Research Protocol

Individualized MRI-Based Stroke Prediction Score Using Plaque Vulnerability

Clinical impact of the use of IMPROVE for selection of patients for carotid revascularisation

A randomized controlled multicentre non-inferiority trial in symptomatic patients with 30-99% carotid stenosis

Protocol ID	**NL-010345**
Short title	**IMPROVE**
EudraCT number	***not applicable***
Version	**3**
Date	**18 February 2026**
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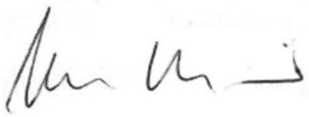
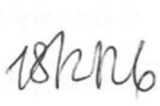
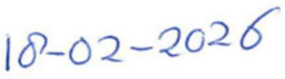
Sponsor or legal representative: **Head of Department:** Prof.dr. J.E. Wildberger		
Principal Investigator: Prof.dr. M.E. Kooi Professor in Medical Physics, especially vascular imaging		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CVA	Cerebral Vascular Accident
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IMPROVE	Individualised MRI- based PRediction scOre using plaque Vulnerability for patients with symptomatic carotid artery diseasE
METC	Medical research ethics

	committee (MREC); in Dutch: medisch ethische toetsingscommissie (METC)
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient Ischemic Attack
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch- wetenschappelijk Onderzoek met Mensen

SUMMARY

Stroke is the 2nd leading global cause of death and disability [Johnson, 2019]. Rupture of a vulnerable carotid plaque causes ~20% of ischemic strokes. Symptomatic patients with carotid stenosis may benefit from surgical removal of the plaque or stenting (revascularisation) to prevent recurrent stroke, but this carries risks. In the Netherlands, carotid endarterectomy accounts for 95% of revascularisation procedures performed in symptomatic patients [Buisman, 2019]. Current patient selection for revascularisation is suboptimal, largely based on stenosis degree without considering plaque vulnerability. Improving risk prediction is therefore crucial and has been formally recognized as a key priority in the Dutch Society for Vascular Surgery's Knowledge Agenda (2022): "How can we better identify patients with carotid stenosis who would or would not benefit from revascularisation?"

Presence of intraplaque haemorrhage (IPH) on MRI is one of the most powerful imaging biomarkers of plaque vulnerability and a superior predictor of stroke compared to traditional clinical factors, including degree of stenosis. The recently developed "Individualized MRI- Based Stroke Prediction Score Using Plaque Vulnerability for Symptomatic Carotid Artery Disease Patients" (IMPROVE) clinical prediction model integrates both IPH on MRI and clinical risk factors to calculate ipsilateral ischemic stroke risk [Nies, 2025a]. This model has demonstrated significantly improved predictive performance over existing scores. A recent decision-analytic study investigated the impact of the use of IMPROVE to select patients with high stroke risk for revascularisation plus OMT (medication and lifestyle advice) and low-risk patients for OMT-only. This decision-analytic study showed that implementation of the IMPROVE decision rule for revascularisation selection can lead to 35% less ipsilateral strokes and perioperative strokes and deaths and a lifetime cost reduction of €6101 per patient, equating to an annual reduction in societal healthcare costs of €18 million in the Netherlands alone [Nies, 2025b].

Rationale: Patient selection for carotid revascularisation to prevent recurrent strokes could be optimised by providing clinicians and patients the IMPROVE score for shared decision-making. **Objective**: The primary objective is to investigate the clinical impact and the cost-effectiveness of the individualised MRI-based IMPROVE decision rule compared to care as usual (CAU) in the selection of TIA and non-disabling stroke patients with 30-99% carotid stenosis for revascularisation.

Study design: Multicentre, randomized controlled non-inferiority trial.

Study population: Patients with a recent TIA or minor ischemic stroke and ipsilateral 30-

99% carotid stenosis according to NASCET criteria.

Intervention (if applicable): For patients that are randomised to the IMPROVE arm, the IMPROVE risk score will be provided as additional information for clinical decision-making on patient stratification for carotid revascularisation plus OMT versus OMT-only. A revascularization procedure in combination with OMT will be advised for patients at high ipsilateral stroke risk (≥10% within 3 years) according to the IMPROVE score, while OMT-only (medication and lifestyle advice) is advised to patients with lower risk scores.

