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Original Article

Physician Approaches to Antithrombotic Therapies for Recently Symptomatic Carotid Stenosis

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ABSTRACT: ***Background:*** Whereas the beneficial effect of antiplatelet therapy for recurrent stroke prevention has been well established, uncertainties remain regarding the optimal antithrombotic regimen for recently symptomatic carotid stenosis. We sought to explore the approaches of stroke physicians to antithrombotic management of patients with symptomatic carotid stenosis. ***Methods:*** We employed a qualitative descriptive methodology to explore the decision-making approaches and opinions of physicians regarding antithrombotic regimens for symptomatic carotid stenosis. We conducted semi-structured interviews with a purposive sample of 22 stroke physicians (11 neurologists, 3 geriatricians, 5 interventional-neuroradiologists, and 3 neurosurgeons) from 16 centers on four continents to discuss symptomatic carotid stenosis management. We then conducted thematic analysis on the transcripts. ***Results:*** Important themes revealed from our analysis included limitations of existing clinical trial evidence, competing surgeon versus neurologist/internist preferences, and the choice of antiplatelet therapy while awaiting revascularization. There was a greater concern for adverse events while using multiple antiplatelet agents (e.g., dual-antiplatelet therapy (DAPT)) in patients undergoing carotid endarterectomy compared to carotid artery stenting. Regional variations included more frequent use of single antiplatelet agents among European participants. Areas of uncertainty included antithrombotic management if already on an antiplatelet agent, implications of nonstenotic features of carotid disease, the role of newer antiplatelet agents or anticoagulants, platelet aggregation testing, and timing of DAPT. ***Conclusion:*** Our qualitative findings can help physicians critically examine the rationale underlying their own antithrombotic approaches to symptomatic carotid stenosis. Future clinical trials may wish to accommodate identified variations in practice patterns and areas of uncertainty to better inform clinical practice.

RÉSUMÉ : Approches des médecins concernant les traitements antithrombotiques destinés à des cas de sténose carotidienne récemment symptomatiques. ***Contexte :*** Alors que l'effet bénéfique des traitements antiplaquettaires destinés à la prévention des AVC de nature récurrente a été bien établi, des incertitudes demeurent quant au protocole antithrombotique optimal à adopter dans le cas de sténoses carotidiennes récemment symptomatiques. Nous avons ainsi cherché à explorer les approches des médecins spécialisés dans les AVC en ce qui regarde la prise en charge antithrombotique de patients présentant une sténose carotidienne symptomatique. ***Méthodes :*** Pour ce faire, nous avons fait appel à une méthodologie qualitative descriptive pour explorer les approches décisionnelles et les opinions des médecins concernant les protocoles antithrombotiques destinés à la sténose carotidienne symptomatique. Pour discuter de la prise en charge de la sténose carotidienne symptomatique, nous avons mené des entretiens semi-structurés avec un échantillon, choisi à dessein, de 22 médecins spécialisés dans les AVC (11 neurologues, 3 gériatres, 5 neuroradiologues interventionnels et 3 neurochirurgiens) provenant de 16 établissements répartis dans quatre continents. Nous avons ensuite procédé à une analyse thématique des transcriptions d'entretiens. ***Résultats :*** Les thèmes importants révélés par notre analyse comprennent les limites des données probantes issues des essais cliniques existants, les préférences concurrentes des chirurgiens et des neurologues/médecins internistes ainsi que le choix d'un traitement antiplaquettaire en attendant la revascularisation. L'utilisation de plusieurs agents antiplaquettaires (par exemple de nature double ou *dual antiplatelet therapy*) chez les patients subissant une endartériectomie carotidienne (EC) était davantage préoccupante que la pose d'une endoprothèse (*stent*) dans l'artère carotide. Des variations régionales ont concerné l'utilisation plus fréquente d'agents antiplaquettaires uniques chez les participants d'origine européenne. Quant aux domaines d'incertitude, on a pu noter la gestion des médicaments antithrombotiques en cas de traitement antiplaquettaire, les implications des caractéristiques non-sténotiques de la maladie carotidienne, le rôle des nouveaux agents antiplaquettaires ou anticoagulants, les tests d'agrégation plaquettaire et le moment idéal pour recourir à des agents antiplaquettaires de nature double. ***Conclusion :*** Nos résultats

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qualitatifs peuvent aider les médecins à examiner de manière critique les fondements de leurs propres approches antithrombotiques en lien avec des cas de sténose carotidienne symptomatiques. De futurs essais cliniques voudront peut-être tenir compte des variations identifiées dans les modes de pratique et des domaines d'incertitude afin de mieux informer la pratique clinique.

Keywords: Carotid stenosis; Transient ischemic attack; Stroke; Antithrombotic medication; Antiplatelet; Equipoise

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Introduction

Carotid atherosclerosis causes 15–20% of ischemic stroke and transient ischemic attacks (TIAs)[1,2] and is associated with high risk of early recurrent stroke, especially in the first few days.[3,4] Whereas the evidence for secondary prevention of stroke with antithrombotic agents is well established, there remains a paucity of rigorous evidence for the optimal antithrombotic regimen for patients with symptomatic carotid artery stenosis ("hot carotid").

The POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) and CHANCE (Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events) trials showed a reduction in the rate of recurrent ischemic stroke in the group that received dual-antiplatelet therapy (DAPT) compared to acetylsalicylic acid (ASA) and placebo with the most benefit in the first few weeks after the index event.[5,6] It is clear from these trials that antithrombotic therapy is an integral component of secondary prevention of stroke within the first few days of an ischemic event. However, what remains unclear is the choice of antithrombotic agents that is likely to be most effective at reducing recurrent ischemic stroke in patients with symptomatic carotid stenosis, particularly while awaiting revascularization.

When facing the challenge of finding the right balance between ischemic stroke prevention and antithrombotic medication-related bleeding in the absence of high-quality evidence, variable practice patterns can be adopted by physicians. Qualitative research can help us achieve a deeper understanding of the rationale and uncertainties underlying current practices, and thus help physicians better appraise their own approaches. In addition, elucidation of existing physician perspectives on this topic could inform the design of randomized-controlled trial (RCTs) that better reflect the practice needs of physician stakeholders and are more likely to help resolve uncertainties.

Our purpose was to explore the themes surrounding antithrombotic regimens that are used in practice for patients with symptomatic carotid stenosis during the perioperative period in depth with each of our participants, thereby achieving a better understanding of the perspectives and practices on this commonly encountered clinical challenge.

