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Original Article

Management Approaches to Intraluminal Thrombi in Acutely Symptomatic Carotid Stenosis

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ABSTRACT: ***Background:*** The presence of an intraluminal thrombus in acutely symptomatic carotid stenosis is thought to represent a high-risk lesion for short-term stroke reccurrence though evidence on natural history and treatment is lacking, leading to equipoise and much variation in practice. The objective of this study was to map these variations in practice (medical management and timing of revascularization), determine the considerations that influence clinician decision-making in this condition and gather opinions that inform the development and design of future trials in the area. ***Methods:*** This was a mixed-methods study using both quantitative survey methods and qualitative interview-based methods. International perspectives were gathered by distributing a case-based survey via the "Practice Current" section of *Neurology: Clinical Practice* and interviewing international experts using established qualitative research methods. ***Results:*** The presence of an intraluminal thrombus significantly increased the likelihood of using a regimen containing anticoagulation agents ($p < 0.001$) in acutely symptomatic carotid stenosis in the case-based survey. Themes that emerged from qualitative interview analysis were therapeutic uncertainty regarding anticoagulation, decision to reimage, revascularization choices and future trial design and anticipated challenges. ***Conclusion:*** Results of this study demonstrate a preference for anticoagulation and delayed revascularization after reimaging to examine for clot resolution, though much equipoise remains. While there is interest from international experts in future trials, further study is needed to understand the natural history of this condition in order to inform trial design.

RÉSUMÉ: Approches de gestion des thrombus intraluminaux dans la sténose carotidienne symptomatique en phase aiguë ***Contexte*** : La présence d'un thrombus intraluminal dans le cas d'une sténose carotidienne symptomatique en phase aiguë est considérée comme une lésion à haut risque de récidive d'AVC à court terme, et ce, bien que les données portant sur l'histoire naturelle de cette lésion et son traitement demeurent insuffisantes. Cette situation conduit à une grande incertitude (*equipoise*) et à des variations dans la pratique. L'objectif de cette étude est donc de cartographier ces variations dans la pratique (gestion médicale et moment choisi pour la revascularisation), de déterminer les considérations qui influencent la prise de décision des cliniciens face à ce problème médical et de recueillir des opinions pouvant informer le développement et la conception de futurs essais cliniques dans ce domaine. ***Méthodes*** : Il s'agit d'une étude mixte utilisant à la fois des méthodes d'enquête quantitatives et qualitatives basées sur des entretiens. Des perspectives internationales ont été recueillies en distribuant un sondage basé sur des cas au moyen de la section *Practice Current* de *Neurology : Clinical Practice* et en interrogeant des experts internationaux à l'aide de méthodes de recherche qualitative éprouvées. ***Résultats*** : Dans l'enquête basée sur des cas, la présence d'un thrombus intraluminal a augmenté, dans le cas d'une sténose carotidienne symptomatique en phase aiguë, de manière significative la probabilité d'utiliser un régime de traitement contenant des agents anticoagulants ($p < 0{,}001$). Les thèmes qui ont émergé de l'analyse qualitative des entretiens sont les suivants : l'incertitude thérapeutique concernant l'anticoagulation, la décision de procéder à des examens additionnels d'imagerie, le choix de revasculariser, la conception d'essais cliniques futurs et les défis anticipés. ***Conclusion*** : Bien qu'il y ait encore beaucoup d'incertitude, les résultats de cette étude démontrent une préférence pour l'anticoagulation et la revascularisation retardée après des examens additionnels d'imagerie visant à examiner la résolution des caillots. Même si les experts internationaux s'intéressent à de futurs essais cliniques, d'autres études sont nécessaires pour comprendre l'histoire naturelle des thrombus intraluminaux afin d'éclairer la conception de ces essais.

Keywords: Carotid artery disease; carotid endarterectomy; cerebrovascular disease; stroke; vascular neurology

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Highlights

- Intraluminal thrombus in the setting of acutely symptomatic carotid artery stenosis increases physician enthusiasm for anticoagulation.
- There remains equipoise in the management of intraluminal thrombus in acutely symptomatic carotid artery stenosis.
- Further work is needed to determine the natural history of carotid intraluminal thrombus before conducting trials in the area.