Comparator: Patients randomised for the control arm (care-as-usual (CAU)) will be selected for revascularisation based on the guidelines for carotid interventions from the European Society for Vascular Surgery. It advises to consider revascularisation for TIA and stroke patients with ≥50% carotid stenosis. Patients with 30-49% stenosis are treated by OMT-only (medication and lifestyle advice). Plaque vulnerability is not taken into account for patient selection in current clinical care in the Netherlands.

Main study parameters/endpoints: Primary: Composite of any stroke or death within 44 days after randomisation or ipsilateral ischemic stroke at any time during subsequent 3-5 years follow up. Secondary: a.o. QALYs, number of revascularization procedures, costs.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Our IMPROVE decision rule has demonstrated superior risk prediction capability compared to the ECST score and a much higher sensitivity with comparable specificity compared to selection criteria that are currently used in CAU to stratify patients for carotid revascularisation. We expect that the IMPROVE risk score will improve selection of patients for carotid revascularisation that can benefit most, but this cannot be guaranteed, since this still needs to be validated in our clinical trial. Patients need to fill in questionnaires at baseline, 44 days after inclusion, and at 1, 2, and 3 up to 5 years after inclusion. The questionnaires will take approximately 10 minutes per time point.

The study will be done in patients with a recent TIA/minor ischemic stroke and 30-99% ipsilateral carotid stenosis since this group has a considerable risk of a recurrent stroke. Current clinical decision-making to select patients for carotid revascularisation is suboptimal and is based on outdated trials that were performed decades ago when imaging of plaque vulnerability was not yet possible.

Our intervention will often result in an extra MRI scan. ~53% of the patients need an extra MRI. In ~47% an MRI is unnecessary since, based on the other risk factors, the stroke risk is already high or low and the MRI result does not affect the risk category. Carotid plaque MRI is safe and has been extensively validated. Patients with MRI contraindications will be excluded.

1. INTRODUCTION AND RATIONALE

BACKGROUND

Stroke is the second leading cause of death and the second largest contributor to global disability-adjusted life years (DALYs) since 2015 [Johnson, 2019]. Ten to twenty percent of all acute ischemic strokes are associated with carotid artery disease [Cheng, 2019]. Patients with carotid artery disease are at increased risk for ischemic stroke through rupture of a vulnerable carotid atherosclerotic plaque [Nies, 2021]. To prevent the risk for recurrent ipsilateral ischemic stroke, the carotid plaque can be removed by carotid endarterectomy (CEA) or compressed by carotid artery stenting (CAS). However, both procedures carry perioperative risks, with 30- day rates of death or any stroke at 4.4% for CEA and 7.2% for CAS [Muller, 2020]. Therefore, it is important to weigh the risks of the procedure against the benefits of carotid revascularization in clinical decision-making. According to current guidelines, patient selection for carotid revascularisation is predominantly based on the degree of carotid stenosis. However, carotid stenosis serves only as a surrogate marker for plaque vulnerability, which results in suboptimal patient selection for intervention. Recent data from the Second European Carotid Surgery Trial (ECST-2) demonstrated that in a cohort of patients with ≥50% carotid stenosis and a 5-year stroke risk below 20%, medical management alone yielded comparable outcomes to carotid revascularisation after two years of follow-up [Donners, 2025]. These findings highlight the urgent need to more accurately identify a subgroup of patients with carotid stenosis who will truly benefit from carotid revascularisation [Nederkoorn, 2025]. To highlight the urge for better stratification of patients for revascularization, our research is also represented as a priority question on the knowledge agenda of the Dutch Society for Vascular Surgery (2022): How can the identification of patients with a carotid stenosis that do or do not have benefit from revascularisation be improved?

MRI can provide detailed information on carotid plaque vulnerability [Nies, 2021] and is considered the best non-invasive imaging modality for this purpose. A hallmark of plaque vulnerability is intraplaque haemorrhage (IPH). In a large meta-analysis based on individual patient data, it was shown that IPH on MRI is a very strong and independent predictor of ipsilateral stroke (hazard ratio [HR]: 11.0; 95%-CI: 4.8-25.1), stronger than any of the known clinical risk factors, including degree of stenosis [Schindler 2020]. Also, our recent PARISK trial confirmed that IPH on MRI is a strong independent stroke predictor, superior to CTA, ultrasound or transcranial Doppler imaging biomarkers [van Dam-Nolen, 2022]. MRI is the only method that allows

accurate assessment of IPH in the carotid plaque. IPH can be recognized as a hyperintense signal in the bulk of the plaque using a 5-minute MRI sequence and a standard neurovascular MRI coil [Nies, 2021].