Methods

The methodology of the Hot Carotid Qualitative Study has been previously published with the first paper from this study exploring physician approaches to carotid imaging and revascularization.[7] We employed a qualitative descriptive methodology[8] to explore the decision-making approaches and opinions of physicians regarding antithrombotic management in patients with recently symptomatic carotid stenosis. For the purposes of this study, we defined "recently symptomatic carotid stenosis" as carotid artery stenosis of ≥50% presenting with a TIA/stroke within the last 2 weeks (i.e., within the highest-risk period generally quoted in the literature) with or without additional intraluminal thrombus.[9]

A snowball sampling strategy with purposive sampling[10] of participants was used for recruitment. The study panel (experts involved in study design) was asked to recommend regional and international colleagues meeting the following eligibility criteria: (1) physicians currently practicing in the field of stroke, who (2) have at least three years of experience in independent practice, (3) have dealt with at least 100 TIAs/strokes in the last year, and (4) have encountered at least 10 symptomatic carotid stenosis cases in the last year. Near the end of each interview, participants were then asked to recommend colleagues fulfilling the above eligibility criteria; thus the term Snowball Sampling. In qualitative descriptive studies, this type of purposive sampling is the "gold standard," with saturation of themes being the optimal determinant of sample size adequacy.[8,11–13] Our interviews involved a deep dive into stroke experts' approaches to the very specific problem of symptomatic carotid stenosis, conducted by interviewers with specialist knowledge. Such an approach achieves high "information power" – referring to the amount of information the sample holds, relevant to the goals of the study – which in turn lowers the number of participants needed to achieve thematic saturation.[21]

Semi-structured face-to-face or telephone interviews were conducted. The interviewers (AG, GJ, and RS) were male neurologists with an interest in stroke neurology, trained in qualitative interviewing by DJTC (MD/PhD with extensive expertise in qualitative methodologies) and used a topic-specific interview guide to ensure consistency in interview style and structure. The interview guide (Supplement) was designed to help interviewees think about their approaches, the challenges they experience when caring for patients with recently symptomatic carotid stenosis, and the factors they consider in their decision making. This interview guide was pilot tested by AG with AAS, BKM, and DJTC. Interviewees were asked to discuss their opinion on the current state of evidence, and their views on how future studies on the antithrombotic management of this population should be undertaken. Each interview lasted 30-60 minutes. The participants knew the interests of the researchers in carotid disease and in future studies in this population. No one else was present during the interviews, and no field notes were made. Interviews were digitally audio-recorded and transcribed verbatim by research assistants.

The results of the qualitative component are reported in accordance with the consolidated criteria for reporting qualitative research (see Supplementary Materials for the COREQ checklist).[11,14] The study was approved by the Conjoint Health Research Ethics Board of the University of Calgary. All participants provided informed consent.

Analysis: Transcripts were imported into NVivo 12 Plus Qualitative Data Analysis software. Data analysis was concurrent with data collection to allow sampling until saturation was reached. Coding was completed by AG and BB. Principles of data analysis from grounded theory were utilized in this process.[15] Opinions and perceptions relating to the choice of antithrombotic regimens were identified and categorized according to conventional qualitative

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Table 1: Characteristics of participants in the study

Age (range) – N (%)	
35–44 years	13 (59.1)
45–54 years	8 (36.4)
55–64 years	1 (4.6)
Sex – N (%)	
Female	4 (18.2)
Male	18 (81.8)
Race – N (%)	
White	15 (68.2)
Black	2 (9.1)
Asian	5 (22.7)
Speciality – N (%)	
Neurology	11 (50.0)
Interventional neuroradiology	5 (22.7)
Neurovascular surgery	3 (13.6)
Geriatrics	3 (13.6)
Region – N (%)	
Europe	11* (50.0)
USA/Canada	9 (40.9)
Asia	2* (9.1)
Africa	1* (4.5)
Caribbean	1* (4.5)
Australia	1 (4.5)
Primary Work Setting – N (%)	
Academic/University Hospital	20 (90.9)
Non-Academic Hospital	2 (9.1)
Years of Independent Practice – Median (IQR)	9.5 (6–19)
Percentage of time spent in clinical practice – Median (IQR)	55 (30–80)
Patients with TIA/Stroke seen in the last 12 months – Median (IQR)	200 (162–400)
Patients with acutely symptomatic carotid stenosis seen in the last 12 months – Median (IQR)	27.5 (20–50)
Preferred carotid revascularization procedure – N (%)	
Carotid endarterectomy	16 (72.7)
Carotid artery stenting	6 (27.3)

*Percentages add up to >100% because one participant practised in both Europe and Asia, one in both Africa and USA, and one in both the Caribbean and USA.

content analysis,[15,16] a method of interpreting interview data with the goal of describing phenomena of interest. This involved the following steps: 1) achieving immersion by first reading the interview transcript in its entirety to acquire an overall sense of the phenomenon (supported by transcribing the initial transcripts and reviewing the subsequent transcripts); 2) reading the interviews line-by-line and highlighting words that capture key concepts, which become the codes; 3) taking notes of initial impressions, thoughts, and interpretation; 4) systematically applying them to the transcripts (open coding); and 5) sorting codes that are related to each other into themes and subthemes (focused coding). Definitions were then developed for existing codes, themes, and subthemes, and exemplars of these were reported in the findings.

The process was reflexive and interactive as continual data collection and data analysis would shape each other. AG, GJ, and BB reviewed the transcripts for the initial three interviews independently with the objective of establishing a preliminary coding template that was then used for all subsequent data analysis. All interviews were then analyzed by at least two reviewers. The team met to review coding and discuss coding strategy and sought to explore different reviewers' unique perspectives when discrepancies were noted. Although trade names for medications were often used by participants, we shared our results using generic names.

Results

We interviewed 22 stroke physicians between May 2018 and June 2021. In total, 24 physicians were approached (18 male and 6 female), and 2 refused due to other commitments (0 male and 2 female). There was representation from various fields within stroke care: 11 neurologists, 3 UK-based geriatricians, 5 interventional neuroradiologists, and 3 neurovascular surgeons. Participants were based in 16 different centers representing experiences from around the world including Canada, the United States, United Kingdom, Australia, Spain, Germany, Zimbabwe, Jamaica, the Czech Republic, and India (Table 1).

