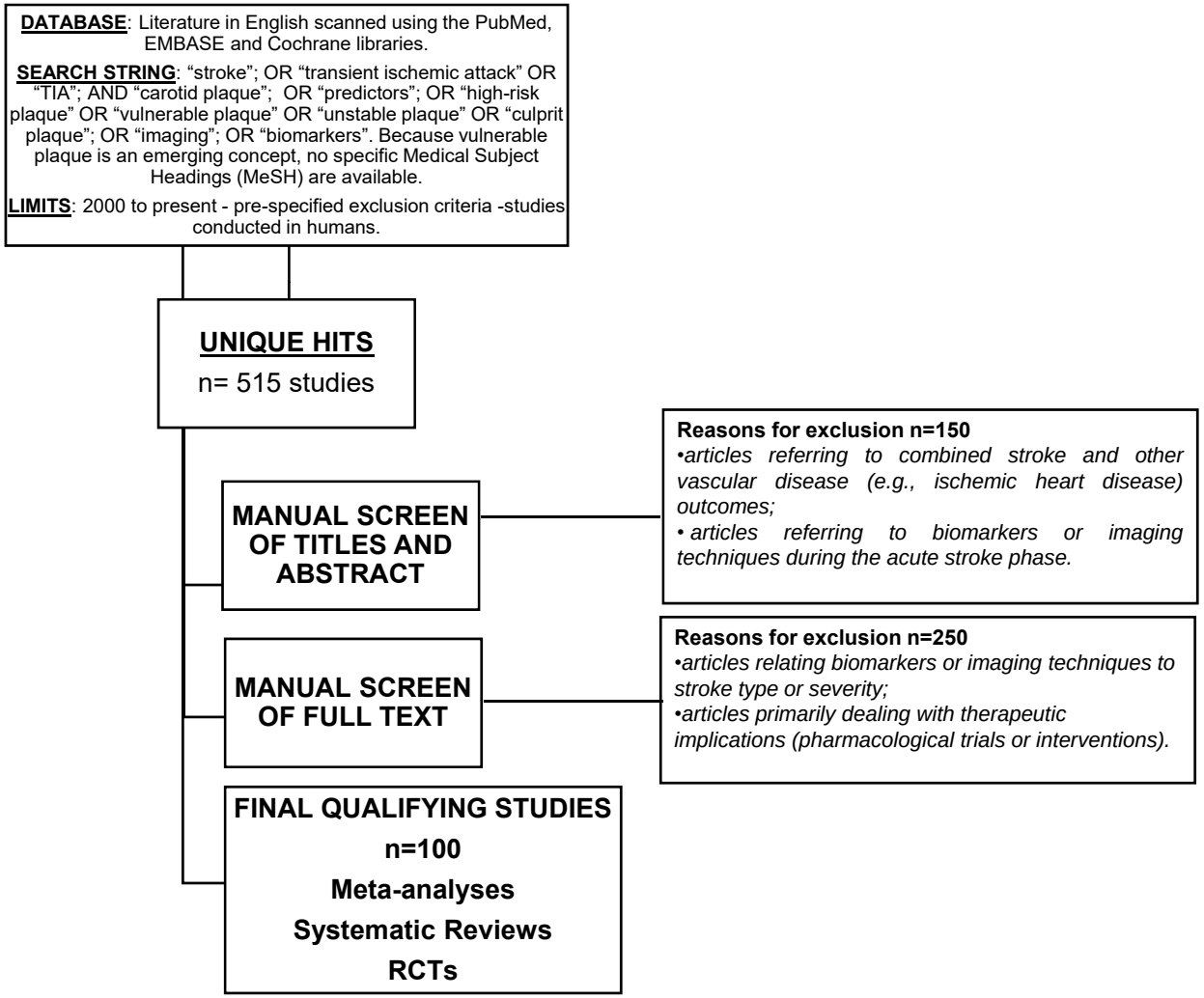
DATABASE: Literature in English scanned using the PubMed, EMBASE and Cochrane libraries.
SEARCH STRING: "stroke"; OR "transient ischemic attack" OR "TIA"; AND "carotid plaque"; OR "predictors"; OR "high-risk plaque" OR "vulnerable plaque" OR "unstable plaque" OR "culprit plaque"; OR "imaging"; OR "biomarkers". Because vulnerable plaque is an emerging concept, no specific Medical Subject Headings (MeSH) are available.
LIMITS: 2000 to present - pre-specified exclusion criteria -studies conducted in humans.
UNIQUE HITS
n= 515 studies
MANUAL SCREEN OF TITLES AND ABSTRACT
Reasons for exclusion n=150
•articles referring to combined stroke and other vascular disease (e.g., ischemic heart disease) outcomes;
• articles referring to biomarkers or imaging techniques during the acute stroke phase.
MANUAL SCREEN OF FULL TEXT
Reasons for exclusion n=250
•articles relating biomarkers or imaging techniques to stroke type or severity;
•articles primarily dealing with therapeutic implications (pharmacological trials or interventions).
FINAL QUALIFYING STUDIES
n=100
Meta-analyses
Systematic Reviews
RCTs

