Aus dem Institut für Schlaganfall- und Demenzforschung
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# Rolle komplizierter Karotisplaques beim akuten ischämischen Schlaganfall

## Role of complicated carotid artery plaques in acute ischemic stroke

Kumulative Habilitationsschrift
zur Erlangung der *venia legendi* der Medizinischen Fakultät
der Ludwig-Maximilians-Universität München
für das Fachgebiet Neurologie


vorgelegt von
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# 1. Einleitung

## 1.1 Allgemeine Informationen zum Schlaganfall

Der Schlaganfall ist weltweit die zweithäufigste Todesursache und stellt die häufigste Ursache für bleibende Behinderungen dar.[1] Die Lebenszeitprävalenz für einen Schlaganfall lag im Jahr 2016 bei 24,9%.[2] In der Europäischen Union erlitten im Jahr 2017 1,12 Millionen Menschen einen Schlaganfall, zur gleichen Zeit wurden 9,53 Millionen Menschen in der Europäischen Union gezählt, die einen Schlaganfall überlebten.[3] Es ist davon auszugehen, dass durch die demographische Entwicklung einerseits und die bessere Schlaganfallversorgung andererseits die Anzahl der Schlaganfall-Überlebenden perspektivisch weiter steigen wird.

Ein Schlaganfall entsteht als Folge einer Durchblutungsstörung des Gehirns. In ca. 90% ist der Schlaganfall durch die Unterbrechung der Blutzufuhr und einen darauffolgenden Sauerstoffmangel bedingt (**ischämischer Schlaganfall**). In ca. 10% kommt es zu einer Gefäßruptur mit folgender Einblutung ins Gehirn (**hämorrhagischer Schlaganfall**).[4] In beiden Fällen, sowohl beim ischämischen Schlaganfall, als auch beim hämorrhagischen Schlaganfall, ist die Konsequenz der Infarkt als irreversibler Zelltod von Nervenzellen im Gehirn.[5]

Die klinischen Beschwerden, die mit einem Schlaganfall einhergehen können, sind vielfältig und abhängig von der Lokalisation des Infarktes.[5] So können beispielsweise Läsionen in motorischen Arealen zu Lähmungserscheinungen wie einer Hemiparese, Infarkte in sensiblen Arealen zu Gefühlsstörungen wie Hypästhesien, Infarkte in der Sehrinde zu Gesichtsfelddefekten, Infarkte im Kleinhirn zu Schwindel sowie Koordinationsstörungen und Infarkte im Hirnstamm zu Blickbewegungsstörungen führen. Diese Symptome können sich teils zurückbilden. Oft sind jedoch residuelle Beschwerden unterschiedlicher Ausprägung bei Schlaganfall-Überlebenden zu finden.

Nach einem erstmaligen Schlaganfall erleiden zwischen 5,1 und 11,1% der Überlebenden innerhalb eines Jahres ein Schlaganfall-Rezidiv.[6,7] Es ist daher von wesentlicher Bedeutung, eine **adäquate Sekundärprophylaxe** einzuleiten.[8] Medikamentös stehen verschiedene Therapieansätze zur Verfügung. In der Regel wird nach einem ischämischen Schlaganfall noch auf der Stroke Unit als Schlaganfall-Spezialstation ein Medikament zur Thrombozytenfunktionshemmung wie Acetylsalicylsäure oder Clopidogrel verabreicht. Diese Medikamentengruppe ist jedoch nicht bei allen Schlaganfall-Patienten zur Verhinderung eines Rezidivs geeignet. Im Fall von kardial-bedingten Schlaganfällen wie z.B. durch Vorhofflimmern wird eine orale Antikoagulation benötigt, um weitere Schlaganfälle zu verhindern.[9]

Besonders schwierig gestaltet sich die Wahl der adäquaten Sekundärprophylaxe bei Schlaganfällen unbekannter Ursache. Solche Schlaganfälle, die zudem ein embolisches Infarktmuster aufweisen, engl. embolic stroke of undetermined source (ESUS),[10] können

verschiedene Ursachen haben. Unter der Annahme, dass ein ESUS durch eine kardiale Embolie bedingt sein könnte, untersuchten die beiden Studien *NAVIGATE-ESUS* (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undertermined Source)[11] und *RESPECT-ESUS* (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and SAfety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicyclic Acid in Patients with Embolic Stroke of Undetermined Source)[12] die Verhinderung rekurrenter Schlaganfälle unter einer Thrombozytenfunktionshemmung und einer oralen Antikoagulation. In beiden Studien zeigte sich entgegen der ursprünglichen Hypothese, dass ein ESUS kardial bedingt ist und ESUS-Patienten daher von einer oralen Antikoagulation profitieren müssten, keine Überlegenheit einer oralen Antikoagulation gegenüber einer Thrombozytenfunktions-hemmung. Daher stellt sich die Frage nach alternativen Ursachen und Strategien zur Sekundärprophylaxe eines ESUS.[13]

## 1.2 Schlaganfall-Ätiologien

Die Wahl der richtigen Sekundärprophylaxe ist maßgeblich von der Schlaganfall-Ätiologie abhängig, so dass der **Identifizierung der Schlaganfall-Ätiologie** eine maßgebliche Bedeutung zukommt. Zur Klassifikation von ischämischen Schlaganfällen wird die TOAST *(Trial of Org 10172 in Acute Stroke Treatment)*-Klassifikation angewendet,[14] in der Schlaganfälle gemäß ihrer Ursache in fünf Kategorien eingeteilt werden:

- Makroangiopathie (*large artery atherosclerosis*)
- kardiale Embolie (*cardioembolism*)
- Mikroangiopathie (*small vessel occlusion*)
- Schlaganfall durch eine andere bekannte Ursache wie z.B. eine Dissektion (*stroke of other determined etiology*) und
- Schlaganfall unbekannter Ursache (*stroke of undetermined etiology*), auch kryptogener Schlaganfall genannt.

Um die Schlaganfall-Ätiologie herauszufinden, wird bereits auf der Stroke Unit[15] eine ausführliche **Schlaganfall-Diagnostik** eingeleitet. Dazu gehören neben der zerebralen Bildgebung mittels Computertomographie (CT) oder Magnetresonanztomographie (MRT) eine Ultraschall-Untersuchung der hirnversorgenden Gefäße zur Erkennung von Gefäßstenosen, eine Echokardiographie zur Erkennung von kardialen Erkrankungen, das EKG-Monitoring inkl. eines Langzeit-EKGs zur Detektion von Herzrhythmusstörungen wie einem Vorhofflimmern und die Bestimmung von Laborparametern beispielsweise zur Erkennung von Blutgerinnungsstörungen.[5] Diese Standard-Diagnostik kann in Einzelfällen um weitere Untersuchungen wie eine Liquoranalyse, z.B. bei juvenilen Schlaganfall-Patienten, erweitert

werden. Trotz dieser ausführlichen Diagnostik bleibt die Schlaganfall-Ätiologie in bis zu 30% der Fälle unklar, so dass diesen Patienten keine spezifische Sekundärprophylaxe angeboten werden kann.[16]

## 1.3 Vulnerable Plaques als Schlaganfall-Ursache

Gemäß der TOAST-Kriterien wird für die **Diagnosestellung eines makroangiopathischen Schlaganfalls** eine mehr als 50%ige Stenose des entsprechenden hirnversorgenden Gefäßes gefordert.[14] In den letzten Jahren gibt es zunehmend Hinweise darauf, dass es unzureichend ist, allein anhand des Stenosegrades einen Schlaganfall als atherosklerotisch bedingt und damit als makroangiopathischen Schlaganfall zu klassifizieren. Vielmehr scheinen neben dem Stenosegrad die Plaque-Morphologie und die Plaque-Zusammensetzung eine wesentliche Rolle für das Schlaganfall-Risiko zu spielen, was in den TOAST-Kriterien nicht berücksichtigt wird.[17,18]

Merkmale einer erhöhten **Plaque-Vulnerabilität** zeigten sich beispielsweise in histologischen Studien häufiger in Plaques von Patienten mit einer symptomatischen Karotisstenose als in Plaques von Patienten mit einer asymptomatischen Karotisstenose nach einer Thrombendarteriektomie.[19] Zudem sind Zeichen einer erhöhten Plaque-Vulnerabilität häufiger in Plaques von kürzlich symptomatischen Patienten im Vergleich zu später operierten Patienten vorhanden gewesen.[20]

Die Atherosklerose gilt als chronische, fortschreitende Erkrankung.[21] Sie ist ein dynamischer Prozess, welcher zur Plaque-Ruptur führen kann. Es ist jedoch nicht ersichtlich, warum das Risiko einer Plaque-Ruptur alleine an einem cutoff-Wert für den Stenosegrad von 50% festgemacht werden soll.[22] Daher erscheint es unzureichend, sich allein auf den Stenosegrad zu beschränken ohne die Plaque-Vulnerabilität zu berücksichtigen. Eine erhöhte Plaque-Vulnerabilität tritt bereits auf bevor eine hämodynamisch relevante Stenose erkennbar ist.[17]

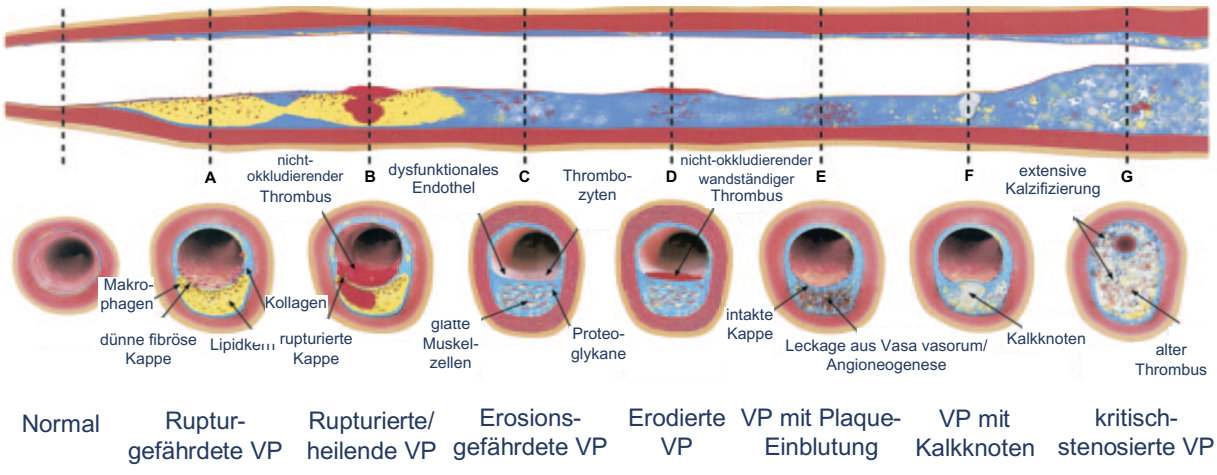



**Abbildung 1**. Entwicklungsstadien vulnerabler Plaques (VP), nach Naghavi et al.[17]

Als **vulnerable Plaques** werden solche bezeichnet, die entweder bereits rupturiert sind oder ein hohes Risiko für eine Ruptur aufweisen.[17,23]

Eine Untergruppe dieser vulnerablen Plaques sind **komplizierte Plaques**, welche auf eine stattgehabte Ruptur hinweisen. Merkmale dieser komplizierten Plaques sind eine rupturierte fibröse Kappe, eine Plaque-Einblutung oder ein der Plaque-anhaftender Thrombus.[24] Diese Merkmale können einzeln oder in Kombination auftreten und definieren komplizierte Plaques.

Atherosklerotische Plaques werden über ihre Entwicklungsstufe gemäß der **American Heart Association (AHA)** in verschiedene Plaquetypen klassifiziert. Die komplizierten Plaques entsprechen AHA-Typ VI Plaques.[24]

| AHA-Klassifikation | Merkmale |
|---|---|
| Typ I | Lipoproteine mit Makrophagen-Invasion und Schaumzellen |
| Typ II | "Fatty streaks", d.h. mehrlagige Schaumzellen und lipidhaltige glatte Muskelzellen |
| Typ III | Prä-Atherom mit extrazellulären Lipidtropfen |
| Typ VI | Atherom mit Lipidkern |
| Typ V | Fibroatherom mit Synthese von Kollagen und Proteoglykanen |
| Typ VI | komplizierte Plaque mit Plaque-Einblutung, rupturierter fibröser Kappe oder Thrombus |
| Typ VII | kalzifizierte Plaque |
| Typ VIII | fibrosierte Plaque |

**Tabelle 1.** Plaquetypen gemäß der American Heart Association (AHA)-Klassifikation, nach Stary et al.[24]

## 1.4 Plaque-Imaging zur Darstellung vulnerabler Plaques

Die Methode der Wahl zur Klassifizierung von Plaques in die verschiedenen Plaquetypen ist die Histopathologie. Diese Methode ist jedoch auf *ex vivo* – Untersuchungen limitiert, z.B. auf die Analyse von Plaquematerial nach einer Thrombendarteriektomie zur operativen Plaque-Entfernung. Als bildgebendes Verfahren eignet sich die Magnetresonanz-tomographie (MRT) zur *in vivo* – Plaque-darstellung, da sie sehr gut mit der Histopathologie korreliert (Abbildung 2).[25,26] Mit dieser Methode können Plaque-Charakteristika detektiert werden, die mit einer erhöhten Plaque-Vulnerabilität einhergehen.[27,28]

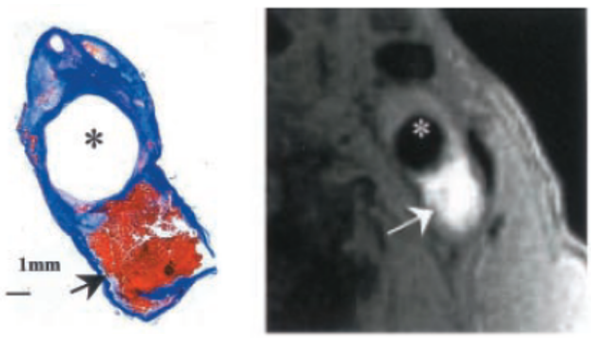



**Abbildung 2.** Korrelat der Plaque-Darstellung in der Histopathologie (links) mit dem MRT in T1-gewichteten Sequenzen (rechts) mit Kennzeichnung des Lumens (Stern) und der Einblutung (Pfeil), nach Cai et al.[26]

Die MRT-Plaquebildgebung ist daher in der Lage, komplizierte Plaques *in vivo* zu detektieren und damit Aussagen zur Vulnerabilität von Plaques zu treffen.[29,30]

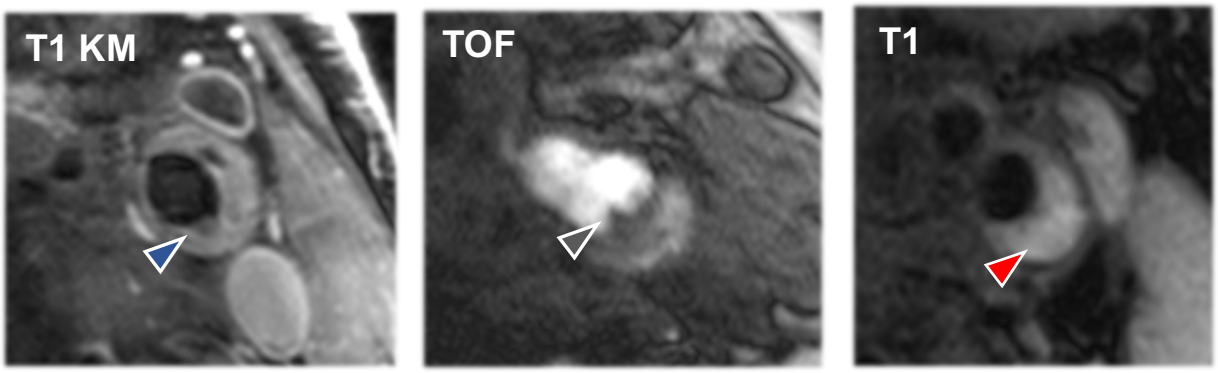



**Abbildung 3.** Kernspintomographische Darstellung einer rupturierten fibrösen Kappe (blaue Pfeilspitze) in T1-gewichteten Sequenzen 5 Minuten nach Kontrastmittelgabe (T1 KM), eines wandständigen Thrombus (graue Pfeilspitze) in der Time-of-flight (TOF)-Sequenz und einer Plaque-Einblutung (rote Pfeilspitze) in der T1-gewichteten Sequenz, nach Kopczak et al.[30]

Für eine ausführliche Plaque-Bildgebung sind spezielle Oberflächenspulen zur besseren Auflösung und die Gabe von Kontrastmittel zur Darstellung der rupturierten fibrösen Kappe nötig (Abbildung 4).


**Abbildung 4.** Beispielhafte Darstellung der MRT-Plaquebildgebung mit Oberflächenspulen und Kontrastmittelgabe (mit freundlicher Genehmigung von F. Thaler)

Mit dieser Methode können beispielsweise Plaques von Patienten nach einem akuten Schlaganfall im Detail mit qualitativer Angabe der Plaque-Charakteristika und quantitativer Messung der Plaque-Morphologie untersucht werden.

In einer Pilotstudie erhielten 32 Patienten mit einem kryptogenen Schlaganfall eine solche ausführliche MRT-Plaquebildgebung.[31] Die Einschlusskriterien für die Pilotstudie waren ein akuter ischämischer Schlaganfall und exzentrische Plaques mit einer Plaquedicke von >2mm. In dieser Pilotstudie zeigte sich, dass 38% der Patienten ipsilateral eine komplizierte Plaque (AHA Lesion Type VI) in der A. carotis hatten, wohingegen kontralateral keine komplizierten Plaques vorgefunden wurden (p=0,001, Abbildung 5). Das häufigste Merkmal komplizierter Plaques war die Plaque-Einblutung mit 75%, gefolgt von einer rupturierten fibrösen Kappe mit 50% und einem Thrombus in 33% der Fälle.

Die Ergebnisse dieser Pilotstudie deuteten bereits darauf hin, dass komplizierte Plaques eine wichtige Rolle bei Patienten mit einem kryptogenen Schlaganfall einnehmen.

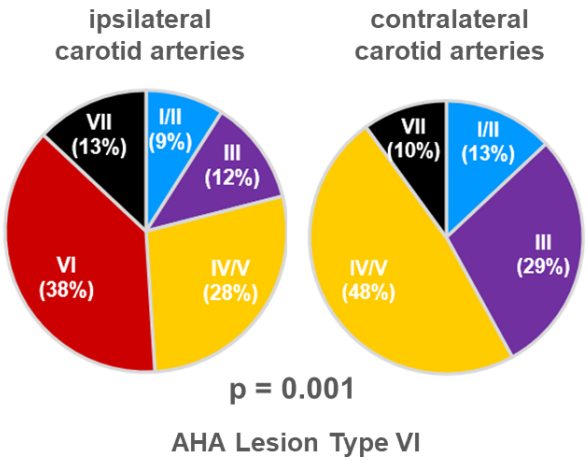



**Abbildung 5.** Plaque-Typen gemäß AHA-Lesion Type-Klassifikation in ipsilateralen und kontralateralen Carotiden bei Patienten mit einem kryptogenen Schlaganfall, nach Freiliger et al.[31]

Jedoch war die Pilotstudie als eine explorative, monozentrische Studie konzipiert. Zudem war die Fallzahl mit 32 Patienten gering und es wurden nur Patienten mit einem kryptogenen Schlaganfall eingeschlossen.

Um die o.g. Aspekte zu berücksichtigen, wurde die **CArotis Plaque Imaging in Acute Stroke (CAPIAS)-Studie** als multizentrische Studie an den vier Stroke Units des LMU Klinikums, des Klinikums rechts der Isar, des Universitätsklinikums Freiburg und Universitätsklinikums Tübingen durchgeführt (Abbildung 6).

Zu den Einschlusskriterien zählten ein akuter ischämischer Schlaganfall in den letzten 7 Tagen, ein Infarkt-Nachweis im MRT mit einer Diffusionsstörung (streng einseitig, nur im vorderen Stromgebiet), ein Alter über 49 Jahre und eine Plaquedicke von mindestens 2mm auf einer Seite in der A. carotis. Daher wurden Patienten eingeschlossen, die entweder ipsilateral,


**Abbildung 6.** Zentren der CAPIAS-Studie (Quelle: Institut für Schlaganfall- und Demenzforschung, ISD)

kontralateral oder bilateral Plaques aufwiesen. Eine Karotisstenose mit einem Stenosegrad von ≥70% gemäß NASCET-Kriterien war ein Ausschlusskriterium für die Studie.[32]

Alle Studienpatienten erhielten neben der üblichen Schlaganfall-Diagnostik (cerebrales MRT, Duplex-Ultraschall der hirnversorgenden Gefäße, transthorakale und ggf. transösophageale Echokardiographie, Langzeit-EKG über mind. 24 Stunden, laborchemische Untersuchungen, ggf. weiterführende Untersuchungen wie eine Liquoranalyse) auch ein ausführliches Plaque-Imaging wie in Abbildung 4 dargestellt. An allen Studienzentren wurden 3T Siemens MRT-Scanner zur Plaque-Darstellung eingesetzt. Die Auswertung der Plaque-Bildgebung erfolgte zentral und unabhängig durch zwei spezialisierte Radiologen, die für den klinischen Status des Patienten verblindet waren.

Mit dem o.g. Studiendesign wurden Plaques in der A. carotis ipsilateral und contralateral bei Patienten mit einem akuten ischämischen Schlaganfall untersucht.

## 2. Zielsetzung der habilitationsrelevanten Arbeiten

Die der Habilitation zugrundeliegende Hypothese ist, dass komplizierte Plaques eine relevante Schlaganfall-Ursache darstellen, auch wenn diese Plaques noch keine höhergradige Stenose verursachen (Abbildung 7).