Our content analysis revealed 8 themes related to antithrombotic therapy choices, including: evidence and limitations of clinical trials, personalized medicine in secondary stroke prevention, factors favoring DAPT, factors promoting single antiplatelet therapy over DAPT, considerations for anticoagulation in symptomatic carotid stenosis, timing of initiation and duration of therapy for DAPT, revascularization while on DAPT, and future clinical trials.

Evidence and Limitations of Clinical Trials

Most respondents spontaneously identified several key clinical trials, such as the POINT and CHANCE trials, as important in informing their decisions. However, they acknowledged that these two trials did not address the impact of dual-antiplatelet therapy for large-artery disease specifically.

CHANCE and POINT point us in the direction of DAPT being beneficial; but they're all-comers, not focused on patients with large vessel disease; [. . .] [we're] extrapolating from various sources to work out whether dual antiplatelets generally reduce stroke risks in the early phase. [But there is also] a risk of hemorrhage which is quite clear because the operating time [with carotid endarterectomy (CEA)] is slightly longer and the risk of neck hematoma with dual antiplatelet is higher. So we have that balance [. . .] to consider. (Neurosurgeon 1, UK)

I think the evidence for carotid disease in particular is not so strong [. . .] We always extrapolate subgroups from the minor stroke trials [like] POINT [. . .] although patients [who were] going to surgery imminently were generally excluded from these trials . . . There is always this notion that these patients are at high risk and that need dual antiplatelet therapy but there is not good high-level data for that. (Neurologist 7, Canada)

All participants had experience with ASA and clopidogrel as the principal choices for DAPT. However, a few participants mentioned using other agents that either have some emerging evidence or for which there is a paucity of evidence for use in stroke/TIA (Figure 1, Table 2).

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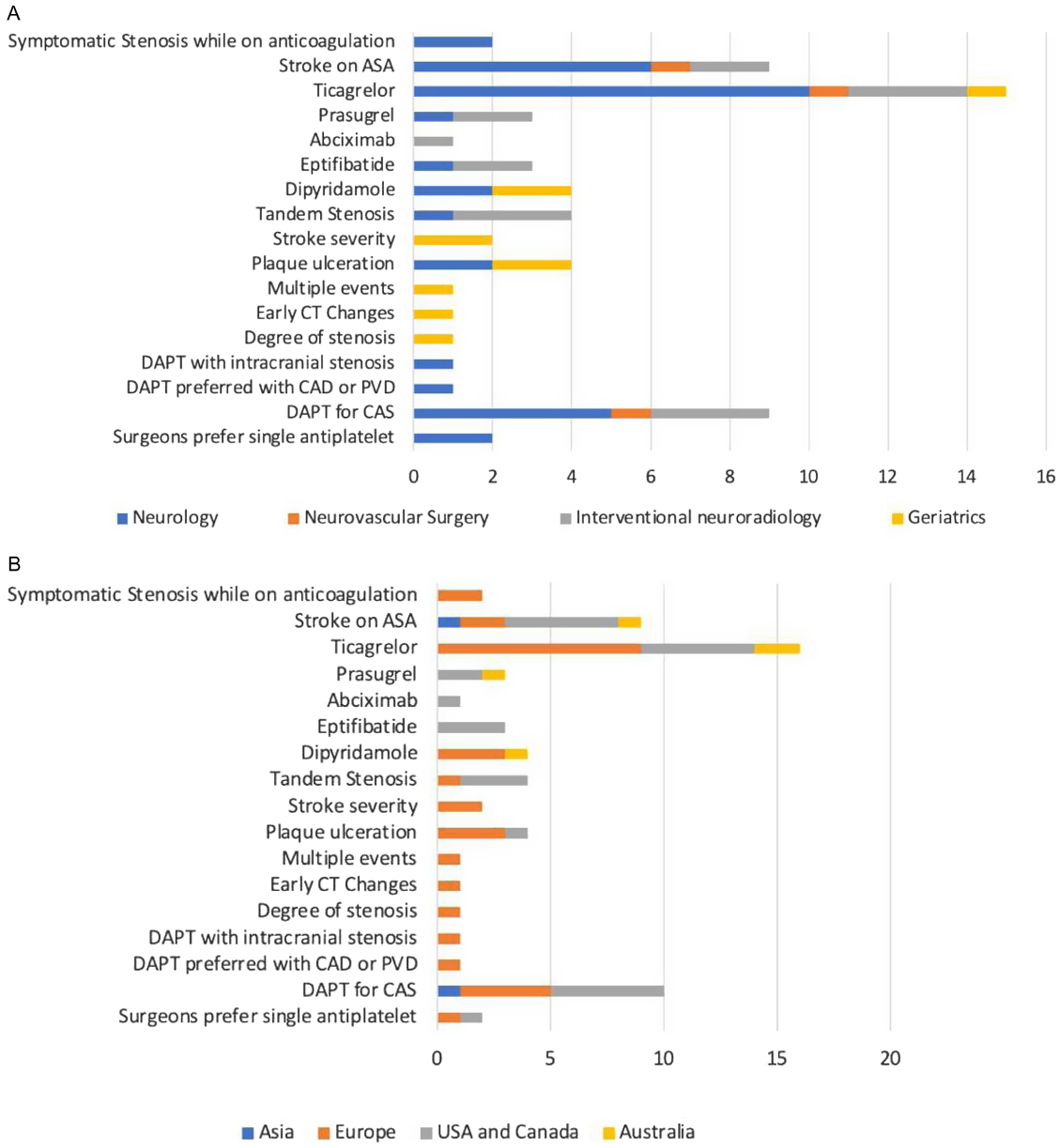

Figure 1: Coding matrix chart for discussions about antithrombotic management of hot carotids, by (A) specialty and (B) region.

I've also given [Abciximab], intravenous (IV) [Eptifibatide], ± rectal ASA. The reason I find these IV agents helpful in the acute setting is because of how long it takes ASA and clopidogrel to kick in, given the upfront risk of early re-occlusion with many of these carotids in the acute setting. (Interventionalist 3, Canada)

Many other participants also discussed the importance of considering these alternative antithrombotic agents, but only in the context of future clinical trials:

I am open to [trialing anti-thrombotic regimens] if there is something new and better. What is the role of ticagrelor [. . .] The cardiologists are certainly using it more and more now. (Neurologist 2, UK)

Personalized Medicine in Secondary Stroke Prevention

Several participants valued having more quantifiable metrics for evaluating the activity of antithrombotic medications (Table 2), citing insights form the CHANCE-2 RCT about the benefit of ticagrelor over clopidogrel in CYP2C19 loss-of-function carriers with stroke/TIA.[17] However, others were skeptical of the value of such testing in practice.