Introduction

Acutely symptomatic carotid stenosis, often referred to as a "hot carotid,"[1,2] describes the situation where a patient presents within hours to days of a new stroke or Transient ischemic attack (TIA) related to carotid artery stenosis (≥50% stenosis).[1,2] This etiology of stroke represents a high risk of recurrent events[3–7] and is a condition with much equipoise in terms of management.[1,2] The hot carotid is further complicated by an intraluminal thrombus (ILT) in as many as 3.1% of cases, the majority of which are due to atherosclerotic plaque rupture.[8–11] Carotid ILT, also referred to as a carotid free-floating thrombus,[9,12] is generally defined as a thrombus arising from the carotid arterial wall with circumferential blood flow at its distal aspect.[8,9,12]

The presence of an ILT in the hot carotid is thought to increase the risk of short-term recurrent ischemia while on medical therapy[9,10,12] though there is an absence of high-quality evidence to support this claim. In addition to concern regarding medical therapy of ILT in the hot carotid, observational studies and post hoc analysis from the NASCET trial have suggested that the presence of an ILT increases the risk of periprocedural stroke and mortality with carotid revascularization.[13,14] These studies however are outdated, do not reflect current procedural techniques, were done before the widespread use of dual antiplatelets in stroke and did not consistently report preoperative anticoagulation in the presence of ILT.[15] We suspect that significant equipoise exists regarding the management of ILT in the hot carotid. In this study, we sought to better understand how physicians navigate this uncertainty, specifically as it relates to anti-thrombotic management and the timing of carotid revascularization as well as exploring considerations regarding future study in the area.

The objective of this study was to use mixed methods to (1) map the varying practice patterns of international experts in carotid ILT management, (2) explore the experiences and practical considerations that inform their management and uncertainties encountered in the process and (3) understand clinician perspectives regarding future trials in patients with carotid ILT. The results of this study will encourage critical reflection of individual and institutional practice patterns as well as informing the development and design of future trials on carotid ILT.

Methods

This was a mixed-methods study of physician approaches to the management of the hot carotid using survey and interview-based methods. The quantitative data included here are from a worldwide (English language) case-based survey of physicians conducted through the "Practice Current" section of *Neurology: Clinical Practice*, and the methodology has been previously reported.[16] This survey was part of a larger study of acutely symptomatic carotid stenosis (hot carotid), and descriptive results have been previously published.[16]

The questions in the survey were based on a representative case (included in Supplement 1) and were oriented around medical management and revascularization decisions in acutely symptomatic carotid stenosis with and without an associated ILT. The survey was open between September 6, 2018, and November 10, 2019. Demographic questions in the survey included years in practice and practice location (country). Additionally, the preferred method of carotid revascularization in hot carotid cases (endarterectomy or stenting) was asked though not specifically in the context of ILT.

IBM SPSS Statistics (Version 26) was used to analyze the data. Univariable analysis of the use of anticoagulation, dual antiplatelet therapy (DAPT) or single antiplatelet therapy (SAPT) between the ILT and non-ILT cases was done via a Fisher exact test, and the cutoff for significance was $p < 0.05$. Multivariable logistic regressions were also completed to adjust for confounding factors (region of practice, years in practice and preferred revascularization procedure (CEA or CAS). The preferred revascularization technique was controlled for as it is possible that procedural nuances and differences in timing between techniques may influence the selection of antithrombotic regimens; however, as a sensitivity analysis, we also examined the regression results when not controlling for this variable. Results were expressed as adjusted odds ratios and 95% confidence intervals were determined.

The interview-based component of the study used a qualitative descriptive methodology[17] to explore the decision-making approaches, opinions and attitudes of physicians regarding the management of patients with acutely symptomatic carotid stenosis. The methods of this study as well as the results of these interviews regarding general imaging, medical management and revascularization in acutely symptomatic carotid stenosis without ILT have been reported elsewhere.[1,18] The interview and qualitative methodology are outlined in brief below and further details can be found in previous publications related to this study.[1,18] Interviews were conducted entirely in English and took place between May 2018 and June 2021.