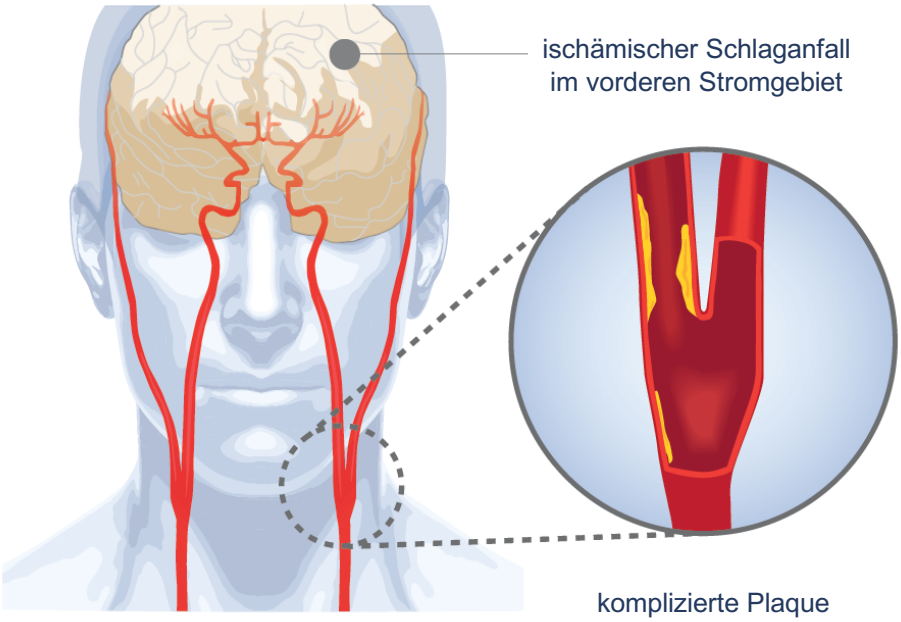



**Abbildung 7.** Komplizierte Plaques in der ipsilateralen A. carotis als Schlaganfall-Ursache
(Quelle: Frau A. Weingart, Dr. med. A. Kopczak; Institut für Schlaganfall- und Demenzforschung, ISD)

## 2.1 Komplizierte Plaques bei Patienten mit einem akuten Schlaganfall

Die **vordefinierten Studienhypothesen der CAPIAS-Studie** waren, dass
1) komplizierte Plaques bei Patienten mit einem kryptogenen Schlaganfall häufiger ipsilateral als kontralateral zum Schlaganfall auftreten und dass
2) ipsilaterale komplizierte Plaques häufiger bei Patienten mit einem kryptogenen Schlaganfall als bei Patienten mit einem kardioembolischen oder mikroangiopathischen Schlaganfall als kombinierte Referenzgruppe vorzufinden sind.[30]
Patienten mit einem makroangiopathischen Schlaganfall und >50-69%igen Karotisstenose gemäß NASCET-Kriterien dienten dabei als zusätzliche Vergleichsgruppe.

## 2.2 Komplizierte Plaques und das Rezidivrisiko für eine erneute zerebrale Ischämie

Bestandteil der CAPIAS-Studie waren zudem Follow-up Untersuchungen über einen Zeitraum von 3 Jahren, um das erneute Auftreten einer zerebralen Ischämie zu erfassen. Für diese Analysen wurden Patienten mit einer ipsilateralen komplizierten Plaque verglichen mit denjenigen Patienten, die keine solche komplizierte Plaque ipsilateral zum Schlaganfall aufwiesen. Die **vordefinierten Studienhypothesen der longitudinalen Untersuchungen** waren, dass
1) Patienten mit einer ipsilateralen komplizierten Plaque eine höhere Rezidivrate an ischämischen Schlaganfällen oder transienten ischämischen Attacken (TIA) aufweisen als Patienten, die keine komplizierte Plaque ipsilateral zum Schlaganfall hatten und dass
2) bei Patienten mit einer ipsilateralen komplizierten Plaque häufiger neue ischämische Läsionen in der zerebralen MRT-Bildgebung nach einem Jahr auftreten als bei Patienten, die keine komplizierte Plaque ipsilateral zum Schlaganfall zeigten.[33]

# 3. Ergebnisse

## 3.1 Beschreibung des Patientenkollektivs der CAPIAS-Studie

Im Rekrutierungszeit von Februar 2011 bis Juli 2018 wurden 234 Patienten in die CAPIAS-Studie eingeschlossen. Das ursprüngliche Rekrutierungsziel von 300 Patienten konnte aufgrund der langsamen Rekrutierung nicht erreicht werden, so dass die Studie vorzeitig beendet wurde. Erst nach der Beendigung der Rekrutierung erfolgten die statistischen Analysen zur Studienauswertung. Von den 234 eingeschlossenen Patienten wurden 26 Patienten aufgrund der Ätiologie ausgeschlossen. Dazu gehörten Patienten,

- bei denen die Ätiologie nicht eindeutig bestimmbar war, da konkurrierende Schlaganfall-Ursachen vorlagen,
- bei denen die Schlaganfall-Diagnostik nicht komplettiert wurde und damit keine eindeutige Aussage zur Ursache des Schlaganfalls getroffen werden konnte und
- Patienten mit einer nicht zur Fragestellung passenden Ätiologie (z.B. Dissektion, intrakranielle Stenose).

Von den verbliebenen 208 Patienten war die Plaque-Bildgebung in 12 Patienten für eine valide Auswertung unzureichend, so dass schließlich 196 Patienten für die finale Analyse verblieben.

Von den 196 Patienten hatten 104 Patienten einen kryptogenen Schlaganfall. In die kombinierte Referenzgruppe gingen 73 Patienten (54 Patienten mit einem kardioembolischen und 19 mit einem mikroangiopathischen Schlaganfall) ein. Die zusätzliche Vergleichsgruppe bildeten 19 Patienten mit einem makroangiopathischen Schlaganfall und >50-69%iger Stenose.

| | CS (n = 104) | CES/SVS (n = 73) | p Value* | LAS (n = 19) | p Value† |
|---|---|---|---|---|---|
| Demographic characteristics | | | | | |
| Age, yrs | 71.8 ± 9.1 | 76.3 ± 9.5 | **0.002** | 72.5 ± 10.9 | 0.767 |
| Male | 83 (79.8) | 45 (61.6) | **0.010** | 13 (68.4) | 0.364 |
| NIHSS | | | | | |
| 0–5 | 80 (76.9) | 49 (67.1) | 0.149 | 16 (84.2) | 0.480 |
| 6–10 | 16 (15.4) | 15 (20.5) | 0.373 | 3 (15.8) | 0.964 |
| >10 | 8 (7.7) | 9 (12.3) | 0.303 | 0 (0.0) | 0.356 |
| Vascular risk factors | | | | | |
| Hypertension | 73 (70.2) | 54 (74.0) | 0.615 | 14 (73.7) | 0.844 |
| Hypercholesterolemia | 34 (33.0) | 25 (34.7) | 0.703 | 6 (35.3) | 0.878 |
| Diabetes mellitus | 21 (20.4) | 19 (26.0) | 0.466 | 4 (21.1) | 0.694 |
| BMI, kg/m$^2$ | 26.8 ± 3.6 | 25.6 ± 3.5 | **0.037** | 28.6 ± 4.1 | **0.046** |
| Current smoker | 20 (32.3) | 11 (33.3) | 0.225 | 3 (23.1) | 0.233 |
| Ever smoker | 62 (59.6) | 33 (45.2) | 0.076 | 13 (68.4) | 0.076 |
| History of cardiovascular disease | | | | | |
| Coronary heart disease | 19 (18.5) | 17 (23.3) | 0.217 | 2 (11.8) | 0.289 |
| Myocardial infarction | 12 (11.8) | 11 (15.3) | 0.190 | 0 (0.0) | 0.214 |
| TIA‡ | 9 (8.8) | 4 (5.6) | 0.738 | 2 (11.1) | 0.738 |
| Stroke‡ | 14 (13.5) | 14 (19.2) | 0.573 | 4 (21.1) | 0.509 |
| Previous medication | | | | | |
| Antihypertensives | 65 (63.1) | 65 (89.0) | **<0.001** | 11 (57.9) | 0.426 |
| Statins | 30 (29.1) | 27 (37.0) | 0.250 | 9 (47.4) | 0.099 |
| Oral anticoagulants | 1 (1.0) | 19 (26.0) | **<0.001** | 0 (0.0) | 0.844 |
| Antiplatelet drugs | 34 (33.0) | 27 (37.0) | 0.271 | 10 (52.6) | 0.086 |
| Stroke-related interventions | | | | | |
| Thrombolysis | 18 (17.5) | 17 (23.3) | 0.341 | 3 (15.8) | 1.000 |
| Thrombectomy | 5 (5.1) | 11 (15.1) | **0.031** | 0 (0.0) | 1.000 |

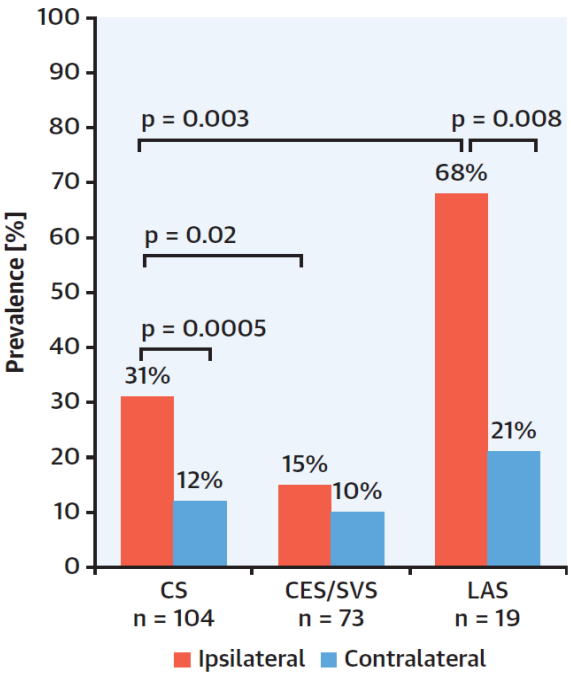
**Tabelle 2.** Charakteristika von Patienten mit einem kryptogenen Schlaganfall (CS) verglichen mit Patienten mit einem kardioembolischen (CES)/mikroangiopathischen (SVS) Schlaganfall (p value*) sowie verglichen mit Patienten einem makroangiopathischen Schlaganfall (LAS; p value†). ‡ vor dem Index-Ereignis. (Quelle: Kopczak et al.[30])

Patienten mit einem kryptogenen Schlaganfall waren jünger (71,8 ± 9,1 vs. 76,3 ± 9,5 Jahre, p=0,002), häufiger männlich (79,8% vs. 61,6%, p=0,010) und hatten einen höheren Body Mass Index (BMI) (26,8 ± 3,6 kg/m$^2$ vs. 25,6 ± 3,5 kg/m$^2$, p=0,037) als Patienten in der kombinierten Referenzgruppe (Tabelle 2).

Unterschiede in den Vorerkrankungen und im Schweregrad der neurologischen Ausfälle gemessen an der National Institutes for Health Stroke Scale (NIHSS) bestanden nicht. Bzgl. der Medikation vor dem Schlaganfall war die Einnahme von Antihypertensiva (63,1% vs. 89%, p<0,001) und oralen Antikoagulanzien (1% vs. 26%, p<0,001) seltener bei Patienten mit einem kryptogenen Schlaganfall als bei Patienten der kombinierten Referenzgruppe. Zudem wurde bei Patienten mit einem kryptogenen Schlaganfall seltener eine Thrombektomie (5,1% vs. 15,1%, p=0,031) als bei Patienten der kombinierten Referenzgruppe durchgeführt.

Im Vergleich zu Patienten mit einem makroangiopathischen Schlaganfall hatten kryptogene Schlaganfall-Patienten einen niedrigeren BMI (26,8 ± 3,6 kg/m$^2$ vs. 28,6 ± 4,1 kg/m$^2$, p=0,046). Darüber hinaus bestanden keine statistisch signifikanten Unterschiede zwischen diesen beiden Patientengruppen.

## 3.2 Komplizierte Plaques als Schlaganfall-Ursache




Komplizierte Plaques waren in der Gruppe der **kryptogenen Schlaganfall-Patienten häufiger ipsilateral als kontralateral** (31% vs. 12%, p=0,0005) vorhanden (Abbildung 8, erste primäre Studienhypothese). Bei Patienten der kombinierten Referenzgruppe war kein signifikanter Seitenunterschied gegeben (15% vs. 10%, p>0,05). Der größte Unterschied im Vorhandensein komplizierter Plaques ipsilateral vs. kontralateral zum Schlaganfall war in der Gruppe der Patienten mit einem makroangiopathischen Schlaganfall erkennbar (68% vs. 21%, p=0,008).

**Abbildung 8.** Vorhandensein komplizierter Plaques ipsilateral (rot) und kontralateral (blau) zur Ischämie bei Patienten mit einem kryptogenen Schlaganfall (CS), kardioembolischen (CES)/ mikroangiopathischen (SVS) Schlaganfall sowie makroangiopathischen Schlaganfall (LAS). (Quelle: Kopczak et al.[30])

Ipsilaterale komplizierte Plaques waren damit **bei kryptogenen Schlaganfall-Patienten häufiger als bei Patienten aus der kombinierten Referenzgruppe** (31% vs. 15%, p=0,02, zweite primäre Studienhypothese), aber seltener als bei Patienten mit einem makroangiopathischen Schlaganfall (31% vs. 68%, p=0,003).

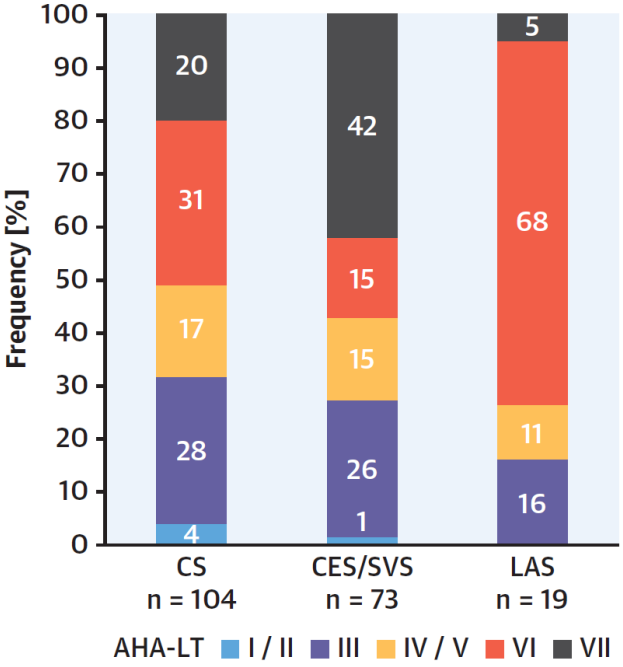



**Abbildung 9.** Verteilung der Plaquetypen (lesion type, LT) gemäß American Heart Association (AHA)-Klassifikation ipsilateral zum Schlaganfall bei Patienten mit einem kryptogenen Schlaganfall (CS), kardio-embolischen (CES) und mikroangiopathischen (SVS) Schlaganfall sowie einem makroangiopathischen Schlaganfall (LAS). (Quelle: Kopczak et al.[30])

Die Verteilung der Plaquetypen ipsilateral zur Läsion gemäß AHA-Klassifikation unterschied sich innerhalb der Gruppen (Abbildung 9). Während bei kryptogenen Schlaganfall-Patienten die **komplizierte Typ VI-Plaque mit 31% am häufigsten** war, waren in der kombinierten Referenzgruppe die stabileren kalzifizierten Typ VII-Plaques mit 42% am häufigsten vertreten. Die meisten komplizierten Plaques Typ VI-Plaques waren ipsilateral bei Patienten mit makroangiopathischen Schlaganfall vorhanden. Insgesamt ähnelte das Verteilungsmuster der Patienten mit makroangiopathischen dem Muster bei kryptogenen Schlaganfall-Patienten mehr als dies in der kombinierten Referenz-gruppe der Fall war.

In der MRT-Bildgebung wurde das Vorhandensein von Plaque-Charakteristika untersucht, die komplizierte Plaques definieren. Diese können einzeln oder in Kombination auftreten. Beispielhaft wird in Abbildung 10 eine komplizierte Plaque mit Vorhandensein aller Charakteristika (Plaque-Einblutung, rupturierte fibrösen Kappe, wandständiger Thrombus) in verschiedenen MRT-Sequenzen dargestellt.

Für die Darstellung der Plaque-Einblutung eignet sich am besten eine T1-gewichtete Sequenz (dark blood, fat-saturated). Die fibröse Kappe ist am besten in den T1-gewichteten Sequenzen 5 min nach Kontrastmittelgabe erkennbar. Für die Detektion eines wandständigen Thrombus eignet sich beispielsweise eine Time-of-flight (TOF) – Sequenz.

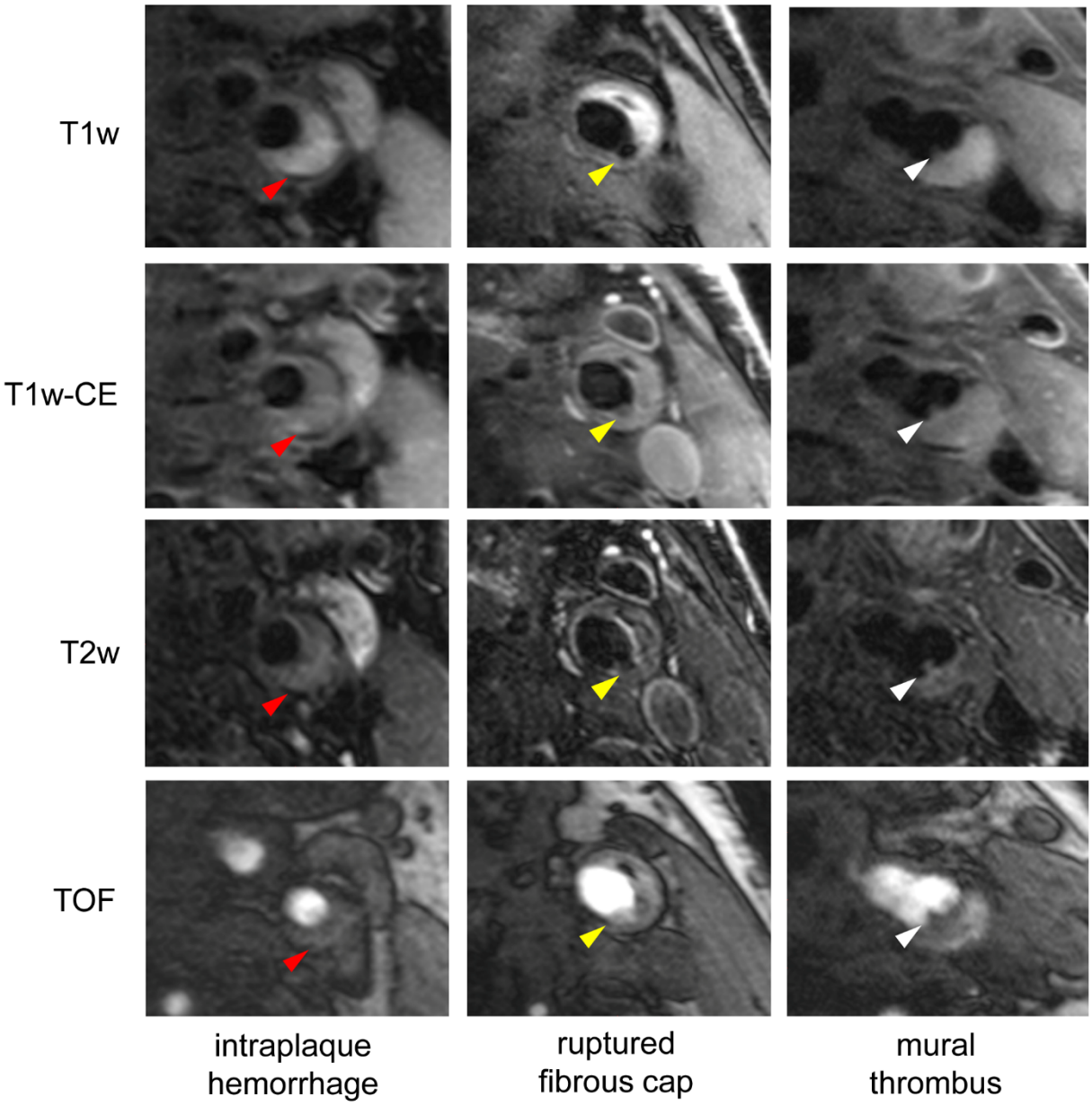



**Abbildung 10.** Beispiel einer komplizierten Plaque mit Plaque-Einblutung (rote Pfeilspitze), rupturierter fibröser Kappe (gelbe Pfeilspitze) und wandständigem Thrombus (weiße Pfeilspitze); MRT: T1-gewichtete Sequenz ohne (T1w) und 5 min nach Kontrastmittel-Gabe (T1w-CE), T2-gewichtete Sequenz (T2w), Time of flight (TOF)-Sequenz. (Quelle: Kopczak et al.[30])

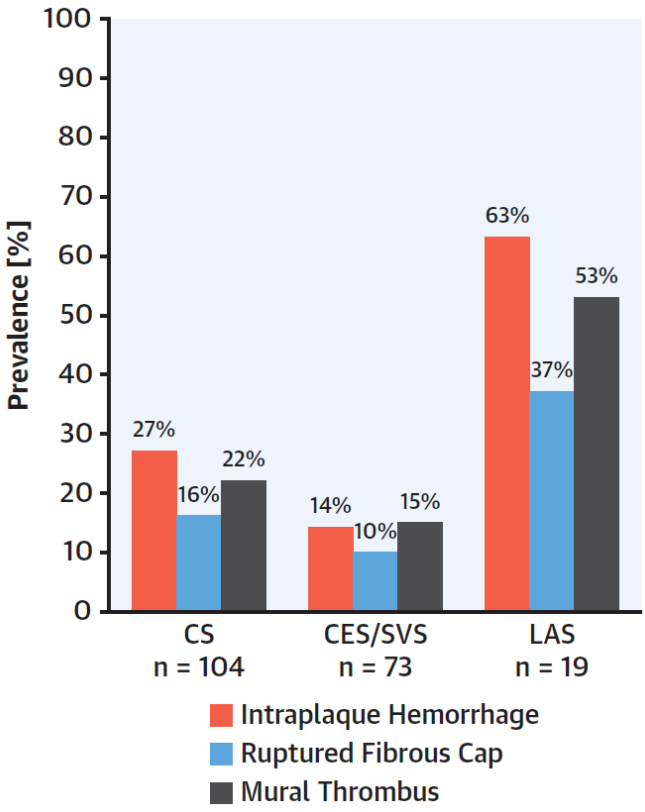



**Abbildung 11.** Häufigkeit einer ipsilateralen Plaque-Einblutung (rot), einer rupturierten fibrösen Kappe (blau) und eines wandständigen Thrombus (schwarz) bei Patienten mit einem kryptogenen Schlaganfall (CS), kardioembolischen (CES)/mikroangiopathischen (SVS) Schlaganfall sowie einem makroangiopathischen Schlaganfall (LAS). (Quelle: Kopczak et al.[30])

Das häufigste dieser drei Charakteristika von komplizierten Plaques war die **Plaque-Einblutung** (Abbildung 11). Diese war bei 27% aller ipsilateralen Plaques bei Patienten mit einem kryptogenen Schlaganfall erkennbar. Patienten aus der kombinierten Referenzgruppe hatten in 14% eine ipsilaterale Plaque-Einblutung, wohingegen Plaque-Einblutungen bei Patienten mit einem makroangiopathischen Schlaganfall in 63% auftraten.