We do not do [clopidogrel] resistance testing as routine for acute presentations even though in our endovascular practice, three out of four of us tend not to use [clopidogrel], we use prasugrel or [ticagrelor] without antiplatelet testing [. . .] I think the data is pretty convincing that [clopidogrel]resistance is a real entity and poses real risk for patients. (Interventionalist 5, USA)

Participants expressed uncertainty regarding how best to manage a patient who has a stroke while on one or more antithrombotic agents. Many favored adding a second agent rather than making a switch (Table 2).

If they are failing on [ASA] I would add [clopidogrel]. Having a double agent would be better rather than switching to another agent. (Interventionalist 1, Canada)

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Table 2: Summary of themes and supporting quotes

Evidence and limitations of clinical trials	*(Neurologist 2, UK) POINT and CHANCE weren't trials looking antithrombotic therapy just for large artery disease; these were trials for TIAs and minor strokes. But [hot carotid] patients are considered to be high-risk patients and therefore I suspect they are the patients who are most likely to benefit from dual antiplatelet treatment.*
Role of newer anti-platelet agents that have not been proven in large stroke trials	*(Neurologist 1, Australia) [. . .] We would like to have [ASA] and Ticagrelor on board when we do a stent [. . .] We give them [ASA] for the first 24 hours [after their event] and then we make sure they haven't got an intracranial hemorrhage and then give them Ticagrelor after that.* *(Interventional 1, Canada) I am talking about medications that have been available for many years. There are lot of new medications now [for which] we don't have good evidence. Prasugrel, for example, [or] other antiplatelet medications as even monotherapy or combination therapy. I would like to see some evidence on that but at the end of the day I think there will be practicality issues on any kind of regimen.* *(Interventionalist 2, Germany) I think that we have better anti-aggregation agents now than clopidogrel, [given] all the non-responders [with CYP2C19 mutations] and we have agents like ticagrelor [that merit further study].*
Personalized medicine; testing for antiplatelet resistance and platelet aggregation	*(Neurologist 2, UK) I would test Clopidogrel resistance in anyone who has had an event on clopidogrel but many people question what the meaning of the result is. So if they have some resistance, what is the titre? [Does it necessarily mean] any further event would occur? Because the major trials did not look at clopidogrel resistance and it was still beneficial. But I think [with respect to] individualization of treatment, it would be helpful if there is a test and it is validated and it can be shown to accurately predict clopidogrel and aspirin resistance – surely it might help us in anti-platelet decisions.* *(Neurosurgeon 2, Canada) [when asked about whether they test for antiplatelet resistance] Not really. Until there are actually platelet aggregation tests that are meaningful, We do it. But I don't know whether it's that meaningful. If you talk to a hematologist the only way you can really tell [if the drug is working] is by the bleeding time*
Antithrombotic management of stroke while on another antithrombotic agent	*(Neurologist 3, Canada) No, it doesn't matter if they are on aspirin or not on aspirin. I just give them double antiplatelets, I don't worry about it. I think that the specific things that you see in the [stroke] community are the people who say "take an extra aspirin" which actually is probably substantially ineffective.* *(Neurologist 7, Canada) So, if they are already on an anti-platelet what we would generally do again, taking into account the risk of hemorrhage, is add a second anti platelet. I would keep the one that they were on whether it be [clopidogrel]or [ASA] and add the other one.*
Factors favoring DAPT	*(Geriatrician 2, UK) If they have evidence of a [stroke] lesion on [the brain] scan, that equals higher risk. [If the] ABCD2 score is higher. History of other vascular events or multiple vascular events or cerebrovascular events in the time period around when they are being seen. If [. . .] on carotid ultrasound, the plaque looks nasty or ulcerated, then [I am] more inclined for DAPT* *(Neurology 6, UK) I tend to put people on DAPT also if they have intracranial stenosis or if they have what looks like irregular plaque pathology in their large arteries, irrespective of the degree of stenosis – so [my decision] is not based solely on measurement of stenosis.*
Factors promoting single antiplatelet therapy over DAPT	*(Neurologist 1, Australia) In terms of infarct volume we do feel that for large infarcts we are less comfortable with dual antiplatelets. So that is why in an acute setting of a massive infarct after we've done thrombectomy we generally would go just with aspirin that first 24 hours until we [have] characterized how big the infarct is.* *(Geriatrician 1, UK) If their NIHSS [National Institutes of Health Stroke Scale score] was 4 or more [. . .] depending on what their imaging looks like and particularly if the BP is high, [if they are] older there is an increased risk of sICH [symptomatic intracranial hemorrhage], I might use a single antiplatelet agent.*
Considerations for anticoagulation in hot carotids	*(Neurologist 8, India) We have had situations where patients had recurrent events even when on DAPT. So then we switched from clopidogrel to heparin and then stopped heparin 3 days prior and then took them for surgery.* *(Neurologist 6, UK) If you anticoagulate [patients with ILT] for a period of few weeks you may see the vessel goes from apparent 90% stenosis to 30% stenosis and the clot disappears. [. . .] We start with heparin and thereafter it depends on the individual circumstances and choice. I would tend to feel more comfortable with warfarin, but I am also open to putting people directly on anticoagulants, and I think the degree of comfort would vary among my colleagues. We probably would use the low molecular weight heparin [first].*
Antithrombotic management in patients with microbleeds on MRI	*(Geriatrics 2, UK) [Regarding microbleeds] If they have definitely had an ischemic event, I would still cover them [with anti-thrombotic drugs] in the high-risk period, but I would go to a single agent rather than DAPT. [I would] definitely discuss risks and benefits with the patients.*
Timing of initiation and duration of therapy for DAPT	*(Neurologist 6, UK) I think our feeling is because [surgical wait time] is unpredictable you should never wait [to start DAPT] and because our surgeons are quite tolerant of people being on dual antiplatelet therapy it is not such a big concern so [the patient] should be on what seems the right medical therapy.* *(Neurosurgery 1, UK) So [duration of DAPT] has been an area of debate in our department. We do discuss it regularly. Most of us are now happy to put on dual antiplatelets [before the procedure] and our stand is to continue them on the treatment that they have already been on – aspirin and clopidogrel. We would continue that throughout the surgery and 3 weeks post procedure.*