Participants were recruited using a snowball sampling strategy with purposive sampling.[19–21] Participants were sought to ensure sampling of different specialties (neurology and/or internal medicine/geriatrics [for the United Kingdom alone where internists/geriatricians frequently lead stroke teams], neurovascular surgery, interventional neuroradiology) and geographic region (United States of America [USA]/Canada, Latin America or Caribbean, Europe, Africa, Asia and Oceania).

Interviews were conducted until saturation of themes was reached.[17,22–25] Snowball sampling was used to recruit interview participants.[21] Semi-structured interviews were conducted by neurology residents/fellows with an interest in stroke neurology. Interviewers (A.G., G.J. and R.J.S.) were trained in qualitative interviewing by D.J.T.C. (MD/PhD with extensive qualitative methodology experience), and a topic-specific interview guide was used to ensure consistency of interview style and structure. Interview guides were developed based on principles of "grounded theory"[26,27] and were intended to encourage interviewees to think about their approaches, the challenges they experience and factors they consider in decision-making when caring for a patient with a hot carotid. The guide was pilot tested before use in the study (included in Supplement 1).

Interviews were digitally recorded and transcribed verbatim by research assistants. Transcripts were imported into NVivo 12 Plus Qualitative Data Analysis software to facilitate analysis and thematic coding by two reviewers (A.G. and B.B.). Opinions relating to ILT in the hot carotid were identified and categorized based on conventional qualitative analysis methods.[28] All

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Table 1. Survey respondents' choice of antithrombotic management with and without associated ILT. Chi-squared test using Fisher's exact methods reported as *P*-values

Use of anticoagulation in hot carotid with and without ILT			
	No ILT *n* (%)	**ILT *n* (%)**	**Chi-squared – Fisher's exact (*P*-value)**
SAPT	311 (50.1%)	120 (19.1%)	<0.001
DAPT	238 (38.3%)	97 (15.0%)	<0.001
Anticoagulation (± antiplatelet agent)	72 (11.6%)	399 (66.0%)	<0.001
Total *N*	621	616	

ILT = intraluminal thrombus; SAPT = single antiplatelet therapy; DAPT = dual antiplatelet therapy.

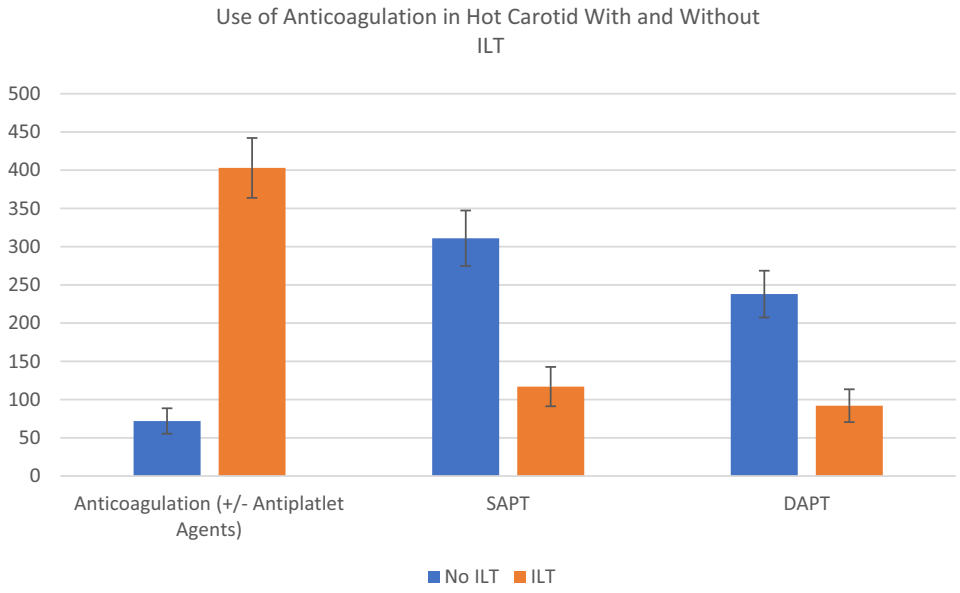

Figure 1. Survey respondents' choice of antithrombotic management with and without associated intraluminal thrombus (ILT). Error bars represent 95% confidence intervals. SAPT = single antiplatelet therapy; DAPT = dual antiplatelet therapy.