Bezogen auf alle ipsilateralen komplizierten Plaques wiesen 89% aller eine Plaque-Einblutung auf. In der Gruppe der kryptogenen Schlaganfall-Patienten hatten 88% aller ipsilateralen komplizierten Plaques das Merkmal einer Plaque-Einblutung.

Zusätzlich zur qualitativen Plaque-Analyse erfolgte eine quantitative Messung der Plaque-Bestandteile (Tabelle 3).

| | CS (n=102) | CES/SVS (n=72) | p Value* | LAS (n=17) | p Value† |
|---|---|---|---|---|---|
| Plaque burden | | | | | |
| Minimum lumen area, $mm^2$ | 15.3 ± 8.3 | 15.4 ± 7.0 | 0.946 | 10.6 ± 3.3 | **<0.001** |
| Maximum wall area, $mm^2$ | 52.3 ± 23.2 | 45.8 ± 16.1 | **0.041** | 54.9 ± 18.8 | 0.664 |
| Maximum total vessel area, $mm^2$ | 107.2 ± 38.1 | 96.8 ± 27.0 | **0.035** | 90.0 ± 25.7 | 0.075 |
| Maximum normalized wall index | 0.63 ± 0.13 | 0.60 ± 0.11 | 0.123 | 0.73 ± 0.12 | **0.001** |
| Plaque composition | | | | | |
| Maximum LRNC, % | 20 ± 23 | 11 ± 18 | **0.006** | 32 ± 22 | **0.038** |
| Maximum calcified area, % | 5 ± 8 | 6 ± 6 | **0.015** | 7 ± 9 | 0.061 |
| Maximum hemorrhage area, % | 9 ± 21 | 2 ± 7 | **0.024** | 17 ± 24 | 0.092 |

**Tabelle 3.** Quantitative Plaque-Analyse ipsilateraler Plaques mit Bestimmung der Plaque-Last (Plaque burden) und der Plaque-Zusammensetzung (Plaque composition), u.a. des Fettkerns (lipid-rich necrotic core, LRNC) bei Patienten mit einem kryptogenen Schlaganfall (CS), kardioembolischen (CES) und mikroangiopathischen (SVS) Schlaganfall sowie mit einem makroangiopathischen Schlaganfall (LAS), Angabe ± SD, nach Kopczak et al.[30]

Bzgl. der Plaque-Last zeigten Patienten mit einem kryptogenen Schlaganfall eine größere maximale Wanddicke und eine größere maximale gesamte Gefäßfläche als Patienten aus der kombinierten Referenzgruppe.
Im Vergleich zu Patienten mit einem makroangiopathischen Schlaganfall und >50-69%iger Stenose nach NASCET hatten Patienten mit einem kryptogenen Schlaganfall wie erwartet ein kleineres Gefäßlumen und einen kleineren normalisierten Wandindex. Unterschiede in der maximalen Wanddicke oder der maximalen gesamten Gefäßfläche ergaben sich zwischen den beiden Gruppen nicht. Bei kryptogenen Schlaganfall-Patienten hat demnach die erhöhte Plaque-Last noch nicht zu einer Lumen-Einengung wie bei Patienten mit einem makroangiopathischen Schlaganfall geführt.

Die Plaque-Zusammensetzung ipsilateraler Plaques ähnelte bei kryptogenen Schlaganfall-Patienten eher der Plaque-Zusammensetzung bei Patienten mit einem makroangiopathischen Schlaganfall als bei Patienten aus der kombinierten Referenzgruppe.
Ipsilaterale Plaques von kryptogenen Schlaganfall-Patienten hatten im Vergleich zu ipsilateralen Plaques von Patienten aus der kombinierten Referenzgruppe einen größeren Fettkern und eine größere Einblutungsfläche. Im Vergleich zu Patienten mit einem makroangiopathischen Schlaganfall war die Einblutungsfläche von ipsilateralen Plaques kryptogener Schlaganfall-Patienten nominell kleiner, wobei der Unterschied nicht statistisch signifikant war.

Die Ergebnisse der quantitativen Analysen zeigen, dass ipsilaterale Plaques von Patienten mit einem kryptogenen Schlaganfall in der Plaque-Last als auch in der Plaque-Zusammensetzung denen von Patienten mit einem makroangiopathischen Schlaganfall ähnlicher sind als denen von Patienten mit einem kardioembolischen oder mikroangiopathischen Schlaganfall.

Zusammenfassend konnte damit gezeigt werden, dass **komplizierte Plaques bei kryptogenen Schlaganfall-Patienten** häufiger ipsi- als kontralateral auftreten. Im Vergleich zu anderen Schlaganfall-Ätiologien sind ipsilaterale komplizierte Plaques häufiger bei Patienten mit einem kryptogenen Schlaganfall zu finden als bei Patienten mit einem kardioembolischen oder mikroangiopathischen Schlaganfall (Referenzgruppe), aber seltener als bei Patienten mit einem makroangiopathischen Schlaganfall und >50-69%iger Stenose nach NASCET (zusätzliche Vergleichsgruppe).
Darüber hinaus ähneln Plaque-Charakteristika und die Plaque-Morphologie bei kryptogenen Schlaganfall-Patienten denen von makroangiopathischen Schlaganfall-Patienten. Es ist davon auszugehen, dass sich diese Plaques im Verlauf zu stenosierenden Plaques hin entwickeln würden, wobei dann ab einem Stenosegrad von >50% die Ätiologie gemäß der TOAST-Kriterien als makroangiopathisch eingestuft werden würde.

Die Ergebnisse der CAPIAS-Studie erhärten damit die Hypothese, dass **komplizierte Plaques eine Schlaganfall-Ursache** darstellen.

## 3.3 Komplizierte Plaques als Risiko für eine erneute zerebrale Ischämie

In dem CAPIAS-Patientenkollektiv der 196 Patienten hatten 56 Patienten eine ipsilaterale komplizierte Plaque. Zur Beantwortung der Frage, ob Patienten mit einer ipsilateralen komplizierten Plaque zum Zeitpunkt des Index-Schlaganfalls ein höheres Risiko für zukünftige ischämische Schlaganfälle oder TIAs haben, fand eine Nachbeobachtung der Patienten über einen Zeitraum von 3 Jahren statt (Abbildung 12).

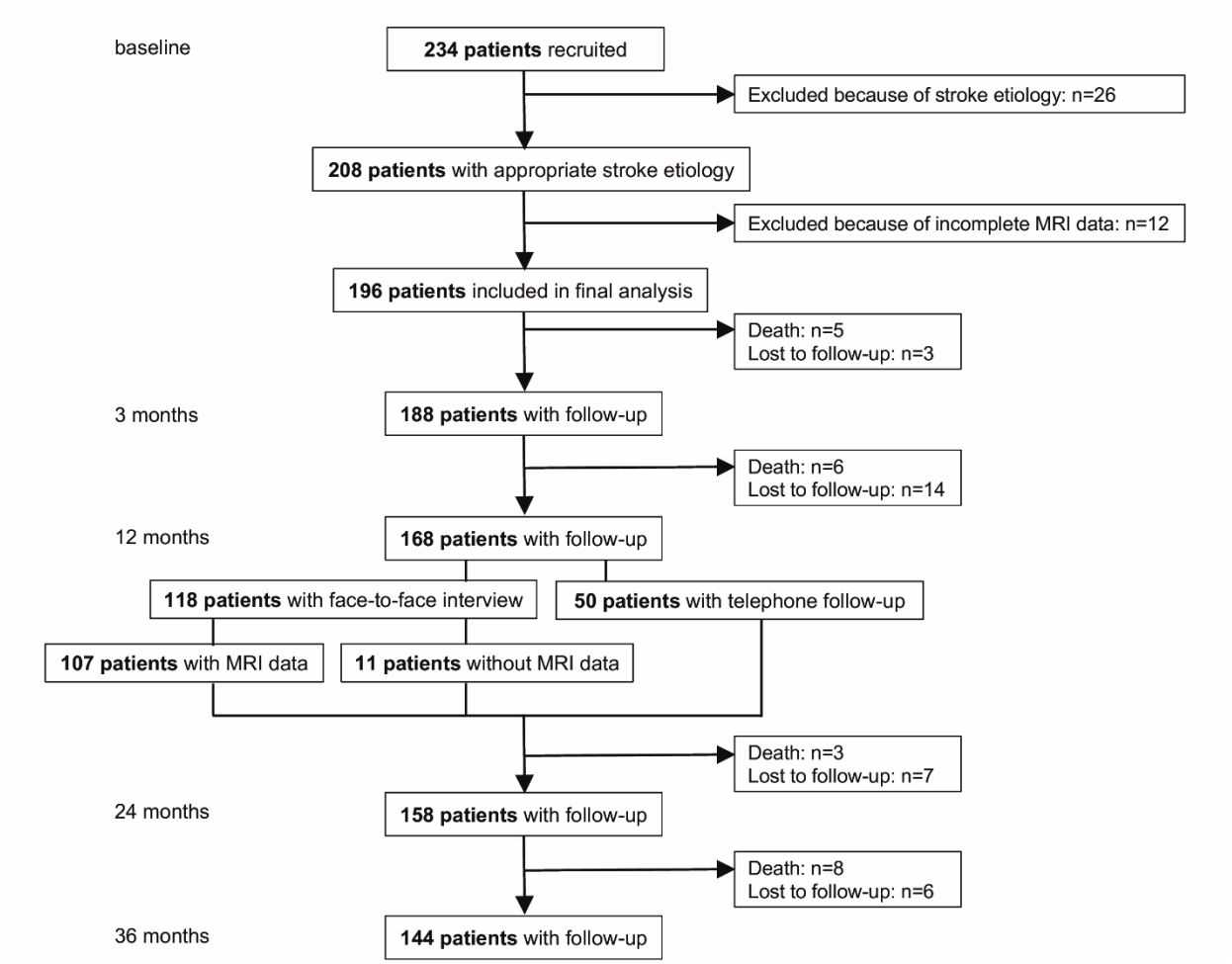



**Abbildung 12.** Studienprofil der CAPIAS-Studie mit telefonischen Befragungen nach 3, 12, 24 und 36 Monaten nach dem Schlaganfall. Nach 12 Monaten wurden die Patienten zu einer persönlichen Visite inkl. cerebralem MRT und erneutem Plaque-Imaging einbestellt; nach Kopczak et al.[33]

Die letzte Nachuntersuchung nach 3 Jahren beendeten 144 von 196 Patienten. Während der Nachbeobachtungszeit erhielten 13 Patienten eine Karotis-Thrombendarteriektomie oder ein Stenting der ipsilateralen A. carotis. Diese Patienten wurden zum Zeitpunkt der Intervention von der Analyse zensiert.

Während einer mittleren Nachbeobachtungsdauer von 30 Monaten traten bei 21 Patienten erneute ischämische Schlaganfälle oder TIAs auf.

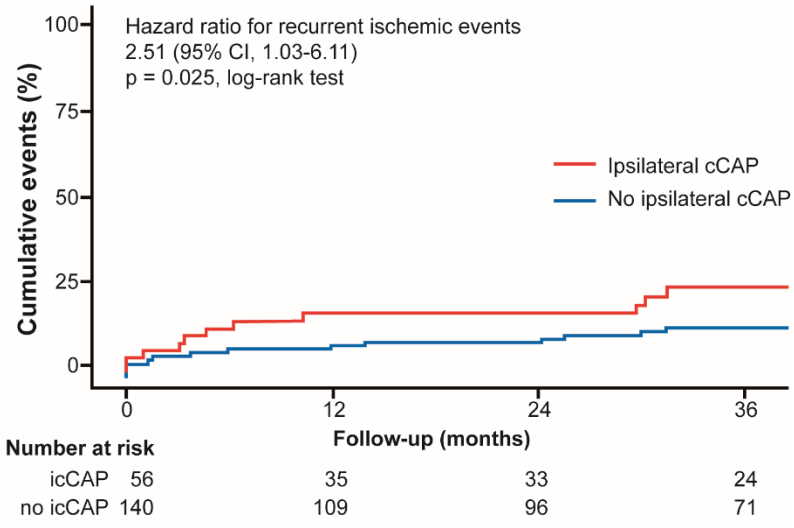



**Abbildung 13.** Kumulative Rezidivhäufigkeit bei Patienten mit ipsilateraler komplizierter Plaque (rot) und bei Patienten, die keine ipsilaterale komplizierte Plaque aufwiesen (blau); nach Kopczak et al.[33]

**Rezidivereignisse waren bei Patienten mit einer ipsilateralen komplizierten Plaque häufiger** als bei Patienten, die keine komplizierte Plaque ipsilateral zum Index-Schlaganfall aufwiesen (Inzidenzrate [3-Jahres-Intervall]: 9,50 vs. 3,61 pro 100 Patientenjahre, p=0,025; Abbildung 13). Adjustiert für Alter und Geschlecht waren ipsilaterale komplizierte Plaques mit einem **2,5fach erhöhten Risiko für einen erneuten ischämischen Schlaganfall oder eine TIA** innerhalb von 3 Jahren assoziiert (Hazard Ratio [HR] 2,51, 95% Konfidenzintervall 1,03-6,11, p=0,043; Abbildung 13).

Die Unterschiede in der Rezidivhäufigkeit in Abhängigkeit vom Vorhandensein ipsilateraler komplizierter Plaques waren in der Gruppe der Patienten mit einem kryptogenen Schlaganfall noch stärker ausgeprägt (10,92 vs. 1,82 pro 100 Patientenjahre, p=0,003) zu.

In der Cox-Regressionsanalyse adjustiert für Alter und Geschlecht waren ipsilaterale komplizierte Plaques **bei Patienten mit einem kryptogenen Schlaganfall mit einem 5,6fach erhöhten Risiko für einen erneuten ischämischen Schlaganfall oder eine TIA** innerhalb von 3 Jahren assoziiert (HR 5,60, 95% Konfidenzintervall 1,43-21,83, p=0,013; Abbildung 14).

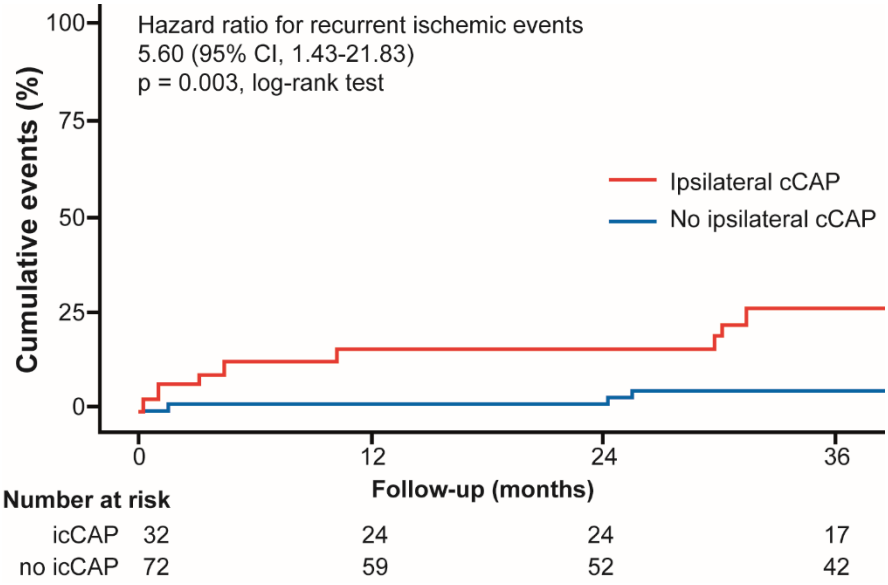



**Abbildung 14.** Kumulative Rezidivhäufigkeit bei Patienten mit einem kryptogenen Schlaganfall mit ipsilateraler komplizierter Plaque (rot) und bei Patienten, die keine ipsilaterale komplizierte Plaque aufwiesen (blau); nach Kopczak et al.[33]

Die Ergebnisse für den kombinierten primären Endpunkt eines erneuten ischämischen Schlaganfalls oder einer TIA blieben signifikant, wenn die Analysen auf **ipsilaterale Rezidivereignisse** beschränkt wurden. Für die Gesamtkohorte ergab sich ein 3,4fach erhöhtes Risiko (HR 3,37, 95% Konfidenzintervall 1,21-9,38, p=0,020) und für die Gruppe der kryptogenen Schlaganfall-Patienten ein 5fach erhöhtes Risiko (HR 5,01, 95% Konfidenzintervall 1,25-20,05, p=0,023) für einen erneuten ipsilateralen ischämischen Schlaganfall oder eine TIA (Abbildung 15). Für den sekundären Endpunkt, den erneuten ischämischen Schlaganfall, war die gleiche Tendenz vorhanden, wobei für diese Analysen keine statistische Signifikanz erreicht werden konnte (Abbildung 15).

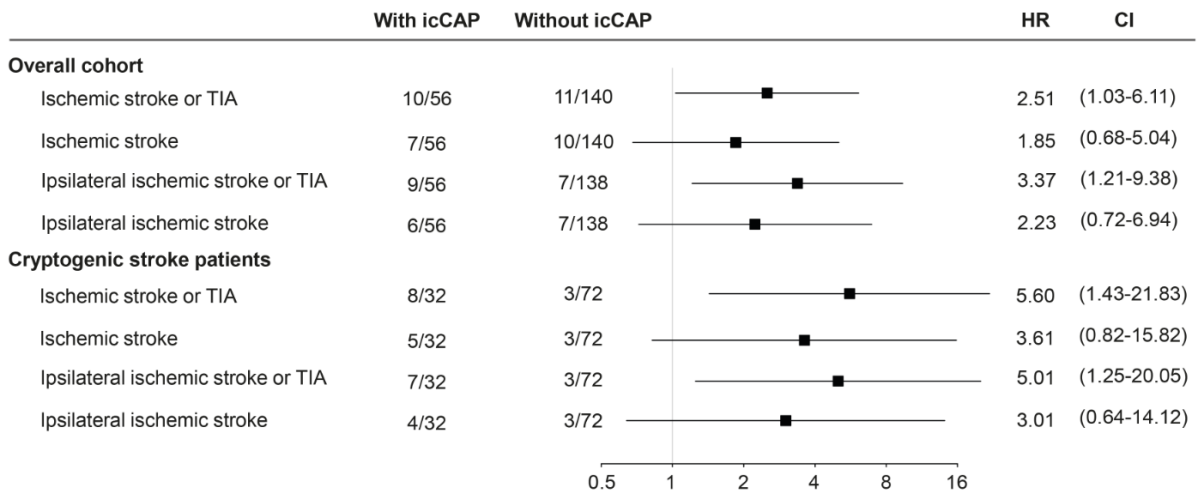



**Abbildung 15.** Hazard ratios für den kombinierten Endpunkt ischämischer Schlaganfall und TIA, für den Endpunkt ischämischer Schlaganfall und für ipsilaterale Rezidiv-Ereignisse. In den Analysen wurde für das Alter und Geschlecht adjustiert. Die Ergebnisse sind für die Gesamtkohorte und für die Gruppe der kryptogenen Schlaganfall-Patienten separat dargestellt; nach Kopczak et al.[33]

Komplizierte Plaques definieren sich durch das Vorhandensein von mindestens einem der drei Merkmale: einer Plaque-Einblutung, einer rupturierten fibrösen Kappe und einem der Wand anhaftenden Thrombus. Von diesen Merkmalen, die in der Plaque-Bildgebung zum Zeitpunkt des Index-Schlaganfalls vorhanden waren, war eine **rupturierte fibröse Kappe** mit dem erneuten Auftreten eines ischämischen Schlaganfalls oder einer TIA sowohl in der Gesamtkohorte (HR 2,61, 95% Konfidenzintervall 1,01-7,05, p=0,041), als auch in der Gruppe der Patienten mit einem kryptogenen Schlaganfall (HR 4,91, 95% Konfidenzintervall 1,31-18,45, p=0,018) assoziiert (Tabelle 4).

| | Recurrent ischemic stroke or TIA | | |
|---|---|---|---|
| | **HR** | **95% CI** | **p value** |
| Overall cohort | | | |
| Ruptured fibrous cap | 2.61 | (1.01-7.05) | **0.041** |
| Intraplaque hemorrhage | 2.34 | (0.94-5.81) | 0.067 |
| Mural thrombus | 1.47 | (0.55-3.91) | 0.443 |
| Cryptogenic stroke patients | | | |
| Ruptured fibrous cap | 4.91 | (1.31-18.45) | **0.018** |
| Intraplaque hemorrhage | 4.37 | (1.20-15.97) | **0.026** |
| Mural thrombus | 2.89 | (0.84-10.01) | 0.093 |

**Tabelle 4.** Assoziation zwischen Plaque-Charakteristika komplizierter Plaques ipsilateral zum Index-Schlaganfall und dem Auftreten eines erneuten ischämischen Schlaganfalls oder einer TIA. Die Analysen wurden für Alter und Geschlecht adjustiert und sind für die Gesamtkohorte und für die Gruppe der kryptogenen Schlaganfall-Patienten separat dargestellt; nach Kopczak et al.[33]

Das Vorhandensein einer **Plaque-Einblutung** erreichte in der Gesamtkohorte keine statistische Signifikanz (HR 2,34, 95% Konfidenzintervall 0,94-5,81, p=0,067), war jedoch in der Gruppe der kryptogenen Schlaganfall-Patienten mit einem erneuten ischämischen Schlaganfall oder einer TIA assoziiert (HR 4,37, 95% Konfidenzintervall 1,20-15,97, p=0,026).

Neue Läsionen im MRT wurden in 35 von 107 Patienten in einem erneuten Studien-MRT 12 Monate nach dem Index-Schlaganfall entdeckt. In 16 Patienten waren diese Läsionen als neue zerebrale Ischämien gewertet worden, bei 11 Patienten handelte es sich um neue Läsionen in den FLAIR-gewichteten Sequenzen durch den Progress einer zerebralen Mikroangiopathie, bei 8 Patienten konnte die Art der Läsion nicht klar zugeordnet werden. Interessanterweise hatten 6 Patienten ein in der klinischen MRT-Bildgebung bestätigtes Schlaganfall-Rezidiv erlitten, aber nur in 4 Fällen war die Läsion im Studien-MRT nach 12 Monaten als FLAIR-positive Läsion erkennbar. In einem Fall konnte die neue ischämische Läsion, die sich im

klinischen MRT mit einer Diffusionsstörung gezeigt hatte, im späteren Studien-MRT nicht mehr detektiert werden; in einem anderen Fall führte die neue Ischämie zur Atrophie. Bei 12 Patienten konnte die Läsion als stummer Infarkt gewertet werden. Es gab keine signifikante Assoziation zwischen ipsilateralen komplizierten Plaques und neuen ischämischen Läsionen im Studien-MRT nach 12 Monaten.