(*Continued*)

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Table 2: (*Continued*)

Evidence and limitations of clinical trials	*(Neurologist 2, UK) POINT and CHANCE weren't trials looking antithrombotic therapy just for large artery disease; these were trials for TIAs and minor strokes. But [hot carotid] patients are considered to be high-risk patients and therefore I suspect they are the patients who are most likely to benefit from dual antiplatelet treatment.*
Revascularization while on DAPT: Variable surgeon preferences	*(Neurologist 9, UK) Historically, some surgeons were not keen on DAPT but things have been shifting and the majority are happy with DAPT. So, I would advocate for that. There are a couple who may still be very keen on not having patients on DAPT and I would be ok with that, but still advocate for [DAPT].* *(Interventional 5, USA) My vascular surgeons don't like when [clopidogrel] is on board when doing a CEA and so then they're just waiting on ASA. If I am going to do stenting then I [use] ASA and Plavix while they're waiting in hospital* *(Interventional 2, Germany) The surgeons are also fine to do open surgery on dual anti-platelet. Not a huge problem for them.* *(Neurologist 5, Czech Republic) Now historically, a few years ago, I would say five or more of our vascular surgeons didn't want these patients to have any antiplatelet. After reviewing some data from studies, they realized they need to accept the fact that patients are on some antiplatelet, and nowadays they are willing to operate [even] on patients that are on dual antiplatelet.*
Future Clinical Trials: Endpoints	*(Geriatrician 3, UK) In general I prefer clinical or patient-derived outcomes to surrogate outcomes. However, I recognize that from clinical trial point of view, to show a between-group difference, sometimes surrogate outcomes are needed. Will that surrogate be enough to change guidelines and outcomes?* *Interventional 2, Germany) Let us say we did a DWI after the procedure. Use this a starting point and do another DWI after 30-days or so, and look at the difference. This would be something that will convince me [of peri-procedural anti-thrombotic benefit]. This doesn't necessarily mean that there would be wide acceptance in the community because they say ok what do I care? I just care about real morbidity and mortality. This is just noise.* *(Neurosurgeon 1, UK) In terms of imaging there are some studies that have looked at silent infarcts and DWI lesions on MRI. Those could be compared in patients on dual vs single antiplatelet therapy. So one option would be to include that as an outcome. You need to have a 30-day or an early MRI brain imaging post-operatively in patients having different types of therapy to see whether there is a difference not only in symptomatic events but also image-related criteria.*
Future Clinical Trials: Potential Comparators	*(Interventional 3, Canada) 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. So for me that would be something like comparing IV [eptifibatide] with say rectal [ASA], or a heparin bolus.* *(Neurologist 10, UK) I suppose it will be nice to have a RCT to compare single v/s dual anti-platelet therapy for those awaiting revascularization [. . .] But the event rates might not high enough for such trials to be [. . .] done quite easily.*

However, two participants considered the idea of "ASA failure" as a misleading term and favored not changing regimen.

The concept of [ASA] failure, is a phrase I dislike, [. . .] and just because somebody has an event does not mean that the treatment is incorrect or it has failed to work. [. . .] It does mean you need to think about [whether] you have pursued the correct mechanism. [. . .] But it doesn't mean we would necessarily change antiplatelet therapy. (Neurologist 6, UK)

Factors Favoring DAPT

Respondents identified several factors that would push them towards favoring DAPT over single antiplatelet therapy. These included patients with planned stenting or other medical indications for DAPT such as cardiac stenting and peripheral vascular disease (Figure 1) (Table 2).

Coronary disease [. . .] is a common thing that we encounter where there is an existing need to be on dual therapy. Peripheral vascular disease [. . .] is less common and they tend not to be on multiple agents. (Neurology 6, UK)

Other considerations for DAPT reported by the participants included the number of ischemic events, plaque features, and presence of significant intracranial stenosis (Table 2). The participants underscored the importance of considering comorbid medical conditions and other medications of patients with symptomatic carotid stenosis, when considering stroke prevention regimens, as patients with symptomatic carotid stenosis often harbor other cardiovascular diseases.

There is a high prevalence of coronary artery disease in our population, [. . .] in particular in the large artery atherosclerosis population, so a lot of them are already taking DAPT or have indications to do so because they have coronary stents. We [. . .] need to be flexible about our regimens. (Neurology 6, UK)

Factors Promoting Single Antiplatelet Therapy Over DAPT

All participants listed at least one situation in which they would be less keen on using DAPT, many of which were similar between participants. These included patients with large or severe stroke, multiple medical comorbidities, or frailty (Table 2). In scenarios where a single antiplatelet regimen was preferred, the choice of antiplatelet agent was almost unanimously ASA.

[If the] patient has a history of [. . .] bleeds or [they are] physically frail, on lots of meds, [or have] many comorbidities, then [I am] more concerned about risks of DAPT. Not just risk of bleeding, but of bleeding leading to [. . .] functional decline. (Geriatrician 2, UK)

However, some participants expressed uncertainty regarding the size of stroke and its impact on DAPT decisions.

We don't have a good feel for [whether there is] a point at which the size of the infarct outweighs the benefits of risk [reduction] of recurrence of infarct with DAPT; where does the balance shift?[. . .] In larger strokes the hemorrhage risk goes up and the recurrence risk