interviews were coded by two reviewers, and the team met to review coding and coding strategy and sought to achieve consensus in coding. To synthesize themes from a large number of codes, authors A.G. and B.B. employed the concept of "Grounded Theory" and conventional qualitative content analysis, both of which are recognized methods in qualitative research used to construct theory from systematically gathered qualitative data.[27–29]

The results of the qualitative portion of this study are reported in accordance with the consolidated criteria for reporting qualitative research checklist (Supplement 2).[30]

Results

Quantitative data

Responses from 668 unique participants were recorded over the course of the survey, of which 561 (84.0%) completed the survey in full, though completion of all survey questions was not required. Demographic characteristics of the survey have been previously published[1] and are included in Supplement 3 (Table 1).

In the case presented in the survey of a hot carotid without ILT, 311 of 621 (50.1%) participants indicated they would use SAPT, 238 of 621 (38.3%) would use DAPT and only 72 of 621 (11.6%) would use anticoagulation (Table 1). In the context of ILT, 399 of 611 (66.0%) would use anticoagulation, and only 97 of 612 (15.0%) and 120 of 612 (19.1%) would use DAPT or SAPT, respectively (Table 1). The presence of ILT significantly reduced the likelihood of participants using SAPT or DAPT for their patient ($p < 0.001$) and significantly increased the likelihood of using a regimen containing anticoagulation agents ($p < 0.001$) (Table 1).

The most common antithrombotic regimen selected by respondents in the case of ILT was heparin monotherapy (27.8%), followed by low-molecular-weight heparin monotherapy (16.1%) (Figure 1, Table 2). To control for confounding factors, a multivariable logistic regression was performed examining factors associated with preference for anticoagulation or SAPT in the case of ILT. When controlling for years in practice and preferred method of revascularization, we found that respondents practicing in Europe (aOR 0.44 [95% CI 0.27–0.71]) or Central/South America (aOR 0.34 [95% CI 0.19–0.60]) were less likely to choose a regimen containing anticoagulation for a patient with ILT (Table 3). In the multivariable regression, we also found that respondents from Europe (aOR 3.04 [95% CI 1.68–5.50]) or Central/South America (aOR 2.44 [95% CI 1.22–4.88]) were more likely to use SAPT in the context of hot carotid with ILT (Table 4). Results were similar on sensitivity analyses that did not adjust for the preferred revascularization technique.

Qualitative data

We interviewed 22 physicians between May 2018 and June 2021 (24 approached, 2 refused due to other commitments). The demographic characteristics have been previously reported and are included in

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Table 2. Antithrombotic regimens selected by survey respondents in the case of hot carotid with intraluminal thrombus (ILT). Regimens with less than 10 total responses not included here

Antithrombotic regimens selected in the case of hot carotid with ILT *N* (%)	
Heparin (monotherapy)	171 (27.8%)
Low-molecular-weight heparin (monotherapy)	99 (16.1%)
Aspirin + clopidogrel	93 (15.1%)
Aspirin (monotherapy)	73 (11.9%)
Clopidogrel (monotherapy)	41 (6.7%)
Direct oral anticoagulant (monotherapy)	33 (5.4%)
Heparin + aspirin	25 (4.1%)
Low-molecular-weight heparin + aspirin	20 (3.2%)
Other combinations	61 (9.9%)
Anticoagulation + (clopidogrel or ticagrelor)	50/61 (82%)

Table 3. Factors associated with choosing a regimen containing anticoagulation for a patient with acutely symptomatic carotid stenosis awaiting revascularization, when told that there was an associated intraluminal thrombus. Significant *P*-values are indicated with an asterisk