Zusammenfassend ist das **Vorhandensein von ipsilateralen komplizierten Plaques** bei Patienten mit einem akuten ischämischen Schlaganfall, insbesondere bei Patienten mit einem kryptogenen Schlaganfall, mit **einem erhöhten Risiko für einen erneuten ischämischen Schlaganfall oder einer TIA** assoziiert. Vermehrte klinisch stumme Ischämien konnten bei Patienten mit ipsilateralen komplizierten Plaques im Studien-MRT nach 12 Monaten nicht nachgewiesen werden.

## 4. Publikationen der Habilitationsschrift

1. “Complicated Carotid Artery Plaques as a Cause of Cryptogenic Stroke.”

**Kopczak A***, Schindler A*, Bayer-Karpinska A, Koch ML, Sepp D, Zeller J, Strecker C, Hempel JM, Yuan C, Malik R, Wollenweber FA, Boeckh-Behrens T, Cyran CC, Helck A, Harloff A, Ziemann U, Poli S, Poppert H, Dichgans M, Saam T. Complicated Carotid Artery Plaques as a Cause of Cryptogenic Stroke. *J Am Coll Cardiol*. 2020;76(19):2212-2222.
*contributed equally, IF = 20,589

2. “Reply: Comparison of Different Plaque Imaging Techniques to Detect Complicated Carotid Artery Plaques”

**Kopczak A**, Schindler A, Dichgans M, Saam T. Reply: Comparison of Different Plaque Imaging Techniques to Detect Complicated Carotid Artery Plaques. *J Am Coll Cardiol*. 2021;77(8):1147-1148. IF = 24,094

3. “Complicated Carotid Artery Plaques and Risk of Recurrent Ischemic Stroke or TIA”

**Kopczak A***, Schindler A*, Sepp D, Bayer-Karpinska A, Malik R, Koch ML, Zeller J, Strecker C, Janowitz D, Wollenweber FA, Hempel J-M, Boeckh-Behrens T, Cyran CC, Helck A, Harloff A, Ziemann U, Poli S, Poppert H, Saam T, Dichgans M. Complicated Carotid Artery Plaques and Risk of Recurrent Ischemic Stroke or TIA. *J Am Coll Cardiol*. 2022;79(22):2189–2199.
*contributed equally, IF = 24,094

## 5. Diskussion und Ausblick

In der vorliegenden Habilitationsarbeit konnte gezeigt werden, dass nicht-stenosierende komplizierte Plaques in den Karotiden eine Ursache für einen akuten ischämischen Schlaganfall sind und zudem das Risiko für einen erneuten Schlaganfall oder eine TIA erhöhen.

Dies ist insbesondere für Patienten mit einem **kryptogenen Schlaganfall** von Bedeutung, bei denen die Schlaganfall-Ursache nicht bekannt ist. In dieser Patientengruppe waren komplizierte Plaques signifikant häufiger ipsilateral (31%) als kontralateral zum Schlaganfall (12%) vorhanden. In der kombinierten Referenzgruppe aus Patienten mit einem kardioembolischen oder mikroangiopathischen Schlaganfall, bei denen die Schlaganfall-Ursache demnach als nicht-atherosklerotisch gewertet wurde, zeigte sich kein signifikanter Unterschied in der Häufigkeit von ipsilateralen (15%) und kontralateralen (10%) komplizierten Plaques. Im Gegensatz dazu war in der zusätzlichen Vergleichsgruppe aus Patienten mit einem makroangiopathischen Schlaganfall, bei denen eine Atherosklerose mit bereits >50-69%iger Stenose vorlag, ein deutlicher Seitenunterschied in der Häufigkeit von ipsilateralen (68%) und kontralateralen (21%) komplizierten Plaques erkennbar.
Im Vergleich zwischen den unterschiedlichen Ätiologien waren komplizierte Plaques ipsilateral zum Schlaganfall häufiger bei Patienten mit einem kryptogenen Schlaganfall (31%) als bei Patienten mit einem kardioembolischen oder mikroangiopathischen Schlaganfall (15%), aber seltener als bei Patienten mit einem makroangiopathischen Schlaganfall (68%) vorhanden. Die Ergebnisse der CAPIAS-Studie bekräftigen die Hypothese, dass auch nicht-stenosierende komplizierte Plaques insbesondere bei Patienten mit einem kryptogenen Schlaganfall eine Schlaganfall-Ursache darstellen.

Bei Patienten mit einem kryptogenen Schlaganfall ähnelte die Plaque-Zusammensetzung ipsilateraler Plaques der Plaque-Zusammensetzung von ipsilateralen Plaques bei Patienten mit einem makroangiopathischen Schlaganfall. Pathophysiologisch ist daher von einem **beginnenden Remodelling-Prozess** auszugehen, d.h. diese nicht-stenosierenden Plaques befinden sich in einem Entwicklungsprozess hin zu stenosierenden Plaques mit noch größerer Plaque-Vulnerabilität. Diese Annahme passt zur fortschreitenden Atherosklerose als zugrunde liegender chronischer Erkrankung. Gemäß der TOAST-Klassifikation wird aber erst bei einer >50%igen Stenose die Ätiologie des Schlaganfalls als makroangiopathisch gewertet. Die vorliegende Habilitationsarbeit zeigt, dass auch Plaques mit ≤50%igen Stenosen zu einem Schlaganfall führen können, wenn Charakteristika einer erhöhten Plaque-Vulnerabilität

vorliegen. Der Stenosegrad als einziges Kriterium für atherosklerotisch bedingte Schlaganfälle ist daher kritisch zu sehen und in der Folge dieser Ergebnisse unzureichend.

Das Vorhandensein komplizierter Plaques ipsilateral zum Schlaganfall ist nicht nur eine potenzielle Schlaganfall-Ursache, sondern auch ein **Risikofaktor für zukünftige zerebrale Ischämien**. Für Patienten mit einem kryptogenen Schlaganfall und einer komplizierten Plaque ipsilateral zum Schlaganfall war das Rezidivrisiko 5,6fach erhöht, erneut einen ischämischen Schlaganfall oder eine TIA in einem Zeitraum von 3 Jahren zu erleiden. In der Gesamtkohorte war das Vorhandensein einer ipsilateralen komplizierten Plaque mit einem um den Faktor 2,5 erhöhten Rezidivrisiko im gleichen Zeitraum assoziiert.
Ein erhöhtes Risiko neuer Infarkte in der zerebralen Bildgebung konnte nicht nachgewiesen werden. Dies könnte in dem kürzeren Beobachtungszeitraum von einem Jahr und der geringeren Fallzahl von 107 Patienten liegen, die nach einem Jahr eine erneute zerebrale Bildgebung erhielten. Zudem zeigten beispielhaft Patienten mit einem Schlaganfall-Rezidiv mit Infarktnachweis in den diffusionsgewichteten Sequenzen keine Auffälligkeiten oder lediglich eine Atrophie im Studien-MRT, jedoch keine neue FLAIR-positive Läsion. Dies kann in der unterschiedlichen Entwicklung postischämischer Läsionen begründet sein, teils auch in einer anderen Schichtführung oder einer anderen Schichtdicke beim Studien-MRT als beim MRT in der Akutphase des Rezidivs. Gerade kleinere ischämische Läsionen könnten damit dem Nachweis im Studien-MRT entgangen sein. Ob wie vermutet multiple, kleine kortikale Ischämien im vorderen Stromgebiet als Infarktmuster mit komplizierten Plaques assoziiert sind, werden weitere Analysen aus der CAPIAS-Studie zu den Infarktmustern in der zerebralen Bildgebung zeigen.

Die bisherigen Erkenntnisse zeigen, dass komplizierte Plaques eine Schlaganfall-Ursache und ein Risikofaktor für zukünftige zerebrale Ischämien sind. Dies ist insbesondere für Patienten mit einem kryptogenen Schlaganfall von Bedeutung, bei denen die Schlaganfall-Ursache bisher nicht bekannt war. Aber auch bei anderen Schlaganfall-Ätiologien können ipsilaterale komplizierte Plaques vorliegen und eine Schlaganfall-Ursache darstellen. In der CAPIAS-Studie betrug die Prävalenz ipsilateraler komplizierter Plaques in der kombinierten Referenzgruppe 15%. Bei diesen Patienten ist die Ätiologie als kardioembolisch oder mikroangiopathisch gemäß TOAST-Kriterien eingestuft worden. Das Vorhandensein komplizierter Plaques mit Infarktnachweis im vorderen Stromgebiet auf der gleichen Seite könnte bei diesen Patienten bedeuten, dass de facto konkurrierende Ätiologien vorlagen. Dafür spricht auch, dass das Rezidivrisiko in der CAPIAS-Studie bei Vorhandensein von ipsilateralen komplizierten Plaques nicht nur bei den Patienten mit einem kryptogenen Schlaganfall, sondern im niedrigeren Ausmaß in der gesamten Studienkohorte erhöht war.

Bisher ist die Untersuchung auf eine komplizierte Plaque nicht Bestandteil der **Diagnostik nach einem akuten Schlaganfall**. Die Plaque-Bildgebung, wie sie in der CAPIAS-Studie mit mehreren MRT-Sequenzen, Oberflächenspulen und Kontrastmittelgabe durchgeführt wurde, ist jedoch aufwendig und nicht in die klinische Routine übertragbar. Daher ist eine Vereinfachung der Plaque-Bildgebung notwendig.

In der Plaque-Bildgebung können alle drei Merkmale einer komplizierten Plaque, die Plaque-Einblutung, die rupturierte fibröse Kappe und der wandständige Thrombus, im MRT entdeckt werden. Dass die **Plaque-Einblutung** das häufigste Merkmal einer komplizierten Plaque ist, wurde bereits in der Pilotstudie von Freilinger et al. gezeigt[31] und in der CAPIAS-Studie an einer höheren Patientenzahl mit unterschiedlichen Schlaganfall-Ätiologien bestätigt.[30] Gemäß einer Metaanalyse gehen Plaque-Einblutungen zudem mit einem signifikant erhöhten Schlaganfall-Risiko einher. Dies betrifft sowohl vormals asymptomatische Patienten, die einen erstmaligen Schlaganfall erleiden, als auch Rezidivinfarkte bei Patienten mit einem stattgehabten Schlaganfall.[34]

Einblutungen sind in T1-gewichteten, fettgesättigten Sequenzen als Hyperintensität erkennbar.[35] Am LMU Klinikum ist basierend auf den hier vorliegenden Ergebnissen eine solche T1-gewichtete Sequenz als Plaque-Bildgebung in das MRT-Schlaganfallprotokoll integriert worden. Dies ist mittlerweile mit 3D-Sequenzen sowohl an MRT-Geräten unterschiedlicher Hersteller (GE, Siemens), als auch an MRT-Geräten mit unterschiedlichen Feldstärken von 1,5T und 3T möglich. Die Hypothese ist, dass eine T1-gewichtete, fettgesättigte MRT-Sequenz ohne Halsspulen und ohne Kontrastmittelgabe in der Lage ist, eine Plaque-Einblutung als Marker für eine komplizierte Plaque zu erkennen.

Die Integration des Plaque-Imagings in die klinische Routine wird es ermöglichen, Informationen zur Plaque-Einblutung in einem unselektierten Patientengut von Patienten, die mit der Verdachtsdiagnose eines Schlaganfalls ein MRT erhalten, zu gewinnen. Dieses bildgebende Verfahren hat das Potenzial, die klinische Versorgung von Schlaganfall-Patienten zu verändern.

Ob das Vorhandensein einer Plaque-Einblutung einer **spezifischen Therapie** bedarf, ist derzeit unklar. Vorstellbar sind medikamentöse (z.B. eine spezifische oder doppelte Thrombozytenfunktionshemmung) oder interventionelle (z.B. neuroradiologische oder gefäßchirurgische) Verfahren als mögliche Optionen. Zur Untersuchung dieser Fragestellung müssten diese Optionen mit best medical treatment als Behandlungsform verglichen werden. Ob eine spezifische Therapie angewendet werden sollte und welche Therapieform am besten geeignet ist, um bei Patienten mit Plaque-Einblutungen ischämische Rezidivereignisse zu verhindern, wird in klinischen, randomisierten Studien untersucht werden müssen.

## 6. Zusammenfassung

Komplizierte Karotisplaques können die **Ursache für einen akuten ischämischen Schlaganfall** sein, auch wenn sie noch zu keiner >50%igen Stenose geführt haben. Dies ist insbesondere für Patienten mit einem kryptogenen Schlaganfall von Bedeutung, bei denen die Schlaganfall-Ursache nicht bekannt ist.
In der CAPIAS-Studie konnte gezeigt werden, dass komplizierte Karotisplaques bei Patienten mit einem kryptogenen Schlaganfall signifikant häufiger ipsilateral (31%) als kontralateral zum Schlaganfall (12%) vorhanden waren. Im Vergleich zu anderen Ätiologien waren komplizierte Plaques ipsilateral zum Schlaganfall signifikant häufiger bei Patienten mit einem kryptogenen Schlaganfall (31%) als bei Patienten aus der Referenzgruppe mit einem kardioembolischen oder mikroangiopathischen Schlaganfall (15%), aber seltener als bei Patienten aus der zusätzlichen Vergleichsgruppe mit einem makroangiopathischen Schlaganfall und >50-69%iger Stenose nach NASCET (68%).
Darüber hinaus wiesen ipsilaterale Plaques von Patienten mit einem kryptogenen Schlaganfall einen größeren Fettkern und eine größere Einblutungsfläche als ipsilaterale Plaques von Patienten mit einem kardioembolischen oder mikroangiopathischen Schlaganfall auf. Insgesamt ähnelte die Zusammensetzung ipsilateraler Plaques bei Patienten mit einem kryptogenen Schlaganfall eher der Zusammensetzung ipsilateraler Plaques bei Patienten mit einem makroangiopathischen Schlaganfall, ohne dass bereits eine Lumen-Einengung zu verzeichnen war. Pathophysiologisch ist von einem beginnenden Remodelling-Prozess auszugehen, d.h. diese nicht-stenosierenden Plaques befinden sich in einem Entwicklungsprozess hin zu stenosierenden Plaques mit noch größerer Plaque-Vulnerabilität.

Das Vorhandensein komplizierter Plaques ipsilateral zum Schlaganfall ist nicht nur eine potenzielle Schlaganfall-Ursache, sondern auch ein **Risikofaktor für zukünftige zerebrale Ischämien**. Für Patienten mit einem kryptogenen Schlaganfall und einer komplizierten Plaque ipsilateral zum Schlaganfall war das Rezidivrisiko 5,6fach erhöht, erneut einen ischämischen Schlaganfall oder eine TIA in einem Zeitraum von 3 Jahren zu erleiden. In der Gesamtkohorte war das Vorhandensein einer ipsilateralen komplizierten Plaque mit einem um den Faktor 2,5 erhöhten Rezidivrisiko im gleichen Zeitraum assoziiert.

Bisher ist die Untersuchung auf eine komplizierte Plaque nicht Bestandteil der **Diagnostik nach einem akuten Schlaganfall**. Die Plaque-Bildgebung, wie sie in der CAPIAS-Studie mit mehreren MRT-Sequenzen, Oberflächenspulen und Kontrastmittelgabe durchgeführt wurde, ist aufwendig und nicht in die klinische Routine übertragbar. Daher ist eine Vereinfachung der Plaque-Bildgebung notwendig.

Die Plaque-Einblutung ist das häufigste Merkmal ipsilateraler komplizierter Plaques. Als Untersuchungsmethode bietet eine T1-gewichtete, fettgesättigte Sequenz die Möglichkeit, eine Plaque-Einblutung zu identifizieren. Dazu sind weder Oberflächenspulen, noch die Gabe von Kontrastmittel notwendig. Damit ist es unkompliziert möglich, diese Sequenz in das MRT-Protokoll in der klinischen Routine zu implementieren.

Ob Patienten mit einer Plaque-Einblutung von einer spezifischen Sekundärprophylaxe wie einer Intensivierung der medikamentösen Therapie oder einer Intervention profitieren, ist derzeit noch unklar und wird in klinischen, randomisierten Studien untersucht werden müssen.

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## 10. Anlage

Auf den folgenden Seiten sind die Publikationen 1-3 der Habilitationsschrift beigefügt.

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# Complicated Carotid Artery Plaques as a Cause of Cryptogenic Stroke

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## ABSTRACT

**BACKGROUND** The underlying etiology of ischemic stroke remains unknown in up to 30% of patients.

**OBJECTIVES** This study explored the causal role of complicated (American Heart Association–lesion type VI) nonstenosing carotid artery plaques (CAPs) in cryptogenic stroke (CS).

**METHODS** CAPIAS (Carotid Plaque Imaging in Acute Stroke) is an observational multicenter study that prospectively recruited patients aged older than 49 years with acute ischemic stroke that was restricted to the territory of a single carotid artery on brain magnetic resonance imaging (MRI) and unilateral or bilateral CAP (≥2 mm, NASCET [North American Symptomatic Carotid Endarterectomy Trial] <70%). CAP characteristics were determined qualitatively and quantitatively by high-resolution, contrast-enhanced carotid MRI at 3T using dedicated surface coils. The pre-specified study hypotheses were that that the prevalence of complicated CAP would be higher ipsilateral to the infarct than contralateral to the infarct in CS and higher in CS compared with patients with cardioembolic or small vessel stroke (CES/SVS) as a combined reference group. Patients with large artery stroke (LAS) and NASCET 50% to 69% stenosis served as an additional comparison group.

**RESULTS** Among 234 recruited patients, 196 had either CS (n = 104), CES/SVS (n = 79), or LAS (n = 19) and complete carotid MRI data. The prevalence of complicated CAP in patients with CS was significantly higher ipsilateral (31%) to the infarct compared with contralateral to the infarct (12%; p = 0.0005). Moreover, the prevalence of ipsilateral complicated CAP was significantly higher in CS (31%) compared with CES/SVS (15%; p = 0.02) and lower in CS compared with LAS (68%; p = 0.003). Lipid-rich and/or necrotic cores in ipsilateral CAP were significantly larger in CS compared with CES/SVS (p < 0.05).

**CONCLUSIONS** These findings substantiate the role of complicated nonstenosing CAP as an under-recognized cause of stroke. (Carotid Plaque Imaging in Acute Stroke [CAPIAS]; NCT01284933) (J Am Coll Cardiol 2020;76:2212–22) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Stroke is a major cause of death and the leading cause of permanent disability (1). Defining the underlying etiology is important because strategies for secondary prevention, both early and long-term, vary depending on stroke mechanism (2). The importance of a precise ascertainment of stroke mechanisms has been further illustrated by the recent NAVIGATE-ESUS (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source) and RE-SPECT ESUS (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source) trials, which found no benefit of anticoagulant treatment in patients with embolic stroke of undetermined source (ESUS) (3,4).

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The widely used TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification of ischemic stroke distinguishes 5 major categories of stroke: large artery atherosclerosis, cardioembolism, small vessel occlusion, other determined etiology, and undetermined etiology (5). However, even in settings with extensive diagnostic workup, up to 30% of stroke cases are classified as undetermined, leaving these patients without specific treatment (6).

Although a diagnosis of large artery stroke (LAS) typically requires stenosis >50% (5), there are obvious limitations to a definition of stroke etiology based on a strict cutoff of a single variable. Specifically, there is growing recognition of the importance of atherosclerotic plaque composition and morphology in determining stroke risk (7,8). For example, histological studies on arteries from patients who underwent carotid endarterectomy showed features of plaque vulnerability to be more frequent in patients with symptomatic compared with asymptomatic carotid artery stenosis (9) and in recently symptomatic plaques compared with those removed late after the ischemic event (10).

High-resolution, black-blood carotid magnetic resonance imaging (MRI) enables noninvasive characterization of atherosclerotic carotid artery plaques (CAPs), including features of plaque vulnerability (11). It enables assessment of plaque size, plaque morphology, and plaque composition with good correlation to histopathology (12). Recent meta-analyses on prospective single- and multicenter MRI studies have shown that the presence of intraplaque hemorrhage (IPH), a thin and/or ruptured fibrous cap, or a large lipid-rich and/or necrotic core (LRNC) are associated with increased risk of cerebrovascular events (13,14). Specifically, a meta-analysis of individual patient data found the presence of IPH at baseline increased the risk of ipsilateral stroke in both symptomatic and asymptomatic patients (15).

In a pilot study on 32 patients with cryptogenic stroke (CS) with nonstenosing CAP, we previously found that complicated American Heart Association–lesion type (AHA-LT) VI CAP (cCAP), as defined by IPH, a ruptured fibrous cap, or the presence of a mural thrombus (12), was more frequent ipsilateral to ischemic stroke compared with that of the contralateral side (16). These findings suggested a possible causal role of nonstenosing cCAP in patients with CS. However, the study was conducted as an explorative single-center study with a limited sample size and without inclusion of patients with defined stroke etiologies.

To better define the causal involvement of nonstenosing cCAP in ischemic stroke, we initiated the CAPIAS (Carotid Plaque Imaging in Acute Stroke; NCT01284933) study as a prospective, observational, multicenter study. This study tested the following pre-specified hypotheses: 1) that in patients with CS, the prevalence of cCAP would be higher ipsilateral to the infarct versus contralateral to the infarct; and 2) that the prevalence of ipsilateral cCAP would be higher in CS compared with patients with either cardioembolic stroke (CES) or small vessel stroke (SVS) as a combined reference group, with LAS with NASCET (North American Symptomatic Carotid Endarterectomy Trial) 50% to 69% stenosis serving as an additional comparison group. To address these hypotheses, we used high-resolution MRI at 3T with dedicated surface coils and use of contrast enhancement to allow for both qualitative and detailed quantitative plaque analyses.