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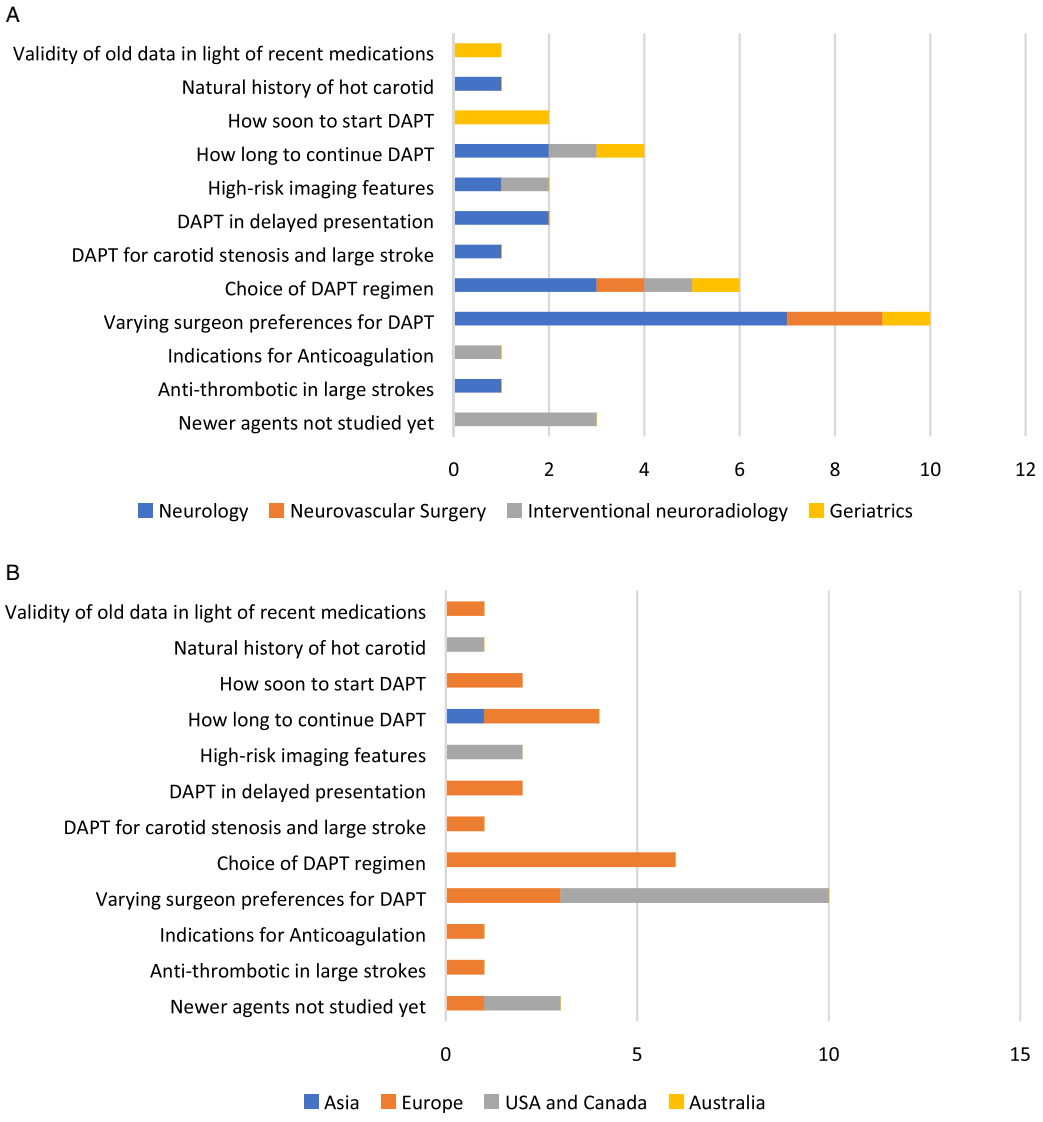

Figure 2: Coding matrix chart for discussions about uncertainties and enduring questions regarding antithrombotic management of hot carotids, by (A) specialty and (B) region.

goes down because the area of injury is already established. In the [carotid stenosis] population, a big stroke would push me away from DAPT. (Neurologist 9, UK)

Although there was uncertainty, participants offered different approaches to managing patients with symptomatic carotid stenosis who had evidence of micro-bleeds, an issue that came up when discussing risks with antithrombotic regimens. Some participants remained keen to prescribe DAPT, while other were more conservative (Table 2):

I wouldn't let micro-hemorrhages put me off because already you are giving DAPT for a short period. You can just give it for a month or possibly till the operation. (Neurologist 2, UK)

Considerations for Anticoagulation in Symptomatic Carotid Stenosis

Participants expressed uncertainty about the role of therapeutic anticoagulation. Several of them would consider anticoagulation in three situations: a patient with concurrent atrial fibrillation, a patient with a mobile plaque or evidence of fresh clot on the plaque, and in patients who have had recurrent events while on DAPT (Table 2):

If the CTA or the ultrasound shows a mobile component or fresh clot and [we] are in a hospital setting, I'll sometimes use a heparin drip [with no bolus] just while I wait [in patients with a small stroke]. Probably with low dose ASA 81 mg. (Interventional 5, USA)

Timing of Initiation and Duration of Therapy for DAPT

Several participants struggled with the ideal timing for initiation of DAPT after stroke and its impact on subsequent care pathways (Figure 2).

I think there is still a lot of uncertainty. My understanding is that greatest benefit for DAPT is when given as early as possible. There are challenges in our pathway to give DAPT really as soon as the patient presents to hospital, which is not always when [they are] seen by a stroke physician. They may not see me until the next morning or if it's a long rounding day, the next afternoon. (Geriatrician 3, UK)

Participants also described uncertainty regarding how long to continue DAPT, particularly after patients are revascularized.

I think these are open questions, [. . .] the duration of anti-aggregation therapies - should it be 3 or 6 weeks or 12 weeks? (Interventional 2, Germany)

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[Once] they've had the surgery and they are a month post-operatively they are out of the high-risk period. On an individual patient basis I'd think about stopping DAPT after 1 month potentially if successful revascularization, or possibly 3 months. (Geriatrician 2, UK)

Revascularization While on DAPT

Both neurologists, internists, and interventionalists were generally in agreement that DAPT is the ideal regimen for those undergoing carotid artery stenting (CAS), although some raised issues related to procedural complications. There were several notable differences in discussion between specialties and regions. Surgeons and interventionalists more often discussed themes related to procedural complications and bleeding than their neurologist counterparts, who were more concerned about recurrent stroke risks. Geriatricians were more often concerned about the implications of frailty and multimorbidity of their patients compared to other specialities. Participants from Europe were more likely to provide examples of contraindications to DAPT than those from other regions.

If [arterial] access is going to be an issue and multiple punctures are required then dual agent could an issue especially if you are having anticoagulation as well. Groin complications can be higher if on dual agent. (Interventionalist 1, Canada)

Participants more often identified uncertainty regarding the use of DAPT in patients undergoing CEA. The most common theme in this regard related to varying surgeon preferences in the choice of antiplatelet agent (Table 2).