Factors associated with choosing a regimen containing anticoagulation				
	Univariable Analysis		Multivariable Logistic regression	
	N(%)	P-Value	Adjusted Odds Ratio (95%CI)	P-value
Preferred Revascularization		0.857		
Carotid Endarterectomy	272/443 (61.4%)		Reference	
Carotid Stenting	115/184 (62.5%)		1.16 (0.77-1.73)	0.482
Years in Practice		0.941		
In training	83/133		Reference	
Less than 10 years	164/256		1.00 (0.64-1.56)	0.985
More than 10 years	116/181		0.93 (0.58-1.51)	0.776
Region		0.01		
North America	127/181 (70.2%)		Reference	
Europe	121/218 (55.5%)		**0.44 (0.27-0.71)**	**<0.001***
Central/South America	50/110 (45.5%)		**0.31 (0.18-0.55)**	**<0.001***
Asia	77/124 (62.1%)		0.69 (0.39-1.22)	0.203
Australia	10/15 (66.7%)		0.87 (0.26-2.95)	0.827
Africa	9/15 (60.0%)		0.80 (0.20-3.28)	0.761

Supplement 3 (Table 2). Interviews lasted 30–60 minutes. Relevant quotes from the interviews are organized thematically and included in Table 5. A coding matrix of interview codes used to develop the themes below is included in Supplement 3 (Figure 3).

Therapeutic uncertainty regarding anticoagulation

The debate about using DAPT versus anticoagulation in the acute management of ILT in the hot carotid emerged as a theme in this study, with no clear consensus or preference among participants Supplement 3 (Figure 1). The decision to favor the use of DAPT or anticoagulation did not display any regional or specialty variation. In terms of decision-making regarding the use of DAPT or anticoagulation, a theme emerged regarding the size of the stroke as being a factor that may dissuade participants from anticoagulating patients. Here participants were weighing the risks of recurrent stroke against the risk of hemorrhagic transformation when choosing an optimal antithrombotic therapy. Participants expressed uncertainty regarding the appropriate management choice in this setting Supplement 3 (Figure 2), noting the absence of high-quality natural history data for this condition with current strategies.

> *Some people anticoagulate these patients. I still tend to give them dual antiplatelets.* (Europe, Neurologist 1)

> *I might be inclined to give heparin depending on the size of the stroke. If it is a large stroke with risk of hemorrhage I would avoid heparin but I would tend to give heparin and aspirin, even both, if the stroke is smaller or a TIA.* (North America, Neurologist 4)

Decision to reimage

There was a preference for reimaging patients in 3–7 days after initiating treatment to look for complete or partial clot resolution

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Table 4. Factors associated with choosing SAPT (*single antiplatelet therapy) for a patient with acutely symptomatic carotid stenosis awaiting revascularization, when told that there was an associated intraluminal thrombus. Significant *P*-values are indicated with an asterisk

Factors associated with choosing SAPT*				
	Univariable Analysis		Multivariable Logistic regression	
	N(%)	P-Value	Adjusted Odds Ratio (95%CI)	P-value
Preferred Revascularization		0.738		0.481
Carotid Endarterectomy	86/443		Reference	
Carotid Stenting	33/184		0.84 (0.52-1.36)	
Years in Practice		0.901		
In training	25/133		Reference	
Less than 10 years	52/256		1.17 (0.65-2.12)	0.4
More than 10 years	34/181		1.26 (0.73-2.18)	0.598
Region		0.005		
North America	20/181		Reference	
Europe	55/218		**3.04(1.68-5.50)**	**<0.001***
Central/South America	23/110		**2.44 (1.22-4.88)**	**0.012***
Asia	18/124		1.52 (0.72-3.20)	0.272
Australia	Mar-15		0.56 (0.07 - 4.56)	0.588
Africa	01-May		0.77 (0.09-6.50)	0.812