**ABBREVIATIONS AND ACRONYMS**

**AHA-LT** = American Heart Association–lesion type

**cCAP** = complicated carotid artery plaque

**CES** = cardioembolic stroke

**CS** = cryptogenic stroke

**DWI** = diffusion-weighted imaging

**ESUS** = embolic stroke of undetermined source

**IPH** = intraplaque hemorrhage

**LAS** = large artery stroke

**LRNC** = lipid-rich/necrotic core

**MRI** = magnetic resonance imaging

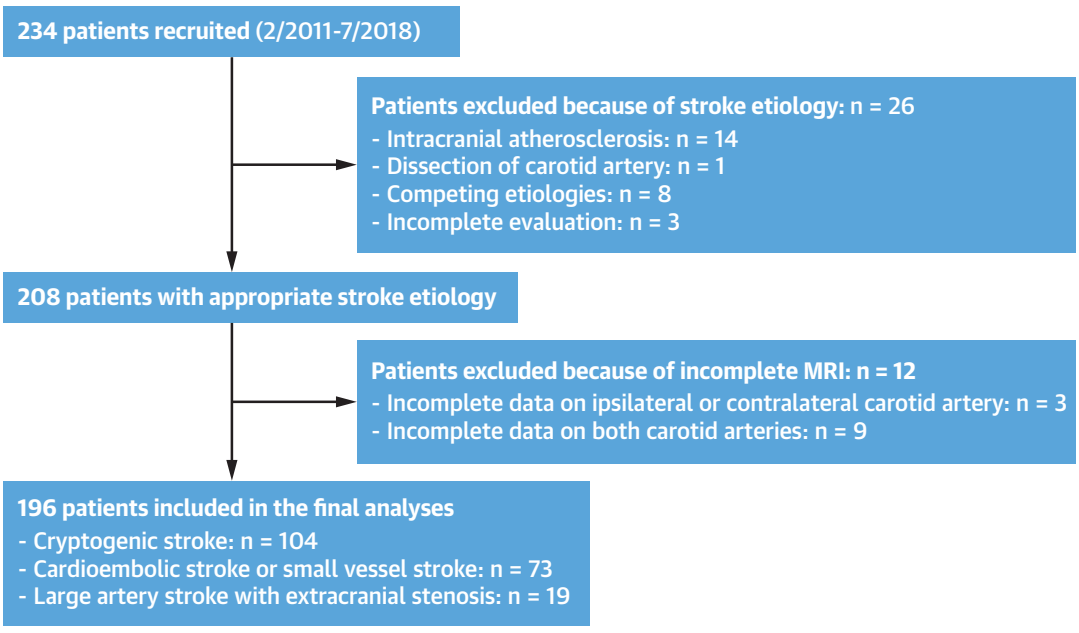
**NWI** = normalized wall index

**SVS** = small vessel stroke

## METHODS

**STUDY DESIGN.** CAPIAS is an observational, prospective, multicenter study conducted at 4 study sites in Germany: Ludwig-Maximilians-Universität Munich, Technical University Munich, University of Tübingen, and University of Freiburg. The study was approved by the local ethics committees. All participants provided written informed consent. The study design, including inclusion and exclusion criteria, was previously reported (17).

**FIGURE 1 Study Profile**




Study profile detailing the reasons for exclusion. MRI = magnetic resonance imaging.

**STUDY POPULATION.** Study participants had to meet all of the following criteria for study inclusion: age older than 49 years; an acute ischemic stroke within the last 7 days, including patients with a symptom duration of <24 h (i.e., patients who met the World Health Organization definition of a transient ischemic attack but had a documented acute ischemic infarct); a corresponding unilateral infarct restricted to the territory of a single carotid artery as defined by a diffusion-weighted imaging (DWI)-positive lesion on brain MRI at 3T; and unilateral (independent of side) or bilateral CAP with a thickness of ≥2 mm as determined by duplex ultrasound. Patients with carotid artery stenosis ≥70% (NASCET) (18) were excluded. The recruitment period was from February 2011 to July 2018. The study originally aimed to recruit 300 patients but was terminated prematurely after inclusion of 234 patients due to slow recruitment. This decision was made before initiation of data cleaning and any statistical analyses.

**STUDY WORKFLOW.** All patients underwent comprehensive diagnostic workup, including laboratory investigations, 12-lead electrocardiography, continuous electrocardiography monitoring for at least 24 h, transthoracic echocardiography, transesophageal echocardiography (when indicated), duplex ultrasound of the extracranial and intracranial vessels, and brain MRI. Additional tests (e.g., cerebrospinal fluid analysis, conventional angiography, screening for prothrombotic conditions) were performed as clinically indicated. Stroke etiology was classified according to TOAST categories (5). Classification was done centrally by trained raters (A.K. and M.L.K.), who were blinded to the plaque imaging data.

Based on the preceding information, patients were divided into the following 3 groups: 1) patients with CS, that is, stroke of undetermined origin with negative evaluation despite complete diagnostic workup and excluding patients with competing etiologies; 2) patients with either CES or SVS as a combined reference group; and 3) patients with LAS and NASCET 50% to 69% stenosis. Patients with other stroke etiologies were excluded from further analyses.

**CAROTID PLAQUE IMAGING.** All study participants underwent high-resolution, black-blood carotid MRI within 10 days of symptom onset. Imaging was done on 3T MRI scanners (Magnetom Verio, Magnetom Skyra, Magnetom Tim Trio, Magnetom Prisma, and

Biograph mMR, all from Siemens Healthineers, Erlangen, Germany) with a dedicated 4-channel surface coil (Machnet B.V., Eelde, the Netherlands). The MRI protocol consisted of a time-of-flight MR angiography, axial pre- and post-contrast black-blood T1-, PD-, and T2-weighted sequences with fat suppression (best in-plane resolution 0.5 × 0.5 $mm^2$) as previously reported (19). Post-contrast T1w imaging was performed 5 min after intravenous injection of 0.1 mmol/kg of body weight gadolinium-DO3A-butrol (Gadovist, Bayer Schering, Leverkusen, Germany).

The carotid plaque MRI data were reviewed in a consensus reading by 2 experienced radiologists (A.S. and T.S.) who were blinded to the clinical status following previously published criteria (12,19). In case of disagreement, a third expert radiologist (A.H.) was consulted, and a consensus decision was made.

Atherosclerotic plaques were classified separately for the ipsilateral and contralateral carotid artery applying the modified AHA criteria (12). MRI allowed differentiation of the following lesion types: AHA-LT I/II (initial lesion with near-normal wall thickness and without calcification); AHA-LT III (diffuse intimal thickening or small eccentric plaque without calcification); AHA-LT IV/V (plaque with a LRNC surrounded by fibrous tissue with possible calcification); AHA-LT VI (complicated plaque with possible surface defect, hemorrhage, or thrombus); AHA-LT VII (calcified plaque); and AHA-LT VIII (fibrotic plaque without lipid core and with possible small calcifications) (12).

For the primary comparisons, we focused on complicated (AHA-LT VI) plaques as pre-specified in the study protocol (17). We further performed area measurements of the lumen, wall, outer wall, and tissue components for all plaques using a custom-designed semiautomatic image analysis tool (CASCADE, University of Washington, Seattle, Washington). The normalized wall index (NWI) was calculated by dividing the wall area by the total vessel area. Tissue components (LRNC, calcification, and IPH; all in relation to the wall area and displayed as a percentage of the vessel wall), the status of the fibrous cap, and presence of juxtaluminal hemorrhage and/or mural thrombus were identified based on previously published criteria (20).

**PRIMARY STUDY COMPARISONS.** The 2 pre-specified primary comparisons were: 1) the prevalence of non-stenosing cCAPs in patients with CS ipsilateral to the infarct compared with contralateral to the infarct; and 2) the prevalence of ipsilateral cCAPs in patients with CS compared with patients with either CES or SVS as the combined reference group. Patients with LAS and NASCET 50% to 69% stenosis served as an additional comparison group.

**TABLE 1 Patient Characteristics**

| | CS (n = 104) | CES/SVS (n = 73) | p Value* | LAS (n = 19) | p Value† |
|---|---|---|---|---|---|
| Demographic characteristics | | | | | |
| Age, yrs | 71.8 ± 9.1 | 76.3 ± 9.5 | **0.002** | 72.5 ± 10.9 | 0.767 |
| Male | 83 (79.8) | 45 (61.6) | **0.010** | 13 (68.4) | 0.364 |
| NIHSS | | | | | |
| 0–5 | 80 (76.9) | 49 (67.1) | 0.149 | 16 (84.2) | 0.480 |
| 6–10 | 16 (15.4) | 15 (20.5) | 0.373 | 3 (15.8) | 0.964 |
| >10 | 8 (7.7) | 9 (12.3) | 0.303 | 0 (0.0) | 0.356 |
| Vascular risk factors | | | | | |
| Hypertension | 73 (70.2) | 54 (74.0) | 0.615 | 14 (73.7) | 0.844 |
| Hypercholesterolemia | 34 (33.0) | 25 (34.7) | 0.703 | 6 (35.3) | 0.878 |
| Diabetes mellitus | 21 (20.4) | 19 (26.0) | 0.466 | 4 (21.1) | 0.694 |
| BMI, $kg/m^2$ | 26.8 ± 3.6 | 25.6 ± 3.5 | **0.037** | 28.6 ± 4.1 | **0.046** |
| Current smoker | 20 (32.3) | 11 (33.3) | 0.225 | 3 (23.1) | 0.233 |
| Ever smoker | 62 (59.6) | 33 (45.2) | 0.076 | 13 (68.4) | 0.076 |
| History of cardiovascular disease | | | | | |
| Coronary heart disease | 19 (18.5) | 17 (23.3) | 0.217 | 2 (11.8) | 0.289 |
| Myocardial infarction | 12 (11.8) | 11 (15.3) | 0.190 | 0 (0.0) | 0.214 |
| TIA‡ | 9 (8.8) | 4 (5.6) | 0.738 | 2 (11.1) | 0.738 |
| Stroke‡ | 14 (13.5) | 14 (19.2) | 0.573 | 4 (21.1) | 0.509 |
| Previous medication | | | | | |
| Antihypertensives | 65 (63.1) | 65 (89.0) | **<0.001** | 11 (57.9) | 0.426 |
| Statins | 30 (29.1) | 27 (37.0) | 0.250 | 9 (47.4) | 0.099 |
| Oral anticoagulants | 1 (1.0) | 19 (26.0) | **<0.001** | 0 (0.0) | 0.844 |
| Antiplatelet drugs | 34 (33.0) | 27 (37.0) | 0.271 | 10 (52.6) | 0.086 |
| Stroke-related interventions | | | | | |
| Thrombolysis | 18 (17.5) | 17 (23.3) | 0.341 | 3 (15.8) | 1.000 |
| Thrombectomy | 5 (5.1) | 11 (15.1) | **0.031** | 0 (0.0) | 1.000 |

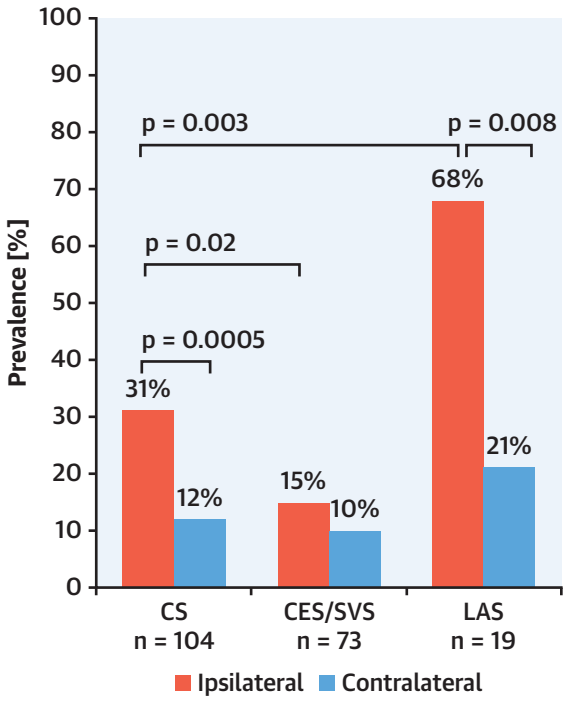
Values are mean ± SD and n (%). **Bold** p values are statistically significant. *p value, group comparisons between patients with cryptogenic stroke (CS) and patients with cardioembolic/small vessel stroke (CES/SVS). †p value, group comparisons between patients with CS and large artery stroke (LAS). ‡Previous to a qualifying event.

BMI = body mass index; NIHSS = National Institute of Health Stroke Scale; TIA = transient ischemic attack.

**STATISTICAL ANALYSES.** Categorical variables are presented as absolute and relative frequencies; continuous variables are presented as mean ± SD. Subject characteristics were calculated with Student's *t*-test for numerical variables. Categorical variables were analyzed with chi-square or Fisher exact tests. Prevalence of cCAPs and differences between stroke etiologies were calculated with Fisher's exact test. For adjustments of p values, we used logistic regression analysis with age, body mass index, and sex as covariates. Prevalence of cCAPs and differences between ipsilateral and contralateral cCAPs within 1 etiology were calculated using McNemar's test.

Plaques characteristics were analyzed with the chi-square or Fisher exact tests. Differences in plaque burden and in plaque composition were assessed with Student's *t*-test for normally distributed variables.

**FIGURE 2 Prevalence of Complicated AHA-LT VI CAPs in Patients With Acute Ischemic Stroke**




Statistical analyses between groups were performed with the Fisher exact test. Analyses within groups were performed using McNemar's test. Only significant unadjusted p values ($p < 0.05$) are shown. AHA-LT = American Heart Association–lesion type. CAP = carotid artery plaque; CES/SVS = cardioembolic/small vessel stroke; CS = cryptogenic stroke; LAS = large artery stroke.

Otherwise, the Mann-Whitney *U* test was applied. Equality of variance was tested with the Levene's test. If equality of variance was not granted, the Welch test, instead of Student's *t*-test, was applied. When indicated, false discovery rate correction was performed across all p values to account for multiple testing (Supplemental Appendix).

All analyses were performed using R version 3.5.3 (R Project for Statistical Computing, Vienna, Austria). A p value of <0.05 was considered statistically significant.

## RESULTS

**PATIENTS.** A total of 234 patients were recruited into the study. Thirty-eight patients were excluded based on nonqualifying stroke etiology or incomplete MRI data, which left 196 patients (mean age: 73.5 ± 9.6 years; median National Institute of Health Stroke Scale: 3 [interquartile range: 1 to 6]) for the final analysis (Figure 1). Of these, 169 patients had stroke symptoms that lasted ≥24 h, and 27 patients had stroke symptoms that lasted <24 h, all with a corresponding DWI-positive lesion. Among the 196 patients with a qualifying stroke etiology, 104 had CS, 73 had either CES or SVS (CES: n = 54; SVS: n = 19), and 19 had LAS. The mean interval from symptom onset to carotid MRI was 4.1 ± 1.5 days, with no significant differences among the diagnostic groups (all $p > 0.1$).

Compared with patients in the reference group, patients with CS were younger (CS: 71.8 ± 9.1 years; CES/SVS: 76.3 ± 9.5 years; $p = 0.002$), were more frequently men (CS: 79.8%; CES/SVS: 61.6%; $p = 0.01$), and had a higher body mass index (CS: 26.8 ± 3.6 kg/m$^2$; CES/SVS: 25.6 ± 3.5 kg/m$^2$; $p = 0.037$) (Table 1). Patients with LAS did not differ from patients with CS with respect to age (LAS: 72.5 ± 10.9 years) and sex (LAS: 68.4% male) ($p > 0.05$ for both comparisons) but had a higher body mass index (LAS: 28.6 ± 4.1 kg/m$^2$; $p = 0.046$) (Table 1).

**PREVALENCE OF COMPLICATED PLAQUES IN PATIENTS WITH CS AND OTHER STROKE ETIOLOGIES.** Focusing on patients with CS, nonstenosing cCAPs were approximately 3 times more frequent in carotid arteries ipsilateral to the infarct compared with the contralateral side (31% vs. 12%; $p = 0.0005$; first pre-specified comparison) (Figure 2, Supplemental Table 1). In contrast, there was no significant side-to-side difference in the prevalence of cCAPs in the reference group (CES/SVS) (ipsilateral: 15%; contralateral 10%; $p > 0.05$) (Figure 2, Supplemental Table 1). Patients with LAS showed a substantially higher prevalence of cCAPs ipsilateral to the infarct compared with contralateral to the infarct (68% vs. 21%; $p = 0.008$).

Comparisons across stroke etiologies revealed that ipsilateral cCAPs were more frequent in CS (31%) than that in the reference group (CES/SVS: 15%; $p = 0.02$; second pre-specified analysis) but less frequent than that of LAS (68%, $p = 0.003$) (Figure 2, Supplemental Tables 1 and 2).

Figure 3 shows the distribution of individual AHA-LTs of CAPs ipsilateral to the infarct stratified by stroke etiology. The most frequent lesion types in CS were complicated AHA-LT VI plaques (31%), followed by AHA-LT III (28%) and calcified AHA-LT VII (20%) plaques (Figure 3, Supplemental Table 3). In contrast, the most frequent lesion types in the reference group (CES/SVS) were calcified AHA-LT VII plaques (42%), followed by AHA-LT III (26%) and AHA-LT IV/V (15%) plaques. Most ipsilateral lesions in LAS were complicated AHA-LT VI plaques (68%), with AHA-LT III plaques being the second most frequent lesion type

(16%), thus resembling the overall distribution of ipsilateral CAPs in CS.

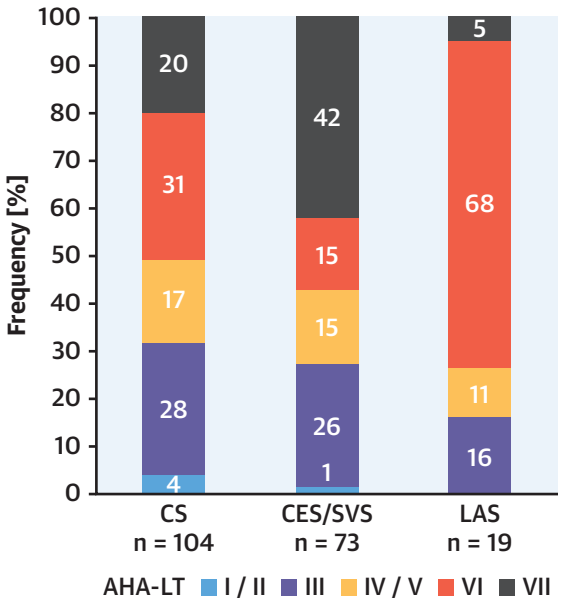
**PREVALENCE OF INDIVIDUAL MRI CHARACTERISTICS DEFINING IPSILATERAL cCAP.** MRI characteristics of complicated (AHA-LT VI) plaques that may be present in isolation or combination are IPH, a ruptured fibrous cap, and a mural thrombus indicating juxtaluminal hemorrhage (**Figure 4**). The most frequent characteristic of ipsilateral cCAP was IPH (**Figure 5**). Specifically, the frequency of IPH in ipsilateral cCAPs was 28 of 32 (88%) in patients with CS and 50 of 56 (89%) in the total sample of 196 patients (Supplemental Table 4).

**PLAQUE BURDEN AND PLAQUE COMPOSITION IN DIFFERENT STROKE ETIOLOGIES.** The quality of images obtained from plaque MRI was sufficient to quantify plaque burden and plaque composition in 191 (97.4%) of the 196 patients included in the final analyses (CS: 102 [98.1%]; CES/SVS: 72 [98.6%]; LAS: 17 [89.5%]).

Minimum lumen area and maximum NWI did not differ between patients with CS and the reference group (all $p > 0.05$) (**Table 2**). Maximum wall area and maximum total vessel area were larger in CS compared with the reference group (**Table 2**), but none of the plaque burden parameters remained significant after adjustment and correction for multiple testing (Supplemental Table 5). Plaque composition differed between CS and the reference group in that patients with CS had a larger maximum LRNC ($p = 0.006$) (**Table 2**) that remained significant after adjustment and correction for multiple testing (Supplemental Table 5).

As expected, minimum lumen area was smaller in LAS compared with CS ($p < 0.001$) (**Table 2**). Also, maximum NWI was higher in LAS compared with that of CS ($p = 0.001$). There was no significant difference in maximum wall area, total vessel area, and calcification area between patients with CS and LAS (all $p > 0.05$). Maximum IPH area was nominally higher in LAS compared with that in CS (17% vs. 9%) but did not reach statistical significance (**Table 2**, Supplemental Table 5). Maximum LRNC was higher in LAS compared with that of CS ($p = 0.038$) but did not remain significant after adjustment and correction for multiple testing ($p > 0.05$). Data on plaque burden and plaque composition in contralateral CAP are shown in Supplemental Table 6.

**FIGURE 3** **Frequency Distribution of Individual AHA-LT in Ipsilateral CAPs in Patients With Acute Ischemic Stroke**



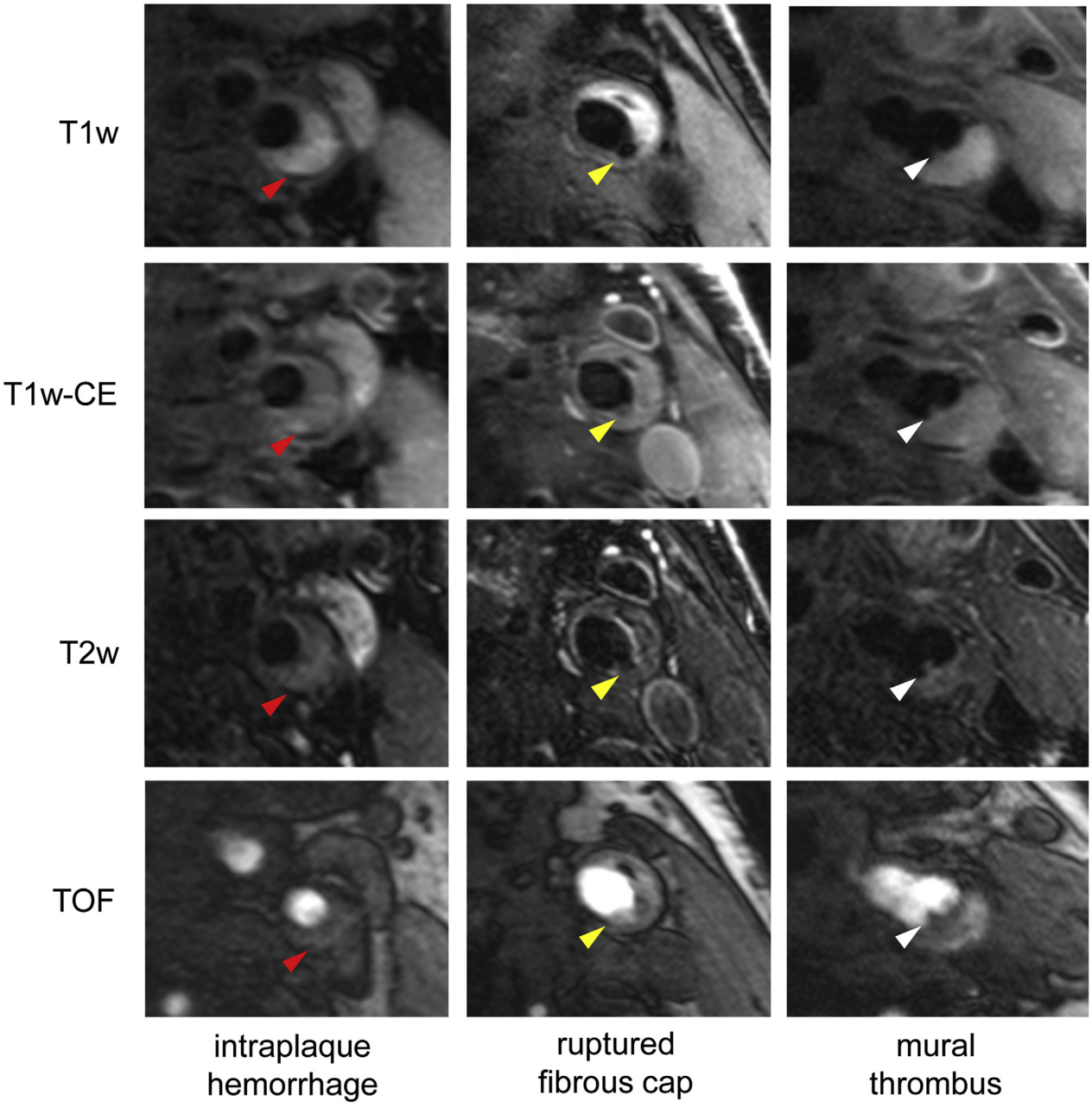

Type I/II: near-normal wall thickness; type III: diffuse intimal thickening or small eccentric plaque; type IV/V: plaque with a lipid or necrotic core surrounded by fibrous tissue with possible calcification; type VI: complicated plaque with possible surface defect, hemorrhage or thrombus; type VII: calcified plaque; and type VIII: fibrotic plaque without lipid core and with possible small calcifications. There were no fibrotic type VIII plaques detected in the sample. Abbreviations as in **Figure 2**.