Previously we were operating on DAPT but some patients developed a wound hematoma. So now [the surgeons] are particular about stopping clopidogrel 3-4 days prior. (Neurologist 8, India)

Future Clinical Trials

Future trials on the antithrombotic management of symptomatic carotid stenosis were an important discussion topic among the participants. Specific aspects of future clinical trials included what outcomes were important to participants, anticipated challenges, and acceptable comparator arms of the trial (Table 2). Participants demonstrated willingness and interest in participating in future trials on this topic. The primary outcome measure most valued by the participants was recurrent stroke at a given time point, followed by death and disability. Other secondary outcomes included hemorrhage, cognitive measures, infarct size, and medication tolerability. There were mixed opinions regarding the acceptability of magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) lesions as outcomes (Table 2).

I think new DWI lesions are a very specific and sensitive way of looking at [stroke outcomes]. I would be interested to see a baseline DWI and then one just before [and] after the procedure. (Neurologist 1, Australia)

[DWI lesions] are a reasonable surrogate marker [. . .], but I don't think this will change the clinical practice if you demonstrate there are fewer small DWI lesions. (Neurologist 5, Czech Republic)

Participants also expressed a preference for more pragmatic or flexible designs integrated well within regular patient care:

I think that we would be keen to be involved in a trial of that sort as long as they are accepted within our pathway and didn't delay our patient treatment. (Neurosurgeon 1, UK)

Often, we find that on paper we would have lots of eligible patients 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. (Geriatrician 3, UK)

Participants also brought up concerns regarding getting buy-in from interventionists or surgeons for trials that include more aggressive antithrombotic regimens.

I could be very interested in any clinical trials [on this topic]. However, I know that neuro-interventionalists are not so prone to do this kind of trial, so I think the most difficult thing would be to try to convince the neuro-interventionalist or the vascular surgeons to randomize these patients before their procedure. (Neurologist 4, Spain)

Discussions regarding comparator arms for clinical trials revealed several potential comparators that participants considered to be acceptable or of interest. These included single antiplatelet vs dual anti platelet, DAPT using ASA and clopidogrel vs ASA and ticagrelor, or DAPT vs anticoagulation in different combinations (Table 2).

There are new antiplatelet therapies like Ticagrelor in ischemic cardiomyopathy has shown to be more effective than clopidogrel . . . maybe this should be one of the drugs to test. (Neurologist 4, Spain)

Discussion

The management of recently symptomatic carotid stenosis is fraught with differing treatment options and patient variability that must be considered in clinical decision making. In this qualitative study, we explored the opinions and attitudes of physicians in the stroke community as they pertain to the perioperative antithrombotic management of patients with recently symptomatic carotid stenosis awaiting revascularisation. Our findings can help practising neurologists better appreciate the commonalities and variations in approaches among stroke experts around the world to this important clinical problem, and thus better critique or refine their own approaches.

When determining the optimal antithrombotic regimen for patients with symptomatic carotid stenosis, participants turned to clinical trial evidence from several trials, most often referring to the POINT and CHANCE trials to support the use of DAPT. However, they also recognized that the trials have limited generalizability to symptomatic carotid patients and that there remain gaps in the evidence. A new recommendation from the most recent guidelines on the management of symptomatic carotid stenosis from the European Society for Vascular Surgery[18,19] highlights the uncertainty regarding optimal management of symptomatic carotid stenosis: "For recently symptomatic carotid stenosis patients in whom carotid endarterectomy is being considered, it is recommended that neurologists/stroke physicians and vascular surgeons develop local protocols to specify preferred antiplatelet regimens (combination therapy *vs.* monotherapy), so as not to delay urgent carotid surgery." This recommendation is inherently flexible and subjective and highlights the uncertainty regarding this topic which prevented the society from making more specific guidelines. The role of newer antithrombotic agents and the need for standardized testing for antiplatelet activity or resistance were also discussed by participants. Importantly, although a minority of participants viewed genetic testing – such as for CYP2C19 mutations for clopidogrel resistance – as a valuable tool, the majority did not see a current or potential future for such testing in their selection of antiplatelet regimens, implying a limited perceived value of such testing in routine practice,[20] despite the findings of the CHANCE-2 trial.[17] Our detailed qualitative findings complement our recent worldwide survey of neurologists on the topic of

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antithrombotic management of symptomatic carotid stenosis, which included 668 neurologists with different levels of experience.[21] Diverse antithrombotic regimens were chosen by the participants for three different symptomatic carotid stenosis scenarios. Whereas monotherapy was favored by 54.4%–70.6% across scenarios, most commonly with ASA, the next most popular choice was indeed DAPT with ASA and clopidogrel (26.0–41.3%).[21] When respondents were asked to indicate factors that would increase their enthusiasm for regimens like DAPT, they responded quite similarly to our qualitative study participants, who favored DAPT for patients undergoing stenting, or with concomitant coronary artery disease or peripheral vascular disease, multiple ischemic events, significant intracranial stenosis, and plaque imaging features like irregularity or ulceration suggesting instability or fragility. Our qualitative analysis was able to provide a more in-depth exploration of the themes related to the above choices in ways that a survey cannot capture. Whereas a survey is limited to what the authors decide a priori, a qualitative study is able to tailor and expand upon discussions to better understand the rationale behind these choices.

Our data also highlight areas of antithrombotic management where there is equipoise or uncertainty. For instance, there was equipoise between the use of single and dual antiplatelet therapy, particularly in patients awaiting CEA. Although our respondents indicated there is data to support the use of DAPT for symptomatic carotid stenosis, they noted limitations of clinical trial data as well as a multitude of clinical scenarios in which respondents felt DAPT would not be appropriate.

Antithrombotic therapy decisions for symptomatic carotid stenosis center around the trade-off between recurrent stroke and bleeding risks, but we identified important interspeciality differences in how these priorities were weighted. Neurologists and geriatricians were more often concerned with recurrent stroke risk and would generally favor more aggressive antithrombotic regimens compared to surgeons and interventionists, who were more often concerned with procedural complications. We also identified some regional differences in approach; for example, participants from Europe were more likely to provide examples of contraindications to DAPT than those from other regions. This was similar to our prior worldwide survey, in which European participants were less likely to recommend a regimen containing DAPT than their North American counterparts.[21] There were several common themes raised by all specialists in all regions, such as the limitations of clinical trial evidence and the changing surgical preferences for DAPT, as well as the problem of stroke while on ASA.