Table 5. Summary of key themes from interviews with representative quotes

Theme	Representative quotes
Therapeutic uncertainty regarding anticoagulation	• "If there is any element of thrombus in the plaque on the CTA (CT angiogram), [I would] add heparin" (North America, Neurovascular Surgeon 1) • "If someone has a big infarct, it pushes me away from anticoagulation due to hemorrhage risk." (Europe, Neurologist 4)
Decision to reimage	• "I would delay and we would do an everyday check with ultrasound and then we would make the decision together with the surgeons. (Europe, Neurologist 3) • "Reimage in 1 week. If it's a significant stenosis, they would be on dual antiplatelets and be considered for revascularization." (Europe, Neurologist 1)
Revascularization timing	• "What we would like to see is that once the patient is on dual antiplatelet or anticoagulation therapy, then we would like to see that this fresh thrombus is actually dissolved and then we would operate only if there is some residual stenosis." (Europe, Neurologist 3) • "Because of the perceived high surgical risk of doing an endarterectomy on a patient with floating thrombus we would opt for cooling down the thrombus or the plaque maybe with a few days [Before Revascularizing]." (North America, Neurologist 4)
Revascularization type	• "We would prefer open surgery. Do thrombectomy with open surgery and if there is still a distal occlusion which requires acute treatment we would go through the stenosis, extract the distal clot and then deal with what is left. We would try with aspiration first, try to get this clot proximally but preferable remove it distally first and deal with that is left." (Europe, Neuroradiologist 1)
Future studies – comparator groups	• "Are we going to be using a heparin drip vs DAPT (dual antiplatelet therapy) before stenting? That's the question I want the answer to." (North America, Neurologist 1) • "If they have a mobile thrombus maybe I would randomize them to compare anticoagulant therapy [versus] double antiplatelets." (Europe, Neurologist 2) • "The minimal acceptable therapy would be DAPT (dual antiplatelet therapy) vs. heparin" (North America, Neurologist 3) • "I think the challenge here is to have a comparison arm that would be clinically acceptable to the treating physician in terms of risk versus benefit." (North America, Neuroradiologist 2)
Future studies – anticipated challenges	• "The core challenge, of course, is to recruit the patients. This is not a very frequent condition." (Europe, Neurologist 3) • "Often, we find that on paper we would have lots of eligible patient for the trial but in reality, there are often reasons why patients are different from what you're expecting. Any trial would have to be flexible and pragmatic in terms of inclusion and exclusion criteria to get large enough numbers." (Europe, Geriatrician 3)

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in patients being considered for revascularization (i.e., suspected stenosis greater than ≥50%). In patients with mild to moderate stenosis, who were not being considered for revascularization, participants favored a longer interval of follow-up imaging, up to 6 weeks after initiating therapy.

> *Our approach in these cases has been to put them on a heparin infusion and then re-image them in 3 days or so to see if the clot has resolved. If there is an associated stenosis, then I won't stent that until I've seen some resolution of the clot. The rationale being that otherwise I might send a piece of the clot flying off during the procedure, if it's unstable.* (North America, Neuroradiologist 2)

Importantly, the rationale for reimaging was not just to ensure the resolution of the clot but also to clarify the true extent of the underlying plaque and its associated degree of stenosis. Participants noted that it can be challenging in the initial imaging to adequately distinguish the boundaries between ILT and the underlying plaque; as such, as the clot resolves in follow-up imaging, it may become evident that the plaque is actually resulting in minimal stenosis – which, for several participants, would dampen their enthusiasm for revascularization.

> *Sometimes cross-sectional imaging would overestimate [the degree of stenosis in the case of ILT] and on [repeat imaging] you might not see the same [degree of stenosis].* (North America, Neuroradiologist 1)

Revascularization choices

In general, participants favored not doing hyperacute revascularization and waiting for clot resolution or partial resolution with medical therapy before proceeding with revascularization if indicated. This was driven by concern about the high risk for perioperative distal embolization events.

> *If there is a mobile thrombus [then] no surgery immediately. Vascular surgery and interventional radiology think risk is too high.* (Asia Neurologist 1)

In cases where revascularization procedures were performed in the context of ILT, there appeared to be a preference for carotid endarterectomy (CEA). The rationale expressed for this preference was a perceived high risk of clot embolization when passing a filter/catheter by the ILT, which is required in carotid artery stenting (CAS), and therefore, there was a desire to avoid this by performing CEA instead.

> *If there is a mobile thrombus in artery, we think there is a very high risk of embolization and the risk is higher if we perform an endovascular treatment because you have to pass through the artery with a filter in all the procedures. There is a risk of embolization that we believe is lower if the patients get endarterectomy.* (Europe, Neurologist 2)

However, some favored stenting over CEA in the setting of ILT. The argument here was that stenting offered a better means of visualizing residual clots using contrast injections while the procedure was in progress.