## DISCUSSION

The 2 main findings of this study were that nonstenosing complicated (AHA-LT VI) CAPs in patients with CS were significantly more frequent ipsilateral to the infarct compared with contralateral to the infarct and that nonstenosing ipsilateral cCAPs were significantly more frequent in CS compared with patients with CES/SVS as the combined reference group (**Central Illustration**). Patients with LAS and NASCET 50% to 69% stenosis had the highest prevalence of ipsilateral cCAPs and largest side-by-side differences in cCAP prevalence, which underscored the importance of ipsilateral cCAPs in anterior circulation stroke. We also found ipsilateral LRNCs, a feature of plaque vulnerability that is not part of the AHA-LT VI definition, were larger in CS compared with the reference group. The most frequent feature of ipsilateral cCAP was IPH. We believe these findings add to the understanding of stroke etiologies and have potential implications for the development of diagnostic algorithms.

Our data, which were obtained in a prospective multicenter study and used cutting-edge MRI technology, substantiated recent evidence for nonstenosing cCAP being an under-recognized cause of

**FIGURE 4 MRI Characteristics of Complicated AHA-LT VI Plaques**




Illustrative examples of MRI plaque imaging data from the CAPIAS (Carotid Plaque Imaging in Acute Stroke) study demonstrating characteristics of complicated AHA-LT VI plaques. The presence of at least 1 of the following criteria defines plaques as AHA-LT VI plaques: intraplaque hemorrhage **(left panel, red arrowhead)**, ruptured fibrous cap **(middle panel, yellow arrowhead)**, or mural thrombus indicating juxtaluminal hemorrhage **(right panel, white arrowhead)**. T1w = T1-weighted; T1w-CE = contrast-enhanced T1-weighted; T2w = T2-weighted; TOF = time of flight.

stroke. Since our initial report (16), there have been several studies on nonstenosing CAP with high-risk features in patients with CS (21-24) or ESUS (25,26). These studies used variable methods for plaque imaging, including MR angiography (22–24), computed tomography angiography (21), and carotid ultrasound using variable definitions of high-risk plaques (25). All of them were single-center studies, mostly on small samples. Most of them found the prevalence of CAPs with high-risk

features to be significantly higher ipsilateral compared with contralateral to stroke (24,25). In addition to demonstrating a side-to-side asymmetry, we found the prevalence of ipsilateral cCAP to be higher in patients with CS compared with a carefully selected reference group, which provided additional evidence for a causal role of cCAP in CS. This conclusion was further supported by our findings in patients with LAS and moderate carotid artery stenosis who had the highest prevalence of ipsilateral cCAPs while likewise showing a pronounced side-to-side asymmetry.

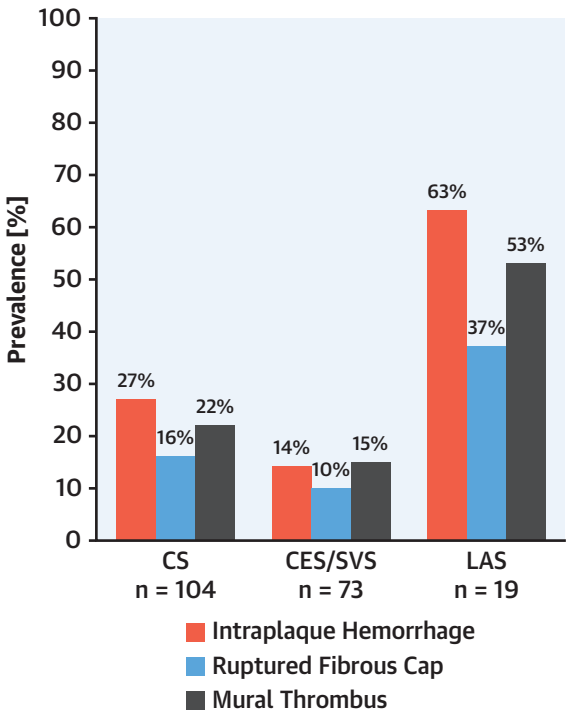
Our entry criteria required a DWI-positive lesion restricted to the territory of a single carotid artery and either unilateral or bilateral CAP. This enabled meaningful analyses while avoiding bias for the 2 main comparisons: the exclusion of patients with infarcts in the posterior circulation avoided selection of patients in whom CAP could be excluded as a possible stroke etiology. The exclusion of patients with bilateral DWI-positive lesions enabled side-to-side comparisons and avoided enriching for patients with a high a priori probability of having a proximal source of embolism from the heart or aortic arch. The requirement for either ipsilateral or contralateral CAP might have enriched for patients with some degree of atherosclerosis. However, this applied equally for patients in the reference group.

As a notable result, we found the prevalence of contralateral cCAP to range between 10% in the reference group and 21% in the LAS group. These percentages compared well with a study in asymptomatic individuals that found the prevalence of cCAP to be 8.1% in subjects with a 1% to 15% stenosis (27). By design, none of our patients had a contralateral DWI-positive lesion. Hence, all contralateral cCAPs in our patients could be considered truly silent. This also implied that a substantial proportion of cCAPs were asymptomatic. We found no significant side-to-side asymmetry in the prevalence of cCAP in the reference group. Thus, cCAP should be interpreted in the context of clinical findings, infarct patterns, and alternative stroke etiologies.

The prevalence values for cCAP and other AHA lesion types reported here could not be generalized to the broader population of patients with stroke. The requirement for both a cranial MRI and a carotid MRI examination with injection of contrast agent might have enriched for patients with less severe stroke and less comorbidity. However, the distribution of National Institute of Health Stroke Scale scores resembled that of large population-based studies (28).

The use of high-resolution, contrast-enhanced MRI enabled us to assess various aspects of plaque morphology. LRNCs, which can reliably be detected by MRI (20), represent heterogeneous tissue composed of cholesterol crystals, debris from apoptotic cells, and calcium particles (8). We found ipsilateral LRNCs to be significantly larger in CS compared with that of the reference group, which emphasized the importance of vulnerable CAP in CS. LRNCs on MRI were shown to correlate with plaque remodeling (29), to be larger in symptomatic patients compared with asymptomatic patients (30), and to be predictive of both plaque rupture (31) and risk of ipsilateral stroke (8,13). We also found LRNCs to be largest in LAS. Collectively, these findings emphasize the role of MRI-defined LRNCs in atherosclerotic stroke.

**FIGURE 5 Prevalence of Individual MRI Characteristics Defining Ipsilateral Complicated AHA-LT VI Plaques in Patients With Acute Ischemic Stroke**




The prevalence of MRI characteristics such as intraplaque hemorrhage **(red)**, ruptured fibrous cap **(blue)**, or mural thrombus indicating juxtaluminal hemorrhage **(gray)** in ipsilateral CAPs. Presence of at least 1 of these MRI characteristics define complicated AHA-LT VI plaques. Abbreviations as in Figures 1 and 2.

**FUTURE WORK.** Carotid MRI studies in patients with symptomatic carotid artery stenosis found high-risk features of CAPs were associated with an increased risk of recurrent ipsilateral stroke or transient

**TABLE 2 Plaque Burden and Plaque Composition of Ipsilateral CAPs in Acute Ischemic Stroke**

| | CS (n = 102) | CES/SVS (n = 72) | p Value* | LAS (n = 17) | p Value† |
|---|---|---|---|---|---|
| Plaque burden | | | | | |
| Minimum lumen area, $mm^2$ | 15.3 ± 8.3 | 15.4 ± 7.0 | 0.946 | 10.6 ± 3.3 | **<0.001** |
| Maximum wall area, $mm^2$ | 52.3 ± 23.2 | 45.8 ± 16.1 | **0.041** | 54.9 ± 18.8 | 0.664 |
| Maximum total vessel area, $mm^2$ | 107.2 ± 38.1 | 96.8 ± 27.0 | **0.035** | 90.0 ± 25.7 | 0.075 |
| Maximum normalized wall index | 0.63 ± 0.13 | 0.60 ± 0.11 | 0.123 | 0.73 ± 0.12 | **0.001** |
| Plaque composition | | | | | |
| Maximum LRNC, % | 20 ± 23 | 11 ± 18 | **0.006** | 32 ± 22 | **0.038** |
| Maximum calcified area, % | 5 ± 8 | 6 ± 6 | **0.015** | 7 ± 9 | 0.061 |
| Maximum hemorrhage area, % | 9 ± 21 | 2 ± 7 | **0.024** | 17 ± 24 | 0.092 |

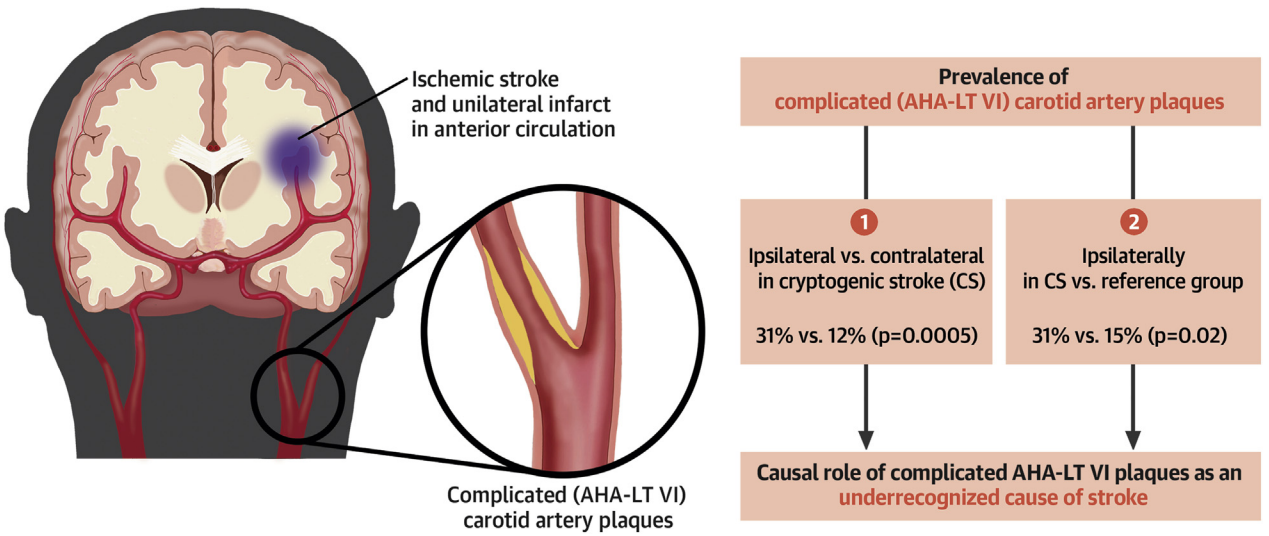
Values are mean ± SD. **Bold** p values are statistically significant. *p value, group comparisons between patients with CS and patients with CES/SVS. †p value, group comparisons between patients with CS and LAS. The unadjusted and uncorrected p values are shown.

CAPs = carotid artery plaques; LRNC = lipid-rich/necrotic core; other abbreviations as in Table 1.

ischemic attack (8,13,14). Whether high-risk features of nonstenosing CAPs are likewise associated with an increased risk of stroke recurrence is poorly investigated (13,14). However, our present findings in patients with acute stroke identified ipsilateral nonstenosing cCAPs to be high-risk lesions. Aspects that need to be addressed by future studies include the risk of stroke recurrence and other vascular events, as well as strategies for secondary prevention (32).

Integrating multisequence high-resolution, contrast-enhanced MRI into the standard diagnostic workflow of acute stroke could prove difficult, thus, we are calling for simpler imaging protocols. Unlike other features of cCAPs, IPH can be reliably detected by standard coils and conventional native T1-weighted sequences (33). We found IPH present in 89% of ipsilateral nonstenosing cCAPs. Hence, IPH might serve as a surrogate marker for cCAPs, although this would need to be formally investigated by comparing conventional imaging with high-resolution, contrast-enhanced MRI, ideally in the setting of acute stroke. Recent studies found a significant side-to-side difference for IPH in patients

**CENTRAL ILLUSTRATION Study Concept and Main Study Results**




**Kopczak, A. et al. J Am Coll Cardiol. 2020;76(19):2212–22.**

The 2 key comparisons exploring the role of complicated American Heart Association–lesion type (AHA-LT) VI plaques in cryptogenic stroke (CS).

with CS or ESUS using conventional MRI (24,25). Accounting for IPH was further shown to reclassify stroke etiologies of up to 15% of patients with anterior circulation infarction (24). However, whether integration of carotid MRI into the diagnostic workflow for anterior circulation stroke would eventually influence individual therapeutic options remains to be investigated.

**STUDY STRENGTHS.** Our study had several strengths. First, CAPIAS was a prospective, multicenter study with plaque imaging obtained within 10 days after symptom onset. Second, all patients had imaging-confirmed stroke with an infarct pattern that was related to the primary study comparisons. Third, sample size by far exceeded that of previous CAP imaging studies with high-resolution carotid MRI (16,25), which enhanced power and enabled comparisons across etiological groups. Fourth, all patients entering the final analysis received comprehensive diagnostic workup, thus minimizing the risk of misclassification with regard to TOAST category. Fifth, we used high-resolution carotid MRI at 3T using dedicated carotid surface coils and a standardized imaging protocol that included contrast-enhanced sequences (19), which enabled detailed assessment of plaque characteristics. Sixth, evaluation of the high-resolution carotid MRI images was done centrally by readers blinded to the clinical data. Finally, the primary comparisons were specified before study onset.

**STUDY LIMITATIONS.** Our study also had limitations, in particular, the long recruitment period. This mostly related to our entry criteria and the requirement for a study-related MRI with injection of a contrast agent. The number of patients with LAS was relatively low. This mostly related to a substantial proportion of patients with a NASCET of 50% to 69% carotid artery stenosis who underwent early carotid endarterectomy or stenting following European guidelines (34). As per our entry criteria, these patients were excluded from study participation. However, and despite the low number of patients with LAS, we found a significantly higher prevalence of ipsilateral cCAPs in LAS compared with CS and a significant side-to-side difference in LAS that further validated our primary comparisons and substantiated the causal role of cCAP in acute stroke. Additional limitations included a relatively low proportion of female patients, the limited age range, and a minimum duration of continuous electrocardiographic monitoring of only 24 h. Also, we excluded patients with CAP <2 mm, which limited the results to stroke patients with some degree of atherosclerosis.

## CONCLUSIONS

Our findings substantiate the role of nonstenosing ipsilateral cCAP as an underrecognized cause of stroke. Whether integration of carotid MRI into the diagnostic workflow for anterior circulation stroke would eventually influence therapeutic strategies remains to be investigated.

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## AUTHOR RELATIONSHIP WITH INDUSTRY

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Nonstenotic cCAPs are under-recognized as a potential cause of ischemic stroke.

**TRANSLATIONAL OUTLOOK:** Additional studies are needed to determine how characterization of atherosclerotic carotid artery lesions by MRI during evaluation of patients with cryptogenic anterior circulation ischemic stroke could influence management.

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**KEY WORDS** AHA–lesion type, carotid artery, complicated plaque, plaque imaging, stroke, stroke etiology

**APPENDIX** For an expanded Methods section and supplemental tables, please see the online version of this paper.

radiations of the left bundle branch, leading to isolated LPFB. Fibrosis mostly occurred in the inferior and lateral LV, a hallmark site of LV ACM (3); 2 patients fulfilled task force criteria, and 2 individuals had pathogenic mutations in the ACM spectrum. Further studies are needed to assess the frequency and clinical significance of axis deviations in ACM.

The limitations of the study include the retrospective design and the long study period, which may imply selection bias despite the monocentric and consecutive inclusion. Also, we did not assess confounding factors in the association between LPFB and ACA/SCD. In fact, a causal link would make little sense mechanistically, and LPFB should be seen more as an "epiphenomenon" of underlying LV fibrosis, which in contrast is a known cause of SCD in NICM (4). Finally, complete heart block could be a possible cause of death in the 5 patients with SCD, and in patient #5, in whom only negative stress tests were performed, we cannot exclude an ischemic SCD.

Our findings suggest that isolated LPFB could be a valuable tool for arrhythmic risk stratification in young people, should be recognized as a pathological finding, and should prompt further investigation to detect underlying structural abnormalities.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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# Assessment of Nonstenotic Carotid Plaques

We read with interest the work by Kopczak et al. (1) describing complicated nonstenotic carotid artery plaques (CAPs) as a possible cause for what we currently call "cryptogenic" stroke. As the investigators point out, the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria only acknowledge carotid plaques that cause >50% stenosis as a cause of stroke. Strokes with ipsilateral nonstenotic (<50% stenosis) carotid plaques are classified as "cryptogenic." However, with the advent of magnetic resonance imaging (MRI) plaque imaging, understanding of CAP architecture has improved. Various studies have shown increased risk of recurrent stroke in the presence of high-risk plaque features (2). In their meticulous study, Kopczak et al. (1) analyzed CAPs using MRI in patients with cryptogenic stroke compared with stroke patients with small-vessel disease or cardioembolic stroke. They found a significantly higher prevalence of complicated CAPs in cryptogenic stroke than in the reference group (31% vs. 15%). In their study, complicated CAPs were assessed on contrast-enhanced MRI, which is usually not part of the emergent stroke work-up. Computed tomography angiography (CTA), on the other hand, is an integral part of the initial assessment of patients presenting with suspected acute stroke. A recent study showed that nonstenotic carotid plaques on CTA in patients with cryptogenic stroke are associated with ipsilateral stroke, but no high-risk CTA plaque features could be identified (3). Evaluating plaque morphology on

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CTA would be a more practical approach than MRI-based plaque assessment: in contrast to MRI, CTA is easy to acquire, robust against patient motion, and importantly, it is obtained in all acute stroke patients on arrival at the hospital. Given the highly interesting and encouraging results of the study by Kopczak et al. (1), we think that further studies to transfer these findings to a CTA paradigm are paramount because this would allow for routine detection of symptomatic nonstenotic carotid disease in the acute setting, thereby further improving management.

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Dr. Goyal has received personal fees from Mentice, Medtronic, Microvention, and Stryker, outside the submitted work; and holds a patent to systems of acute stroke diagnosis issued and licensed. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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# Inflammation in Nonstenotic Carotid Artery Plaques

## One More Factor to Consider?

We read with great interest the work by Kopczak et al. (1), who evaluated the incidence of ipsilateral complicated nonstenotic carotid plaques in patients with recent ischemic stroke. In this retrospective analysis, the authors showed that in patients with cryptogenic stroke, complicated nonstenotic carotid plaques were almost 3× more common ipsilaterally to the lesion compared to the contralateral carotid. Moreover, the prevalence was twice as common as in patients with cardioembolic or small-vessel stroke. Hence, the authors highlighted the significance of the assessment of plaque composition apart from stenosis severity in the evaluation of etiology and further in the classification of ischemic strokes.

Previous international consensus documents have defined as vulnerable actively inflamed plaques with a large lipid core and a thin cap (2). Intraplaque hemorrhage and positive remodeling have also been included as minor vulnerable characteristics. However, in the present study, no mention has been made regarding the inflammatory status of carotid plaques. In 2002, Rudd et al. (3) showed that in patients with symptomatic carotid atherosclerosis, ipsilateral symptomatic carotid plaques accumulated 30% more [18F]-fluorodeoxyglucose than the contralateral asymptomatic lesions did. In accordance with the findings of Kopczak et al. (1), our team showed, in 2015, that in patients with bilateral carotid atherosclerosis and recent acute ischemic stroke, culprit ipsilateral plaques exhibited higher temperatures, as assessed by microwave radiometry, reflecting increased inflammation (4). More importantly, increased carotid temperatures by microwave radiometry have been correlated with increased [18F]-fluorodeoxyglucose accumulation by positron emission tomography and local macrophage infiltration by histopathology and immunohistochemistry, in 21 patients undergoing carotid endarterectomy (5).

In conclusion, contemporary advances in imaging modalities allow complete plaque composition evaluation. The incorporation, however, of this information in patient management, on top of stenosis severity, mandates further studies.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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## REPLY: Comparison of Different Plaque Imaging Techniques to Detect Complicated Carotid Artery Plaques

We thank Dr. Singh and colleagues and Dr. Benetos and colleagues for their thoughtful comments on our recent report (1), which originated from our prospective, observational clinical study at 4 study sites in Germany (CAPIAS [Carotid Plaque Imaging in Acute Stroke]; NCT01284933).