To identify patients with carotid plaques who are at high risk of recurrent ischemic stroke, our research group developed the “Individualized MRI-Based Stroke Prediction Score Using Plaque Vulnerability for Symptomatic Carotid Artery Disease Patients” (IMPROVE) decision rule, based on a clinical prediction model [Nies, 2025a]. The IMPROVE model is currently the only prediction score with sufficient statistical power that incorporates the presence of a vulnerable plaque (IPH on MRI) to estimate the 3-year risk of ipsilateral ischemic stroke in symptomatic patients with an ipsilateral carotid plaque.

IMPROVE significantly outperforms previous models in predicting the risk of recurrent ischemic stroke. In a recent decision-analytic study, we demonstrated that using the IMPROVE decision rule to select patients for carotid revascularisation could reduce the incidence of ipsilateral ischemic strokes combined with perioperative strokes and mortality by 35%, resulting in an annual societal cost reduction of €18 million in the Netherlands alone [Nies, 2025b]. This reduction in number strokes was observed across all stenosis categories (30–49%, 50–69%, and 70–99%). Furthermore, qualitative research consisting of interviews with 40 Dutch clinicians involved in carotid revascularisation decision-making indicated that the IMPROVE decision rule was generally well received by clinicians, while also highlighting the necessity for prospective clinical validation in a randomised clinical trial [Bierens, 2025].

RATIONALE

Selection of symptomatic patients with 30-99% carotid stenosis (NASCET) for carotid revascularisation (CEA or CAS) plus optimised medical therapy (OMT) versus OMT-only can be improved by integrating the risk stratification provided by the IMPROVE model into clinical decision-making. Incorporating this individualized risk assessment is anticipated to optimize patient selection, thereby reducing the incidence of the composite endpoint of ipsilateral ischemic stroke and perioperative stroke and death by approximately 35% and generating an estimated annual reduction of €18 million in societal costs within the Netherlands.

USUAL CARE

According to current European Society for Vascular Surgery (ESVS) guidelines for carotid interventions, CEA should be considered for symptomatic patients with a TIA or

non-disabling stroke and ipsilateral ≥50% stenosis of the ipsilateral internal carotid artery [Naylor, 2023]. All patients with a TIA or non-disabling stroke and ipsilateral <50% stenosis of the ipsilateral internal carotid artery are treated by OMT-only, including statin therapy, anti-platelet therapy and blood pressure control. The decision should be preferably made based on a prediction model for recurrent risk. The ECST model does not include specific risk thresholds and previously demonstrated poor performance [van Dam- Nolen 2022]. Interviews by us with Dutch clinicians revealed moderate variability in clinical practice for managing 50–69% carotid stenosis. Specifically, 7 out of 10 centres routinely recommend revascularisations for all

patients within this stenosis range, whereas the remaining 3 centres limited interventions to patients deemed at high-risk (e.g., age >75 years, presence of cortical symptoms).

THE INTERVENTION TO BE INVESTIGATED

All patients are screened in routine care for carotid stenosis. In the IMPROVE intervention arm, the stroke risk will be assessed using the IMPROVE model [Nies, 2025a], incorporating plaque vulnerability (IPH on MRI), stenosis severity, ischaemic event type (ocular vs. cerebral), age and sex. For high-risk patients (≥10% IMPROVE risk of ipsilateral ischemic stroke recurrence within 3 years) we will advise carotid revascularisation (CEA/CAS) in combination with OMT. For lower risk patients (<10% IMPROVE risk) we will advise to treat them with OMT only. The 10% threshold for stratifying high- and low-risk patients was chosen based on the decision- analytic study by Nies et al., which demonstrated that this cut-off achieved the largest reduction in the combined primary endpoint ipsilateral ischemic stroke incidence and perioperative strokes and mortality [Nies, 2025b].