Figure e-2

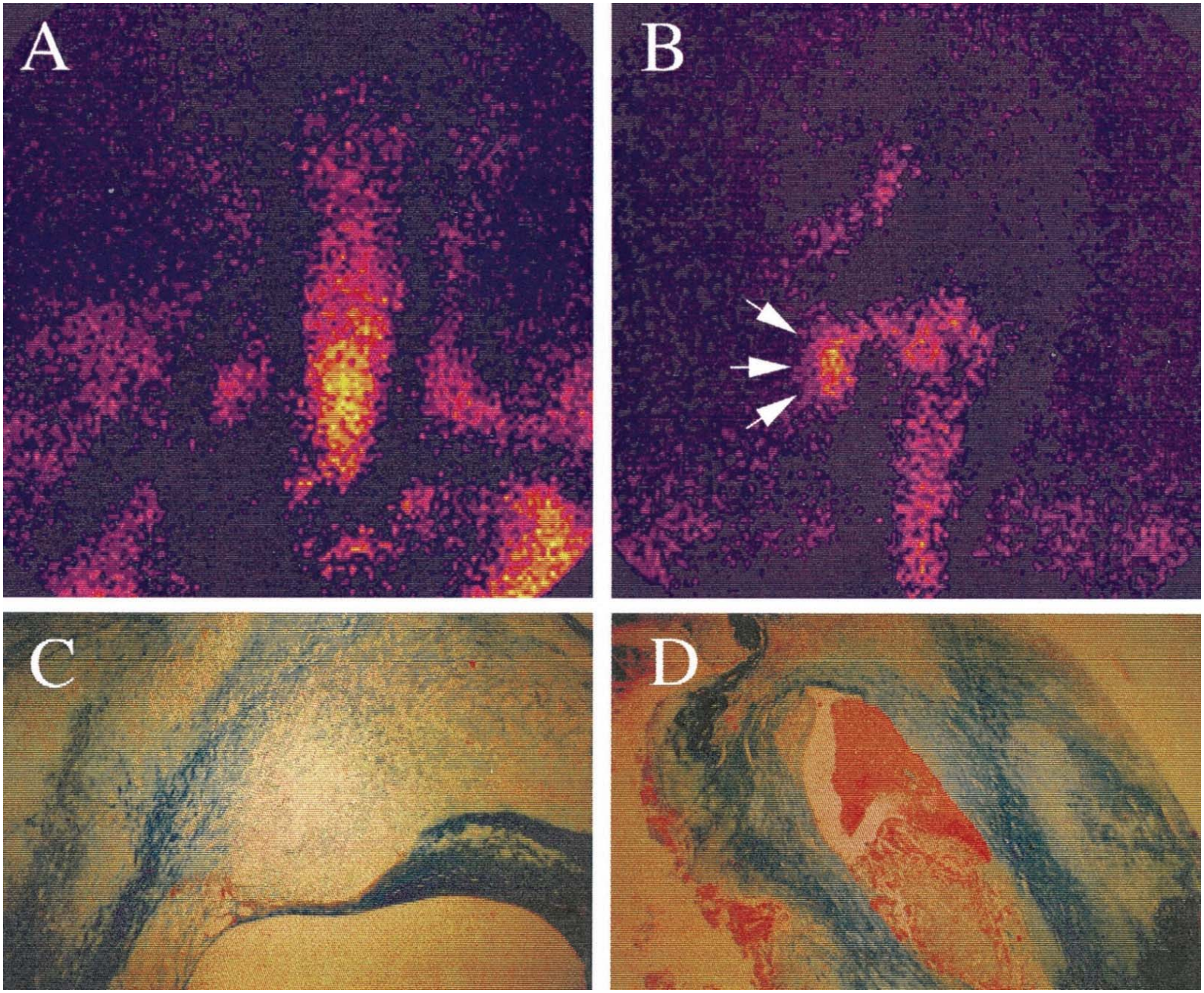

Figure e-3