> *Certainly my recommendation in such cases would be to avoid endarterectomy because with that surgery you won't be able to directly visualize the clot and you have no idea whether you've sent it off as an embolus while you're working on it. On the other hand with stenting, you can keep your eye on any residual clot while you're working.* (North America, Neuroradiologist 2)

Future trial design and anticipated challenges

There was a clear interest in further high-quality studies (i.e., Randomized control trials) on the management of ILT in the hot carotid. Participants identified DAPT as the minimum acceptable therapy and indicated they would be happy to randomize patients to DAPT versus anticoagulation regimens. Experts had an interest in future trials and viewed these as ethical based on the significant equipoise in the area and a lack of high-quality evidence to inform clinical practice.

> *In the acute setting with hot carotid, I think there is enough equipoise that [physicians] would be willing to randomize to that trial.* (North America, Neurologist 3)

In the interviews, multiple experts raised concerns regarding recruitment and achieving an adequate event rate to effectively study ILT management in hot carotid. ILT in the hot carotid might not be encountered frequently enough to achieve rapid enrollment; as such, the experts felt that it was important for trials to have a very inclusive and pragmatic approach to international recruitment in order to avoid further narrowing an already small patient pool. Additionally, there was a desire for future studies to quantify the natural history of ILT to therefore better inform future trial development.

> *The core challenge, of course, is to recruit the patients. This is not a very frequent condition.* (Europe, Neurologist 3)

> *I am swayed by the pathologists who tell me that every time they look at an acute plaque which has been resected they always find fresh thrombus so that means to me well, that doesn't mean that fresh thrombus is more or less dangerous.* (North America, Neurologist 2)

Discussion

The results of this mixed-methods study provide a description of the current practice patterns of stroke physicians in managing ILT in the hot carotid, particularly in relation to antithrombotic management, revascularization and imaging. This data provides insight into the factors that affect physicians' decision-making in these cases as well as mapping interest and considerations regarding future trials of ILT in the hot carotid population.

Results of the quantitative analysis suggest that the presence of an ILT significantly alters antithrombotic management choices by increasing the likelihood of using anticoagulation and decreasing the use of SAPT or DAPT. This is consistent with other reports highlighting enthusiasm and institutional preference for anticoagulation in these cases.[10,31] There does however remain equipoise in antithrombotic strategies, as evident in our survey, where one-third of physicians preferred antiplatelet agents over anticoagulation in cases of ILT, with significant geographic practice variation noted as well, suggesting an unmet need to answer the question of optimal medical therapy in ILT. This equipoise is supported by the thematic analysis of our qualitative interviews. Quantitative analysis of the survey included here suggests that factors that influence decision-making in antithrombotic management may be related to practice region; specifically, when controlling for years in practice and preferred revascularization, physicians from Europe and Central/South America were less likely to use antithrombotic regimens containing anticoagulation in patients with ILT and a hot carotid. Regional variations in practice as we see here have been previously published in other related areas of the stroke literature, for example, geographic variation in thrombolysis rates.[32,33] No clear regional or specialty variation emerged on the topic of antithrombotic management in the interview thematic analysis; however, stroke size and the associated risk of hemorrhagic transformation were identified as important factors in deciding when to use anticoagulation.

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This observed equipoise is consistent with previous literature[9,12] and is likely related to a general lack of high-quality evidence and conflicting reports on the topic. The most robust evidence for antithrombotic management in ILT is a recent meta-analysis of 525 cases derived from a systematic review of case reports and case series of ILT in the hot carotid, which showed no benefit of anticoagulation in reducing adverse outcomes (stroke, TIA, death). Similar results were reported in a 2007 systematic review as well.[9] The nature of this evidence (meta-analysis of case reports/case series) however is low quality. Additionally, given concerns of ascertainment and information bias in prior studies, the authors underscored the need for large-scale prospective cohort data to better inform practice and ensure the feasibility of future trials – a concern that was echoed in our interviews.[12]

Results of the qualitative analysis suggest a preference for avoiding hyperacute revascularization and, ideally, waiting for thrombus resolution following antithrombotic therapy before pursuing revascularization, though few participants commented on this consideration. Compared to the issue of antithrombotic management, there appeared to be less equipoise regarding revascularization timing among interview experts. This is perhaps driven by the somewhat outdated though comparatively more methodologically robust evidence regarding risk of CEA in the presence of ILT.[34,35] For example, a retrospective study of 1160 CEAs performed at 12 sites between 1987 and 1990 found that ILT was associated with a numerically higher frequency of 30-day stroke recurrence 14.3% in ILT versus 5.4% without ILT; however, this was not statistically significant, and there were only 28 patients with ILT included.[34] More recently, in the abovementioned meta-analysis (2019), there was no association of early revascularization (within 72 hours) with the composite outcome of TIA, stroke or death when controlling for other variables in regression analysis though as mentioned the generalizability of this finding is limited.[12] These reviews however rely on outdated data[12,34] and thus do not reflect current procedural techniques and other medical management (e.g., high-intensity statin therapy).