The use of the semi-structured interview format allowed for in-depth exploration of multiple themes that may not have been considered *a priori*; however, there are limitations to our study. We interviewed fewer proceduralists than neurologists/geriatricians, although these perspectives were represented through our purposive sampling strategy which allowed us to explore the perspectives of various groups of stakeholders. Snowball sampling relies on participants to suggest additional colleagues whom they know and as such may have had shared experiences, training or similar ways of thinking about the topic creating a sampling bias. We were able to recruit participants from around the world with various experiences, working and training environments which can mitigate some of this bias that is inherent to our methodology. Qualitative research is often hypothesis generating, and its greatest value lies in understanding the depth of an issue. We were able to achieve thematic saturation in our study, which is a signal that the sample size employed is adequate for qualitative analysis.[8,11–13] We did not delve into the specific dosages of different antithrombotic regimens preferred by our respondents, which may have implications for stroke prevention. For example, prior studies have shown regional variabilities in ASA dosing, and there may be dose-dependent differences in the effectiveness of stroke prevention in patients with larger body habitus.[22] We also had limited representation from low/middle-income countries, which may limit the transferability of our results to such countries. None of the expert opinions quoted are intended to represent the "correct" way to approach this complex issue; rather, qualitative studies of this nature seek to capture different physician opinions to help us illuminate areas of relative consensus and uncertainty to guide future work.

Conclusion

Our findings underscore the heterogeneous management and community equipoise surrounding optimal antithrombotic regimens for patients with recently symptomatic carotid stenosis. The variations in clinical practice that are observed in our study also highlight the need for stronger evidence to help guide clinical decisions regarding antithrombotic management in the peri-procedural period. High-quality randomized controlled trials are of utmost importance to help answer this question, and the design of these trials has to take into account variations in practice and understanding how participants view the risk and benefits of the proposed trials arms. Our results suggest that comparator arms for future trials looking at the peri-procedural antithrombotics for patients undergoing CAS would be more widely accepted if they compared DAPT with ASA and clopidogrel vs ASA and an alternative agent like ticagrelor. For trials looking into antithrombotic management for those undergoing CEA, the comparison for single antiplatelet (ASA) to DAPT would be most helpful as many practitioners were uncertain about the weight of the benefit on ischemic events vs peri-procedural risk of bleeding. Such trials can provide clinically meaningful insights to better delineate safety profiles and reductions of ischemic stroke, while reflecting the priorities of stroke physicians. Teams designing international carotid trials may wish to accommodate identified variations in practice patterns and take into consideration areas of uncertainty, such as managing stroke for patients already on antithrombotic agents, studying newer antithrombotic agents, and evaluating non-stenotic features of carotid disease for risk stratification.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2023.28.

Author contributions. **A. Ganesh** was involved in the conception and design of the study, collected and analyzed the data, co-wrote the first draft, and revised the paper.

B. Beland analyzed the data, co-wrote the first draft, and revised the paper.

G.A.E. Jewett collected data, assisted with analysis, and helped revise the paper.

M. Varma was involved in data collection, analysis, and revision of the paper.

D.J.T Campbell was involved in the design of the study, analysis, and revision of the paper.

R.J. Singh was involved in the design of the study, data collection, and revision of the paper.

A. Al-Sultan was involved in the design of the study and revision of the paper.

B.K. Menon supervised the study and was involved in the conception, design, writing, analysis, and revision of the paper.

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References

1. Petty GW, Brown RD Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. Stroke. 1999;30:2513–6.
2. Flaherty ML, Kissela B, Khoury JC, et al. Carotid artery stenosis as a cause of stroke. Neuroepidemiology. 2013;40:36–41.
3. Amarenco P, Lavallée PC, Labreuche J, et al. One-year risk of stroke after transient ischemic attack or minor stroke. N Engl J Med. 2016;374:1533–42.
4. Eliasziw M, Kennedy J, Hill MD, Buchan AM, Barnett HJ. Early risk of stroke after a transient ischemic attack in patients with internal carotid artery disease. CMAJ. 2004;170:1105–9.
5. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369:11–9.
6. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. N Engl J Med. 2018;379:215–25.
7. Ganesh A, Beland B, Jewett GAE, et al. Physician approaches to imaging and revascularization for acutely symptomatic carotid stenosis: insights from the hot carotid qualitative study. Stroke: Vasc Interv Neurol. 2022;2:e000127.
8. Sandelowski M. Whatever happened to qualitative description? Res Nurs Health. 2000;23:334–40.
9. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2007;6:1063–72.
10. Emmel N. Sampling and choosing cases in qualitative research: a realist approach. London, 2013. Available at https://methods.sagepub.com/book/sampling-and-choosing-cases-in-qualitative-research; accessed September 26, 2022.
11. Gobo G, Qualitative Research Practice, 2004, London: SAGE Publications Ltd. https://methods.sagepub.com/book/qualitative-research-practice; accessed September 26, 2022.
12. Campbell S, Greenwood M, Prior S, et al. Purposive sampling: complex or simple? Research case examples. J Res Nurs. 2020;25:652–61.
13. Robinson OC. Sampling in interview-based qualitative research: a theoretical and practical guide. Qual Res Psychol. 2014;11:25–41.
14. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19:349–57.
15. Chun Tie Y, Birks M, Francis K. Grounded theory research: a design framework for novice researchers. SAGE Open Med. 2019;7:2050312118822927.
16. Campbell DJT, Lee-Krueger RCW, McBrien K, et al. Strategies for enhancing the initiation of cholesterol lowering medication among patients at high cardiovascular disease risk: a qualitative descriptive exploration of patient and general practitioners' perspectives on a facilitated relay intervention in Alberta, Canada. BMJ Open. 2020;10:e038469.
17. Wang Y, Meng X, Wang A, et al. Ticagrelor versus clopidogrel in CYP2C19 loss-of-function carriers with stroke or TIA. N Engl J Med. 2021;385:2520–30.
18. Naylor R, Rantner B, Ancetti S, et al. European society for vascular surgery (ESVS) 2023 clinical practice guidelines on the management of atherosclerotic carotid and vertebral artery disease. Eur J Vasc Endovasc Surg. 2022;65:7–11.
19. Naylor AR, Ricco JB, de Borst GJ, et al. Editor's choice - management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2018;55:3–81.
20. Pan Y, Chen W, Xu Y, et al. Genetic polymorphisms and clopidogrel efficacy for acute ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. Circulation. 2017;135:21–33.
21. Ganesh A, Bartolini L, Singh RJ, et al. Equipoise in management of patients with acute symptomatic carotid stenosis (hot carotid). Neurol Clin Pract. 2021;11:25–32.
22. Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. Lancet. 2018;392:387–99.

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