We agree with the comments by Dr. Singh and colleagues who noted that our contrast-enhanced 3T magnetic resonance (MR) multisequence plaque imaging protocol is too demanding and time-consuming to be integrated into routine clinical care in stroke patients. However, this technique enabled us to perform quantitative and qualitative analyses of plaque composition and morphology. Our data revealed a high prevalence of ipsilateral complicated plaques in patients with cryptogenic stroke with intraplaque hemorrhage (IPH) being a component in 88% of complicated plaques. IPH is a key feature of plaque vulnerability (2), can be accurately and reproducibly identified by magnetic resonance imaging (MRI) (2), and is a strong predictor for ischemic stroke in symptomatic and asymptomatic patients with carotid artery disease (3).

To facilitate the use of plaque MRI in a clinical setting, we are calling for simpler MR protocols focusing on the detection of IPH. This is well in line with a recently published statement by the Carotid Imaging Consensus Group, which suggested use of a single heavily T1-weighted sequence with fat suppression (4). This sequence can be obtained on most MRI scanners using the same field-of-view and coils as are typically used for brain and neck imaging in acute ischemic stroke work-up (4).

Dr. Singh and colleagues have a point to discuss whether computed tomographic angiography (CTA) would not be more broadly available and easier to obtain. However, IPH is difficult to detect on CTA because Hounsfield unit (HU) values of IPH, fibrous tissue, and lipid-rich and/or necrotic core significantly overlap (4). Whereas CTA allows differentiating among soft, hard, and mixed plaques and can visualize ulcers, thrombi, and neovessels, the predictive value of vulnerable plaque features assessed by CTA for future cerebrovascular events remains largely unexplored (4). In contrast, a large number of prospective MR studies and several meta-analyses (2,3) have demonstrated that the presence of IPH on MRI strongly predicts cerebrovascular events.

We would also like to thank Dr. Beneto and colleagues for their valuable comments. As stated correctly, we did not comment on inflammatory parameters in our paper. We agree that [18F]-fluorodeoxyglucose ($^{18}$F-FDG) accumulation detected by positron emission tomography (PET) is another promising method to characterize plaques. In fact, we previously reported on 18 patients who had undergone $^{18}$F-FDG PET-MRI of the carotid arteries and found the presence of complicated plaques to be associated with higher $^{18}$F-FDG uptake (5). Interestingly, patients with unilateral complicated plaques showed $^{18}$F-FDG uptake in both ipsilateral and contralateral plaques, pointing to a generalized inflammatory process. These results warrant further validation. However, $^{18}$F-FDG PET has its limitations for routine application, including the limited availability and radiation exposure.

While there are certainly several high-risk plaque features that determine a plaque's vulnerability, the Carotid Imaging Consensus Group recently concluded that carotid IPH on fat-suppressed T1-weighted imaging currently represents the most promising new imaging biomarker of vulnerable plaques (4). In our opinion, efforts should be made to implement these carotid MRI techniques in a routine clinical setting.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ORIGINAL INVESTIGATIONS

# Complicated Carotid Artery Plaques and Risk of Recurrent Ischemic Stroke or TIA

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## ABSTRACT

**BACKGROUND** Complicated nonstenosing carotid artery plaques (CAPs) are an under-recognized cause of stroke.

**OBJECTIVES** The purpose of this study was to determine whether complicated CAP ipsilateral to acute ischemic anterior circulation stroke (icCAP) are associated with recurrent ischemic stroke or transient ischemic attack (TIA).

**METHODS** The CAPIAS (Carotid Plaque Imaging in Acute Stroke) multicenter study prospectively recruited patients with ischemic stroke restricted to the territory of a single carotid artery. Complicated (AHA-lesion type VI) CAP were defined by multisequence, contrast-enhanced carotid magnetic resonance imaging obtained within 10 days from stroke onset. Recurrent events were assessed after 3, 12, 24, and 36 months. The primary outcome was recurrent ischemic stroke or TIA.

**RESULTS** Among 196 patients enrolled, 104 patients had cryptogenic stroke and nonstenosing CAP. During a mean follow-up of 30 months, recurrent ischemic stroke or TIA occurred in 21 patients. Recurrent events were significantly more frequent in patients with icCAP than in patients without icCAP, both in the overall cohort (incidence rate [3-year interval]: 9.50 vs 3.61 per 100 patient-years; $P = 0.025$, log-rank test) and in patients with cryptogenic stroke (10.92 vs 1.82 per 100 patient-years; $P = 0.003$). The results were driven by ipsilateral events. A ruptured fibrous cap (HR: 4.91; 95% CI: 1.31-18.45; $P = 0.018$) and intraplaque hemorrhage (HR: 4.37; 95% CI: 1.20-15.97; $P = 0.026$) were associated with a significantly increased risk of recurrent events in patients with cryptogenic stroke.

**CONCLUSIONS** Complicated CAP ipsilateral to acute ischemic anterior circulation stroke are associated with an increased risk of recurrent ischemic stroke or TIA. Carotid plaque imaging identifies high-risk patients who might be suited for inclusion into future secondary prevention trials. (Carotid Plaque Imaging in Acute Stroke [CAPIAS]; NCT01284933) (J Am Coll Cardiol 2022;79:2189-2199) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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**ABBREVIATIONS AND ACRONYMS**

**AHA** = American Heart Association

**cCAP** = complicated carotid artery plaques

**DWI** = diffusion-weighted imaging

**FLAIR** = fluid-attenuated inversion recovery

**IPH** = intraplaque hemorrhage

**MRI** = magnetic resonance imaging

**TIA** = transient ischemic attack

Stroke is a leading cause of death and disability and a major cause of cognitive decline.[1,2] Recurrence rates vary depending on stroke etiology.[3-5] We recently demonstrated a role of complicated (American Heart Association [AHA] lesion type VI) nonstenosing carotid artery plaques (cCAP) as an under-recognized cause of ischemic stroke.[6,7] Estimates of the risk of recurrent ischemic cerebrovascular events in patients with acute ischemic stroke and cCAP are required to counsel patients and inform prevention trials, but are currently unavailable.

SEE PAGE 2200

cCAP are defined by the presence of a ruptured fibrous cap, intraplaque hemorrhage (IPH), or mural thrombus[8] and can be accurately and reliably detected by multisequence, black-blood carotid magnetic resonance imaging (MRI) using dedicated surface coils and contrast agent.[9-11] Previous carotid MRI studies in patients with symptomatic carotid artery stenosis have suggested an association between high-risk features of carotid plaques, in particular IPH, and an increased risk of recurrent ischemic stroke or transient ischemic attack (TIA).[12-15] However, there was substantial delay in these studies between the qualifying event and imaging (>1 month on average),[12-17] and they might thus not be reflective of the risks associated with cCAP in the acute phase of stroke. Also, these studies included patients selected for the presence of carotid artery stenosis and typically used imaging protocols that do not permit the detection of a ruptured fibrous cap.

To our knowledge, there are no studies that have related the presence of cCAP or IPH as assessed in the first days after stroke to recurrent ischemic stroke or TIA. Such information is needed, particularly for patients with nonstenosing carotid artery plaques and no recognizable cause of stroke (cryptogenic stroke), to optimize strategies for risk prediction and potentially also for stratifying patients into future secondary prevention trials.

To better define the role of cCAP ipsilateral to acute ischemic anterior circulation stroke and the association with recurrent ischemic stroke or TIA, we initiated CAPIAS (Carotid Plaque Imaging in Acute Stroke; NCT01284933) as a prospective, observational, multicenter study. CAPIAS employed multisequence, contrast-enhanced carotid MRI at 3-T within 10 days from stroke onset using dedicated carotid coils. Baseline results on index events have previously been published.[7] The current study examined the association of ipsilateral cCAP with recurrent ischemic stroke or TIA over 3 years of follow-up with a particular emphasis on patients with cryptogenic stroke. We further analyzed associations of individual cCAP characteristics (fibrous cup rupture, IPH, mural thrombus) with recurrent ischemic stroke or TIA. Finally, we explored the association of ipsilateral cCAP with new brain lesions in patients undergoing brain MRI at 12 months after the index event. Our prespecified hypothesis was that recurrent ischemic stroke or TIA would be more frequent in patients with ipsilateral cCAP compared with patients without ipsilateral cCAP.

## METHODS

**STUDY PARTICIPANTS.** CAPIAS is an observational, prospective, multicenter cohort study conducted at 4 tertiary care centers in Germany: Ludwig-Maximilian-University Munich, Technical University Munich, University of Tübingen, and University of Freiburg. The study was approved by the local ethics committees. All participants provided written informed consent. The study design including eligibility criteria have previously been published.[7,18] In brief, eligible patients were older than 49 years of age, had an acute ischemic stroke within the last 7 days, and had a corresponding unilateral infarct restricted to the territory of a single carotid artery as defined by a diffusion-weighted imaging (DWI)-positive lesion on brain MRI at 3-T. Eligible patients further had unilateral (independent of side) or bilateral carotid artery plaques with a thickness of ≥2 mm as determined by duplex ultrasound. Key exclusion criteria were carotid artery stenosis ≥70% (NASCET),[19] carotid artery dissection, intracranial atherosclerosis as the presumed stroke etiology, competing etiologies, and incomplete evaluation.[7] Stroke etiology was classified according to TOAST criteria.[7,20] The recruitment period was February 2011 to July 2018.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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**PROCEDURES.** All study participants underwent high-resolution, multisequence carotid MRI within 10 days of symptom onset. Imaging was done on 3-T MRI systems using dedicated 4-channel carotid coils and contrast agent as previously described.[7] Magnetic resonance plaque imaging allows differentiation of specific AHA-lesion types (**Table 1**). Complicated (AHA-LT VI) carotid artery plaques were assessed on the basis of published criteria (**Table 1,** Supplemental Table 1).[8] Patients with incomplete carotid MRI data were excluded, leaving 196 patients for analysis (**Figure 1,** Supplemental Table 2).[7] The magnetic resonance plaque imaging results were archived centrally and were not communicated to the study participants or treating physicians.

Patients were followed up through telephone interviews conducted at 3, 12, 24, and 36 months after the index stroke. Assessments were done centrally by qualified investigators. Standardized questionnaires were used to assess new clinical events, medical treatment, and cardiovascular risk factors. If a patient was unable to take part in the interview, the information was obtained from a caregiver or other suitable proxy. Details on the approach used for data ascertainment are described in Supplemental Figure 1. In case of a positive screening for any cerebrovascular outcome event, the information was validated by contacting the hospital, treating neurologist, and general practitioner, in that order.

**CLINICAL OUTCOMES.** The primary outcome was the composite endpoint of recurrent ischemic stroke or TIA. Secondary outcomes included recurrent ischemic stroke and recurrent ipsilateral ischemic stroke or TIA. Ischemic stroke was defined as an episode of neurological dysfunction caused by focal cerebral infarction as documented by a corresponding DWI-positive lesion on brain MRI. TIA was defined as a transient episode of neurological dysfunction suggestive of focal cerebral ischemia without acute infarction. All information recorded from the patient, their hospital records, their neurological records, their general practice records, and their brain imaging results, were used for the adjudication of outcome events. Outcome events were adjudicated on the basis of clinical records. Adjudication was performed by 2 board-certified stroke experts (D.J. and A.K.), who independently reviewed all available records and were blinded to the plaque imaging data. Ipsilateral ischemic events were defined as any event in the distribution of the symptomatic carotid artery or of uncertain vascular distribution.[21] Death was classified into cardiovascular death and noncardiovascular death following consensus criteria.[22] Patients undergoing revascularization were censored at the time of the intervention.

**TABLE 1 AHA-LT Classification Used for MR Plaque Imaging**

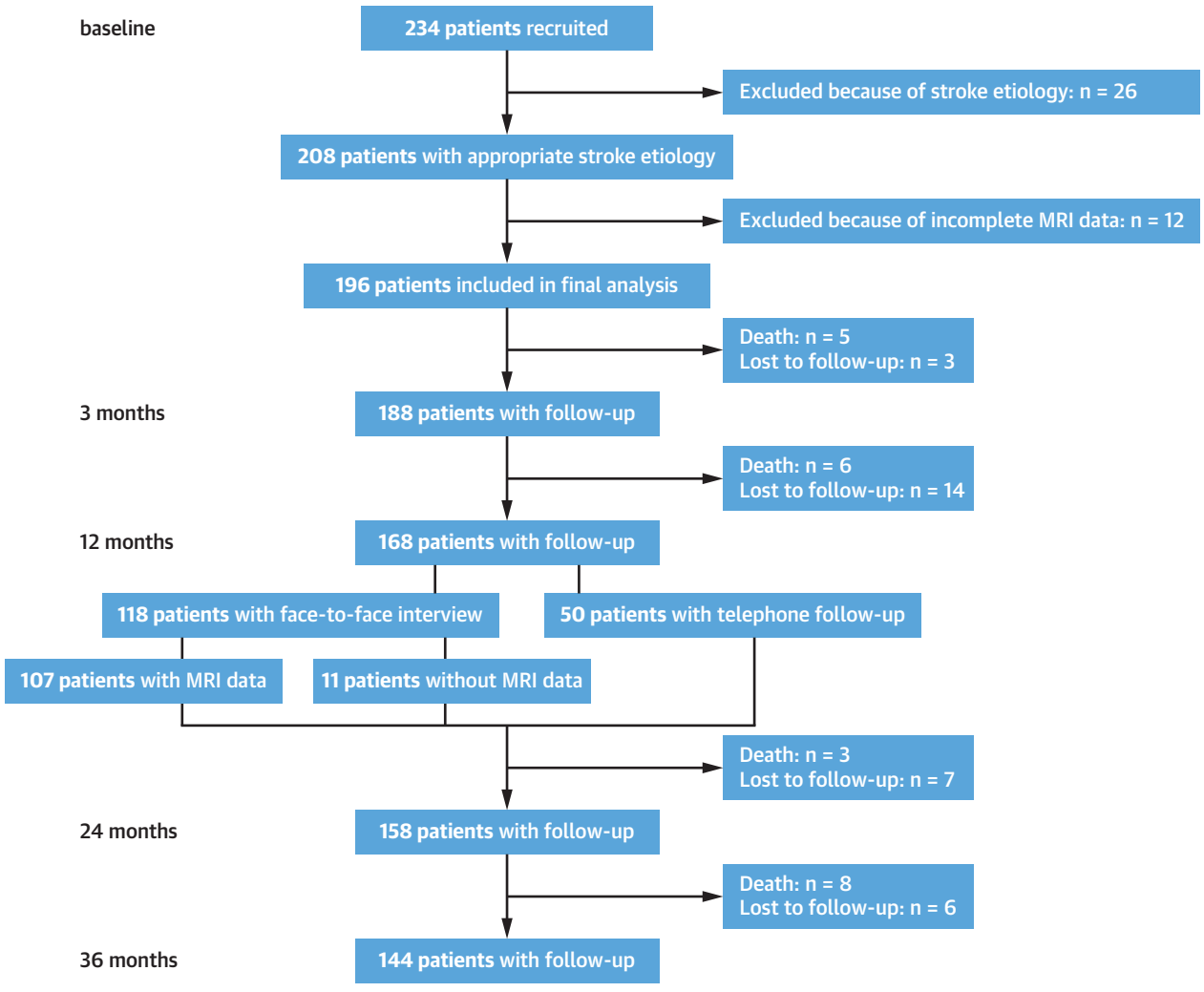
| AHA-LT | Definition |
|---|---|
| AHA-LT I/II | Near-normal wall thickness, no calcification |
| AHA-LT III | Diffuse intimal thickening or small eccentric plaque, no calcification |
| AHA-LT IV/V | Plaque with a lipid or necrotic core surrounded by fibrous tissue with possible calcification |
| AHA-LT VI | Complicated plaque with possible surface defect, hemorrhage, or thrombus |
| AHA-LT VII | Calcified plaque |
| AHA-LT VIII | Fibrotic plaque without lipid core and with possible small calcifications |

Magnetic resonance (MR) imaging allows for differentiation of the following American Heart Association lesion types (AHA-LT) in carotid arteries: AHA-LT I/II, AHA-LT III, AHA-LT IV/V, AHA-LT VI, AHA-LT VII, and AHA-LT VIII. Modified from Cai et al.[8]

**NEW BRAIN LESIONS.** Patients were invited for a second brain MRI scan 12 months after stroke for the detection of new brain lesions. Imaging was done on 3-T MRI systems. The core protocol consisted of a 2-dimensional (2D) fluid-attenuated inversion recovery (FLAIR) sequence (repetition time: 7,000-9,000 milliseconds, echo time: 93-136 milliseconds, slice thickness: 3-4 mm). New brain lesions were detected by comparing the follow-up scans to the baseline brain MRI scans, which had been obtained in the context of clinical routine. Scans were independently reviewed by 2 experienced radiologists (A.S. and D.S.) who were blinded to the clinical status. In case of disagreement, a third expert radiologist (T.S.) was consulted and a consensus decision was made. New brain lesions were divided into 3 categories: 1) definitive new ischemic lesion; 2) progression of preexisting small vessel disease; and 3) new brain lesions that could not be confidently attributed to a specific lesion type.

**STATISTICAL ANALYSIS.** Incident event rates were calculated as the number of incident events divided by the person-time at risk and expressed as incidence rates per 100 patient years. Kaplan-Meier curves along with log-rank tests were used to depict and test the differences of cumulative event rates between patients with and without ipsilateral cCAP. Analyses started at the time of stroke onset and terminated at the earliest occurrence of an outcome event. Analyses were censored at the time of last available follow-up, revascularization, or death, whichever came first. Multivariable Cox proportional hazards regression was used to estimate HRs with 95% CIs adjusted for age and sex. We added 3 sensitivity analyses: an analysis further correcting for minimal lumen area of both the ipsilateral and contralateral carotid artery as a quantitative measure of stenosis grade; a second analysis further correcting for the presence/absence

**FIGURE 1 Study Profile**




Study participants were followed up by telephone interviews conducted at 3, 12, 24, and 36 months after stroke. In addition, patients were invited for a second brain MRI scan 12 months after stroke for the detection of new brain lesions. MRI = magnetic resonance imaging.

of contralateral cCAP; and a third analysis further correcting for diabetes, hypertension, and history of myocardial infarction.

Proportional hazards assumptions were checked by inspecting scaled Schoenfeld residuals (all $P > 0.05$). New brain lesions on MRI were compared in patients with and without ipsilateral cCAP using logistic regression adjusted for age and sex. Categorical variables are presented as absolute and relative frequencies; continuous variables are presented as mean ± SD. Subject characteristics were calculated with Student's *t*-test for numerical variables. Categorical variables were analyzed with chi-square or Fisher exact test. All analyses were performed using R version 4.1.0 (R Project for Statistical Computing). A *P* value <0.05 was considered statistically significant. Because of the exploratory nature of our analysis, *P* values and 95% CIs presented in this report have not been adjusted for multiplicity.

## RESULTS

Among 196 eligible patients with complete carotid MRI data, 104 patients had cryptogenic stroke, 54 had cardioembolic stroke, 19 had large artery stroke, and 19 had small vessel stroke.[7] In total, 188 patients attended at least 1 follow-up visit, and 144 patients completed the follow-up after 3 years (**Figure 1**).

A total of 22 patients died (8 cardiovascular deaths, 14 noncardiovascular deaths), and 30 patients were lost to follow-up.

Overall, 56 (29%) patients had ipsilateral cCAP at baseline (**Table 2**).[7] In total, 13 patients underwent carotid endarterectomy (9 patients with large artery stroke, 2 with cryptogenic stroke) or stenting (2 with large artery stroke) during follow-up (median interval between the qualifying event and the intervention: 8 days [range 2-478 days]). Their characteristics are shown in Supplemental Table 3.

**RECURRENT ISCHEMIC STROKE OR TIA.** Overall, 21 patients experienced a recurrent ischemic stroke (n = 16) or TIA (n = 5), and 4 patients had multiple (n ≥1) recurrent events. The incidence rate (3-year interval) for the combined endpoint of recurrent ischemic stroke or TIA was significantly higher in patients with ipsilateral cCAP (9.50 per 100 patient-years) compared with patients without ipsilateral cCAP (3.61 per 100 patient-years; $P = 0.025$, log-rank test) (**Central Illustration**). In Cox regression models adjusting for age and sex, ipsilateral cCAP were associated with a 2.5-fold increased risk of recurrent ischemic stroke or TIA over 3 years (HR: 2.51; 95% CI: 1.03-6.11; $P = 0.043$) (**Figure 2**). Results remained significant when restricting the analysis to ipsilateral recurrent ischemic stroke or TIA (HR: 3.37; 95% CI: 1.21-9.38; $P = 0.020$) (**Figure 2,** Supplemental Figure 2A). **Figure 2** further shows the HRs for the isolated endpoint of ischemic stroke, which did not reach statistical significance.

More than one-half of patients with recurrent ischemic stroke or TIA (11 of 21 patients, 52.4%) had been classified as having cryptogenic stroke based on their index stroke. Recurrent ischemic stroke or TIA were significantly more frequent in cryptogenic stroke patients with ipsilateral cCAP (incidence rate [3-year interval]: 10.92 per 100 patient-years) compared with cryptogenic stroke patients without ipsilateral cCAP (1.82 per 100 patient-years; $P = 0.003$, log-rank test) (**Figure 3**). In Cox regression models adjusting for age and sex, ipsilateral cCAP were associated with a 5.6-fold increased risk of recurrent ischemic stroke or TIA over 3 years (HR: 5.60; 95% CI: 1.43-21.83; $P = 0.013$) (**Figure 2**). Again, results remained significant when focusing on ipsilateral recurrent ischemic stroke or TIA (HR: 5.01; 95% CI: 1.25-20.05; $P = 0.023$) (**Figure 2,** Supplemental Figure 2B). Results for patients with other stroke etiologies are shown in Supplemental Table 4.

To account for differences in stenosis grade, we added a sensitivity analysis, further correcting for the minimal lumen area of the ipsilateral and contralateral carotid artery. The results for recurrent ischemic stroke or TIA remained significant both in the overall cohort and in patients with cryptogenic stroke (Supplemental Table 5). The same was seen in a second sensitivity analysis further correcting for the presence/absence of contralateral cCAP (Supplemental Table 5). Effects were even more pronounced in a third sensitivity analysis additionally adjusting for diabetes, hypertension, and history of myocardial infarction. We also explored associations between the presence of cCAP irrespective of side (ipsilateral, contralateral, or both) and recurrent ischemic stroke or TIA. The associations were attenuated both in the overall cohort (HR: 2.26; 95% CI: 0.93-5.49; $P = 0.070$) and in patients with cryptogenic stroke (HR: 4.79; 95% CI: 1.20-19.04; $P = 0.026$).