With regard to procedure type, few interviewed experts commented on this consideration. From the results here, however, CEA appears to be the preferred intervention, though equipoise was noted. Specifically, experts were making this decision based on the perceived risk of clot embolization, although contrasting opinions were noted, with some expressing that the risk of embolization in CEA was prohibitively high, while others expressed the same opinion regarding CAS. These results support that there is an absence of literature to inform the decision of CAS versus CEA in ILT cases, and this likely depends on multidisciplinary and context-specific considerations of the treating physician.

The results of the qualitative interviews showed support for future trials examining the management of ILT in the hot carotid. Interviewed experts expressed an interest in a trial that would compare DAPT versus anticoagulation in this group and were agreeable to randomizing these therapies. In preparation for trials, there seems to be a need for high-quality natural history data on patients with ILT in the context of current practices, expanding on the current data that is limited to case series. High-quality data on recurrent stroke outcomes with current practices is needed, and this will help inform estimations of effect size and event rate for powering trials. Preliminary work in this regard has come from a recent prospective cohort study of ILTs (with a range of ILT at different extra and intracranial locations, the majority being carotid ILT), which showed low rates of stroke recurrence (6.6%) and high rates of partial or complete thrombus resolution (74.6%) with medical therapy (heparin plus aspirin).[31]

Limitations

This study does have a few important limitations to acknowledge. The first of which is the sample demographic in both the survey and interview portions of this study. Both the survey and interview were conducted in English, which limited participation from non-English speaking participants. Additionally, there was a significant overrepresentation of North American and European clinicians both in the survey and interviews which could limit the generalizability to other regions. Women were also under-represented in the interviews. Furthermore, given that the survey analysis here was post hoc, the questions were not optimized for all aspects of ILT management and did not include questions regarding how age and stroke size/location would influence management. Additionally, the survey did not ask patients about practice subspecialty (i.e., general neurology, stroke neurology, neuroradiology/interventionalist), which could influence practice patterns. In terms of methodology for the qualitative portion of the study, snowball sampling does have the potential to introduce bias[36] as participants may be more likely to recommend like-minded colleagues for inclusion in the study. That being said, snowball sampling remains one of the most used and well-studied sampling methods in qualitative research.[19,36] Finally, it should be acknowledged that there has been a significant gap in time between data collection and publication (data collection completed in June 2021). Despite this, the questions posed in this study remain relevant in today's context, with very little work being published in the field of carotid ILT in recent years.

Conclusion

The management of ILT in patients with a hot carotid continues to represent a treatment dilemma for physicians. Driven largely by methodologically limited and often outdated data, physicians must determine their management of these cases by weighing the risk of recurrent ischemic events with more conservative therapy against the possible harms of more aggressive therapies such as anticoagulation or hyperacute revascularization. While the results of this study show a preference for anticoagulation and delayed revascularization in patients with ILT and a hot carotid, much equipoise remains. Further study should be conducted to first better understand the natural history of ILT in hot carotid, specifically high-quality prospective cohort studies, followed by pragmatic randomized trials to determine optimal management techniques. Our interviews specifically have helped establish what would be considered top contenders for comparative strategies in future studies (i.e., at least dual antiplatelet vs. anticoagulation). Doing so would provide answers to the management of a condition that continues to be surrounded by much of the same uncertainty as it was in decades past.

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collection and revision of the paper. J.H.W. was involved in the study design and manuscript revision. B.K.M. supervised the study and was involved in the conception, design, writing, analysis and revision of the paper. A.G. was involved in the conception and design of the study, collected and analyzed the data, co-wrote the first draft and revised the paper.

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