**MRI PLAQUE CHARACTERISTICS DEFINING IPSILATERAL cCAP.** The associations of individual MRI

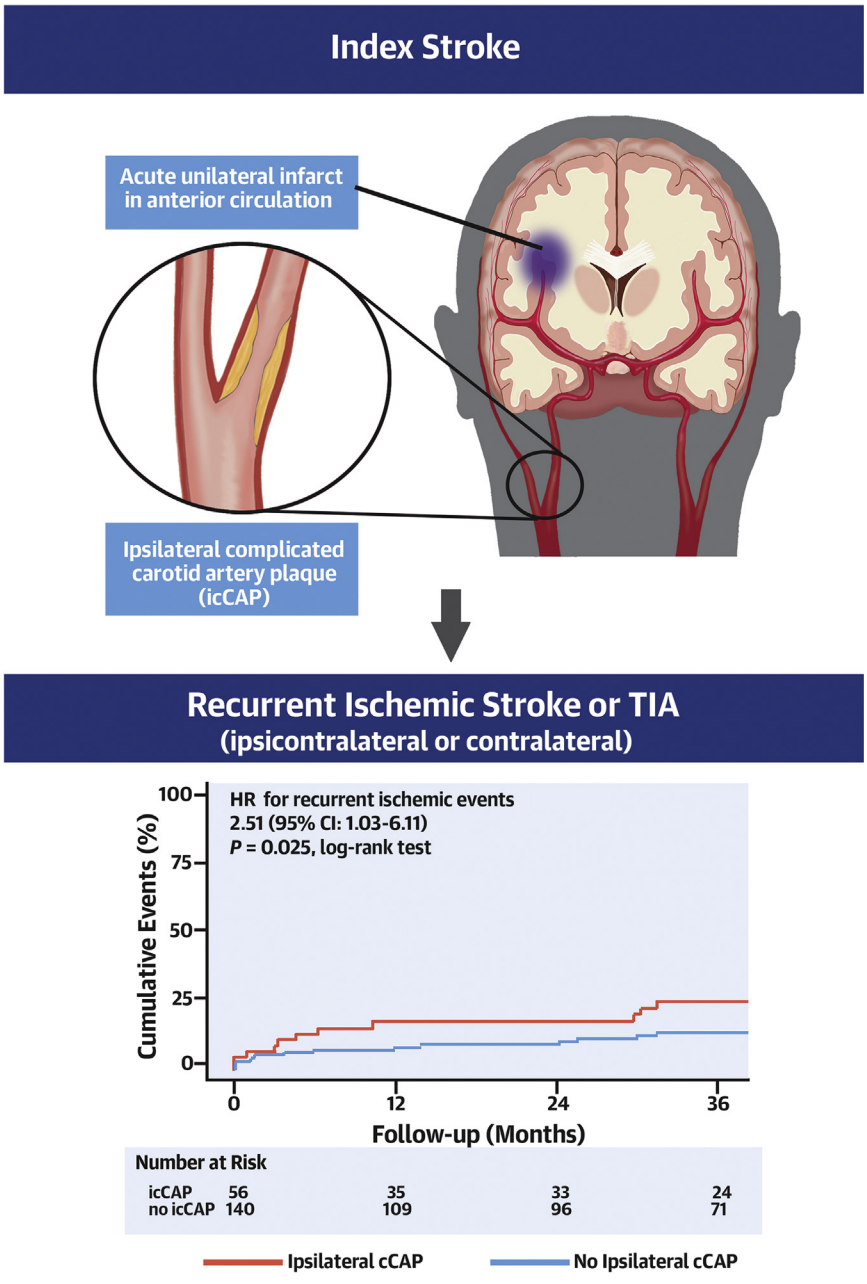
**TABLE 2 Patient Characteristics**

| | With icCAP (n = 56) | Without icCAP (n = 140) | *P* Value |
|---|---|---|---|
| Demographic characteristics | | | |
| Age, y | 73.7 ± 8.4 | 73.4 ± 10.1 | 0.859 |
| Male | 48 (86) | 93 (66) | **0.007** |
| NIHSS | | | |
| 0-5 | 46 (82) | 99 (71) | 0.099 |
| 6-10 | 8 (14) | 26 (19) | 0.474 |
| >10 | 2 (4) | 15 (11) | 0.160 |
| Vascular risk factors | | | |
| Hypertension | 44 (79) | 97 (69) | 0.191 |
| Hypercholesterolemia | 21 (40) | 44 (33) | 0.316 |
| Diabetes mellitus | 13 (24) | 31 (22) | 0.822 |
| BMI, kg/m$^2$ | 27.2 ± 3.6 | 26.3 ± 3.7 | 0.114 |
| Current smoker | 8 (22) | 26 (36) | 0.143 |
| Ever smoker | 36 (64) | 72 (51) | 0.102 |
| History of cardiovascular disease | | | |
| Coronary heart disease | 14 (26) | 24 (17) | 0.162 |
| Myocardial infarction | 6 (11) | 17 (12) | 0.862 |
| TIA[a] | 7 (13) | 8 (6) | 0.088 |
| Stroke[a] | 13 (23) | 19 (14) | 0.099 |
| Stroke-related interventions | | | |
| Thrombolysis | 5 (9) | 33 (24) | **0.022** |
| Thrombectomy | 2 (4) | 14 (10) | 0.162 |
| Carotid plaque imaging | | | |
| Time interval from stroke, d | 4.3 ± 2.4 | 4.1 ± 2.1 | 0.618 |
| Contralateral cCAP | 13 (23) | 10 (7) | **0.002** |
| Ipsilateral min. lumen area, mm$^2$ | 12.6 ± 8.0 | 15.8 ± 7.3 | **0.009** |
| Contralateral min. lumen area, mm$^2$ | 15.7 ± 6.2 | 16.6 ± 7.9 | 0.463 |

Values are mean ± SD or n (%). Baseline characteristics in patients with acute ischemic stroke restricted to the territory of a single carotid artery. Numerical variables were analyzed with Student's *t*-test. For categorical variables, chi-square or Fisher exact test was used. No corrections for multiple testing were applied. *P* values reaching statistical significance are shown in **bold**. [a]Previous to the qualifying event.

BMI = body mass index; cCAP = complicated carotid artery plaque; icCAP = ipsilateral complicated carotid artery plaque; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack.

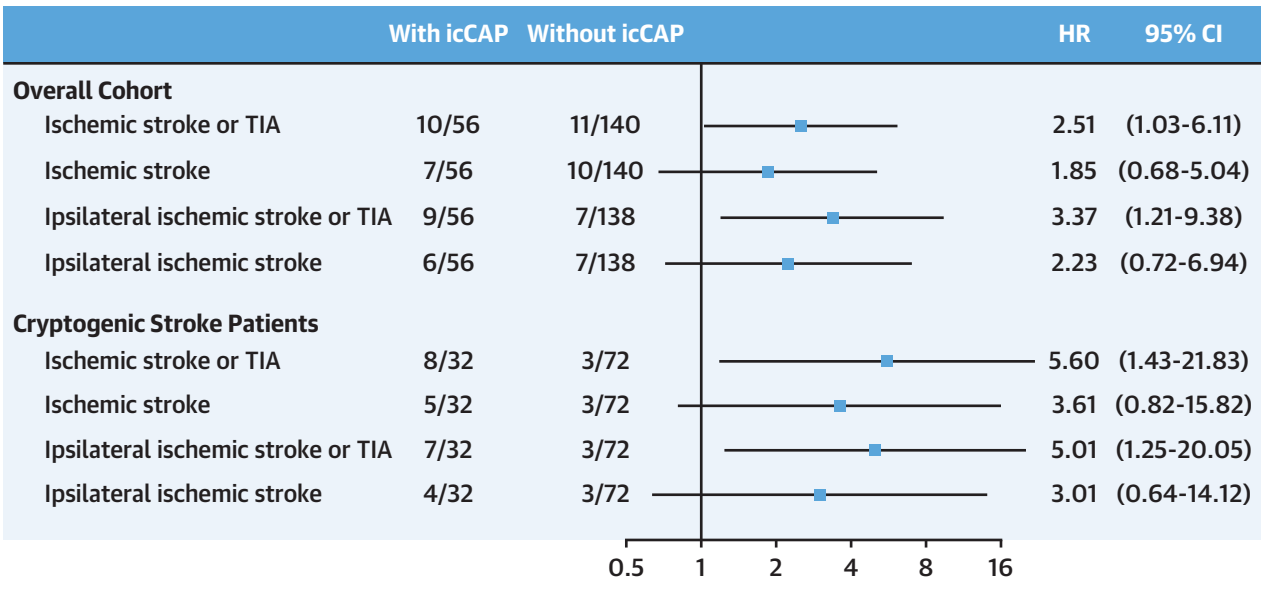
**CENTRAL ILLUSTRATION** Study Concept and Main Study Results




**Kopczak A, et al. J Am Coll Cardiol. 2022;79(22):2189-2199.**

The prospective CAPIAS (Carotid Plaque Imaging in Acute Stroke) study investigated the association between the presence of complicated carotid artery plaques ipsilateral to acute ischemic anterior circulation stroke and the risk of recurrent ischemic stroke or transient ischemic attack (TIA). Recurrence rates were significantly higher in patients with ipsilateral complicated carotid artery plaques than in patients without ipsilateral complicated carotid artery plaques. Shown are the results for the primary endpoint in the overall study cohort. Ipsilateral complicated carotid artery plaques were associated with a 2.5-fold increased risk of recurrent ischemic stroke or TIA. The results were driven by ipsilateral events.

**FIGURE 2** Recurrent Ischemic Stroke or TIA in Patients With icCAP




Shown are the HRs and CIs for the combined primary endpoint of recurrent ischemic stroke and transient ischemic attack (TIA) in patients with ipsilateral complicated carotid artery plaques (icCAP). Also shown are results for ischemic stroke and for ipsilateral ischemic stroke or TIA as secondary endpoints. Results are adjusted for age and sex, without correction for multiple testing, and are displayed separately for the overall cohort and for patients with cryptogenic stroke. Data are n/N.

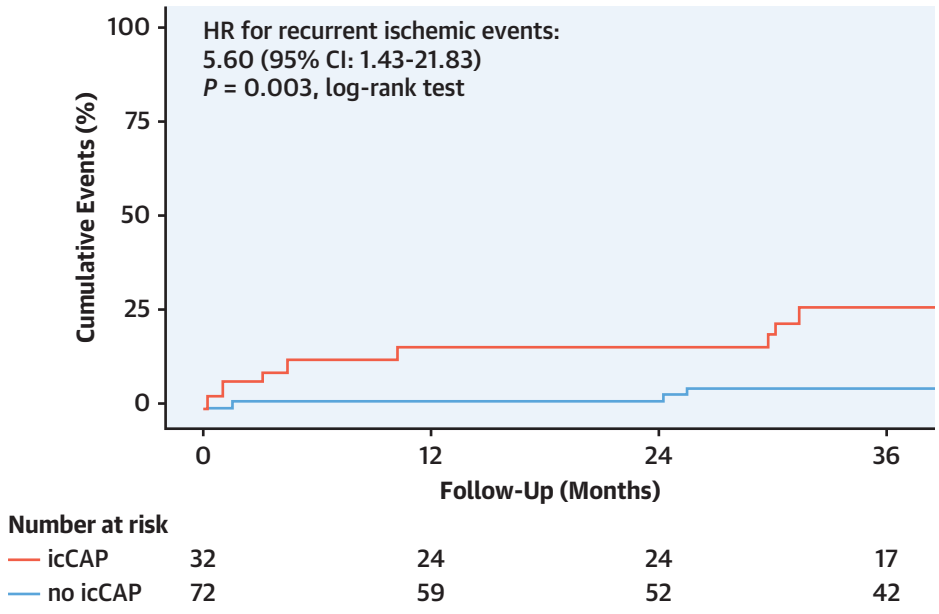
characteristics defining ipsilateral cCAP with risk of recurrent ischemic stroke or TIA are shown in **Table 3**. Presence of a ruptured fibrous cap at baseline was associated with an increased risk of recurrent ischemic stroke or TIA both in the overall cohort (HR: 2.61; 95% CI: 1.01-7.05; $P = 0.041$) and in patients with cryptogenic stroke (HR: 4.91; 95% CI: 1.31-18.45; $P = 0.018$). Although presence of intraplaque hemorrhage did not reach significance in the overall cohort (HR: 2.34; 95% CI: 0.94-5.81; $P = 0.067$), it was associated with an increased risk of recurrent ischemic stroke or TIA in patients with cryptogenic stroke (HR: 4.37; 95% CI: 1.20-15.97; $P = 0.026$).

**NEW BRAIN LESIONS ON 3-T MRI.** A total of 118 patients (67 patients with cryptogenic stroke) returned for a face-to-face visit after 12 months. Follow-up brain MRI scans were obtained in sufficient quality in 107 patients (**Figure 1**). Reasons for not undergoing brain MRI are detailed in Supplemental Figure 3. New brain lesions were detected in 35 of the 107 study participants with interpretable brain MRI scans. In 16 patients they were classified as definitive new ischemic lesions, in 11 patients they were classified as progression of pre-existing small vessel disease, and in 8 patients they could not be confidently attributed to a specific lesion type. In total, 6 of the 107 patients with available brain MRI had experienced a recurrent ischemic stroke. In 4 of them, the corresponding brain lesion was still visible on the 12-month follow-up scan, whereas in 2 cases, the lesion was either not detectable or visible only as local atrophy (Supplemental Figure 4). In 12 patients, the new ischemic lesion was classified as silent ischemic brain infarct. There was no association between ipsilateral cCAP and new brain lesions ($P < 0.05$).

## DISCUSSION

This study found ipsilateral cCAP as detected by high-resolution MRI within 10 days from ischemic stroke onset to be associated with a higher risk of recurrent ischemic stroke or TIA. The results were driven by the results in cryptogenic stroke patients and by events ipsilateral to the index stroke. Among patients with cryptogenic stroke, those with ipsilateral cCAP had a 5.6-fold increased risk of recurrent ischemic stroke or TIA when compared with those without ipsilateral cCAP, although the CI was large. We further found the presence of an ipsilateral ruptured fibrous cap and of IPH to be significantly associated with recurrent ischemic stroke or TIA.

**FIGURE 3** Recurrent Ischemic Stroke or TIA Stratified by Presence of icCAP




Shown are the results for patients with cryptogenic stroke. Recurrence rates of ischemic stroke or TIA as the primary endpoint were significantly higher in patients with icCAP than in patients without icCAP. Presence of icCAP was associated with a 5.6-fold increased risk of recurrent ischemic stroke or TIA. Abbreviations as in Figure 2.

The most important finding in terms of clinical implications is the association between IPH and an increased risk of recurrent ischemic stroke or TIA in patients with cryptogenic stroke. Compared with patients without an ipsilateral IPH, those with an ipsilateral IPH had a 4.4-fold increased risk of recurrent ischemic stroke or TIA, although the CI was large. Unlike other cCAP features, IPH can be reliably detected by standard coils and conventional native $T_1$-weighted sequences,[10,11,23] implying that MR imaging for IPH detection could be integrated into the diagnostic workflow of anterior circulation stroke, as further suggested by a recent study that ascertained IPH from routine neck MR angiography.[24]

The prevalence of ipsilateral IPH in our cohort was relatively high (27% of cryptogenic stroke patients, 26% of the overall sample)[7] similar to a recent study in patients with acute anterior circulation stroke,[24] thus further highlighting the potential utility of this marker for risk stratification and the selection of patients into clinical trials. It should be noted, however, that our study participants had been selected for the presence of carotid artery plaque and were rather mildly affected, as reflected by the National Institutes of Health Stroke Scale at baseline. This, together with the relatively large CIs for recurrence rates, emphasizes the need for additional studies. We envision the next step to be a multicenter study determining the precise prevalence of IPH and associated recurrence rates in unselected patients with anterior circulation stroke. Such a study would enable analyses in relevant subgroups to prepare for future prevention trials.

Treatment options in patients with cryptogenic stroke are limited. The NAVIGATE-ESUS (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source) and RE-SPECT ESUS (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source) trials found no benefit of anticoagulant treatment over aspirin in patients with embolic stroke of undetermined source,[25,26] leaving these patients with standard antiplatelet therapy. Whether patients with cryptogenic stroke and ipsilateral IPH or other cCAP features would benefit from more intensive medical therapy or carotid interventions is currently unknown. Yet, our results of a substantially increased recurrence risk in cryptogenic stroke patients with cCAP suggest that it is reasonable to think about secondary prevention trials in high-risk patients defined on the basis of carotid plaque imaging.

The association of ipsilateral cCAP with recurrent ischemic stroke or TIA remained significant when controlling for the minimal lumen area, indicating that the association is not confounded by stenosis grade. Less than 10% of the study participants had large artery stroke and a NASCET 50%-69% stenosis. Almost one-half of them underwent carotid revascularization, typically within the first 2 weeks after the index event following contemporary guideline recommendations.[27,28] These patients were censored with start of the intervention, thus limiting the contribution of patients with large artery stroke to the study results. Notably, 2 patients with cryptogenic stroke and nonstenosing ipsilateral cCAP also received carotid endarterectomy upon judgement of the treating physicians and were thus censored. Still, we found ipsilateral cCAP to be associated with a higher recurrence rate, highlighting the relevance of cCAP in medically treated patients.

The decision to focus on ipsilateral cCAP in our primary analysis was motivated by published data showing a higher risk of ischemic events in symptomatic compared with asymptomatic carotid artery stenosis and previous results from CAPIAS evidencing a causal relationship between ipsilateral cCAP and index events, particularly in patients with cryptogenic stroke.[7] Lumping ipsilateral and contralateral cCAP into a combined exposure would have implied lumping lesions with potentially different properties and risks. Indeed, associations with recurrent ischemic stroke or TIA were attenuated with the combined exposure in the overall cohort, but given the small number of patients with contralateral cCAP, this observation should be interpreted cautiously. Studies in larger patient cohorts will allow determining the precise risks associated with ipsilateral and contralateral cCAP and the optimal strategy for risk prediction, including in patients with infarcts in multiple vascular territories, who were not represented in CAPIAS.

The association between a ruptured fibrous cap and recurrent ischemic stroke or TIA adds to previous studies in patients with symptomatic or asymptomatic carotid artery stenosis that found thinning or rupture of the fibrous cap to be associated with an increased risk of future stroke or TIA.[13,15,16] Histopathological studies on carotid endarterectomy samples from patients with symptomatic or asymptomatic stenosis found a ruptured fibrous cap to be associated with symptomatic status[29,30] and early stroke recurrence before revascularization.[31] Our current results expand these findings by showing that a ruptured fibrous cap as assessed within the first days after stroke associates with recurrent ischemic stroke or TIA in patients with cryptogenic stroke.

**TABLE 3 Association of Individual Plaque Characteristics With Recurrent Ischemic Stroke or TIA**

| | Recurrent Ischemic Stroke or TIA | |
|---|---|---|
| | **HR (95% CI)** | ***P* Value** |
| Overall cohort | | |
| Ruptured fibrous cap | 2.61 (1.01-7.05) | **0.041** |
| Intraplaque hemorrhage | 2.34 (0.94-5.81) | 0.067 |
| Mural thrombus | 1.47 (0.55-3.91) | 0.443 |
| Cryptogenic stroke patients | | |
| Ruptured fibrous cap | 4.91 (1.31-18.45) | **0.018** |
| Intraplaque hemorrhage | 4.37 (1.20-15.97) | **0.026** |
| Mural thrombus | 2.89 (0.84-10.01) | 0.093 |

Shown is the association of plaque characteristics defining ipsilateral complicated carotid artery plaques with recurrent ischemic stroke or transient ischemic attack (TIA) as the combined primary endpoint. Multivariable Cox Proportional Hazards regression was used to estimate HRs with 95% CIs for the individual plaque characteristics. Results are adjusted for age and sex, without correction for multiple testing, and displayed separately for the overall cohort and for patients with cryptogenic stroke. *P* values reaching statistical significance are shown in **bold**.

Due to the widespread clinical use of 2D-FLAIR sequences at the time of study conception, our brain imaging protocol was not optimized for the detection of new brain lesions: baseline scans had been obtained in the context of clinical routine, and the core protocol for follow-up imaging consisted of a simple 2D-FLAIR sequence without harmonization with the baseline scans. Only 55% of the patients returned for study-related brain MRI, which might have introduced bias, and the follow-up interval was relatively short, thus limiting statistical power. Still, our results offer some insights. First, symptomatic infarcts that had been visible at the time of stroke recurrence were not reliably detected on the follow-up scans. Second, new ischemic lesions were often difficult to distinguish from other processes, in particular the progression of small vessel disease. Third, pre-existing white matter hyperintensities, which are common in stroke patients,[32] might have masked the detection of new lesions on FLAIR images. Therefore, reliable assessment of the association between cCAP and new brain lesions may require alternative strategies, such as serial imaging with DWI sequences and 3D-FLAIR sequences.[33]

**STUDY STRENGTHS.** CAPIAS was a prospective, multicenter study with imaging confirmed stroke, comprehensive diagnostic work-up, and plaque MRI obtained within 10 days after symptom onset. Sample size by far exceeded that of previous carotid plaque imaging studies employing high-resolution carotid MRI.[6,34] We used high-resolution carotid MRI at 3-T, dedicated carotid coils, and a standardized multisequence imaging protocol including contrast-enhanced sequences,[35] thus enabling the assessment of plaque rupture and other plaque features. Analyses

were specified before study onset, and adjudication of endpoints was done centrally by experts blinded to the plaque imaging data.

**STUDY LIMITATIONS.** Our study also had limitations, in particular, the long recruitment period. This mostly related to our entry criteria and the requirement for a study-related MRI with injection of a contrast agent.[7] Second, several patients, mostly with a NASCET 50%-69% stenosis, underwent early revascularization and were therefore censored from statistical analysis, although this did not affect the results in cryptogenic stroke patients. Additional limitations included a relatively low proportion of female patients, the limited age range, and the exclusion of patients with CAP <2 mm, which limited the results to stroke patients with some degree of atherosclerosis.

## CONCLUSIONS

cCAP ipsilateral to acute ischemic anterior circulation stroke are associated with a substantially increased risk of recurrent ischemic stroke or TIA. Carotid plaque imaging identifies high-risk patients who might be suited for inclusion into future secondary prevention trials.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** cCAP ipsilateral to acute ischemic anterior circulation stroke are associated with an increased risk of recurrent ischemic stroke or TIA.

**TRANSLATIONAL OUTLOOK:** In future studies, the presence of cCAP identified by noninvasive imaging could be used to select high-risk patients with prior stroke for clinical trials of novel secondary prevention strategies.

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**KEY WORDS** carotid artery, carotid plaque, intraplaque hemorrhage, ischemic stroke, MRI, stroke recurrence

**APPENDIX** For supplemental tables and figures, please see the online version of this paper.