In both study arms the decision for revascularisation will be made by shared decision-making. A multidisciplinary team of neurologists, vascular surgeons and a neuroradiologist will always be involved. All patients will be fully informed on risks and benefits of revascularisation and the Number Needed to Treat (NNT). In the care as usual (CAU) arm, we conform to the clinical guidelines. The 10% threshold in the intervention arm is not a hard cut-off, since patients and treating physicians can still make a shared decision for no revascularisation, especially in borderline cases. Vice versa, for an IMPROVE stroke risk <10%, where no revascularisation is advised. The attending medical specialist and the patient make the final decision together by shared clinical decision-making.

EXISTING EVIDENCE OF EFFECTIVENESS

Current clinical decision-making for carotid revascularisation is predominantly based on the degree of stenosis, although increasingly incorporating risk models such as the ECST or CAR score, which consider multiple clinical and imaging characteristics. However, these models remain limited in their predictive performance and do not capture plaque vulnerability. In particular IPH on MRI, a hallmark of plaque vulnerability, has emerged as a powerful, independent predictor of stroke. A comprehensive meta-analysis identified IPH as having the highest hazard ratio among all predictors (HR: 11.0; 95% CI: 4.8–25.1) [Schindler, 2020]. Notably, symptomatic patients with <50% stenosis but IPH-positive plaques, who are not revascularized in CAU, face a 4-year ipsilateral ischemic stroke risk of 36% on OMT-only [Schindler, 2020].

The IMPROVE model [Nies, 2025a], based on pooled data from contemporary carotid MRI cohorts, significantly outperforms the conventional ECST score in stroke prediction (C-statistic: 0.82 vs. 0.67). It offers superior sensitivity and specificity in stroke prediction compared to CAU-based stratification by stenosis degree [Nies, 2025a]. Among available risk prediction scores, the IMPROVE model is currently the only model that incorporates the presence of a vulnerable plaque with sufficient statistical power. Alternative models (SCAIL, CaroTID-VasC) are less robust [Kumar, 2023; Kelly, 2020].

Importantly, a decision-analytic study showed that implementation of the IMPROVE score in clinical practice could yield substantial benefits: a cost saving of €6,101 per patient in the Netherlands, a 35% reduction in ipsilateral strokes and perioperative strokes and deaths (2.8% in IMPROVE-based care vs. 4.3% in CAU), and a 20% decrease in revascularisations [Nies, 2025b].

However, these expected clinical and economic benefits have not yet been demonstrated in a prospective, randomized clinical trial. Furthermore, a recent national survey among Dutch vascular neurologists and surgeons identified the lack of clinical evidence for improved outcomes as the main barrier to implementing IMPROVE in daily clinical practice [Bierens, 2025]. The present randomised controlled IMPROVE trial therefore provides the first multicentre, randomised evaluation of the clinical effectiveness, safety, and cost-effectiveness of risk-based patient selection using the IMPROVE model for carotid revascularisation.

2. OBJECTIVES

Primary Objective:

To evaluate the clinical impact and the cost-effectiveness of the individualised MRI-based IMPROVE decision rule compared to CAU in the selection of TIA and non-disabling stroke patients with ipsilateral 30-99% atheromatous carotid artery stenosis for revascularisation.

Our hypothesis is that the IMPROVE decision rule is non-inferior to CAU in terms of the primary outcome (composite of any stroke or death within 44 days after randomisation or ipsilateral ischemic stroke at any time during subsequent follow-up) while significantly reducing associated costs.

Secondary Objective(s):

- To compare QALYs and costs associated with IMPROVE-based care and CAU.
- To investigate and evaluate the willingness of clinicians and patients to use

the IMPROVE decision rule to estimate the patient's risk of stroke recurrence.

3. STUDY DESIGN

This is a randomised controlled non-inferiority trial across 5 university and 5 non-university hospitals in the Netherlands, with a 2-year and 5-month inclusion period and 3+ years of follow-up. This study is funded by ZonMw (DoelmatigheidsOnderzoek Open Ronde 2026). Patients within the control group will be selected for carotid revascularization vs OMT-only as in CAU. In the intervention group, high-risk patients (≥10% predicted risk of ipsilateral ischemic stroke within 3 years on OMT by IMPROVE) will be recommended by the IMPROVE decision rule to undergo carotid revascularisation (CEA/CAS) in combination with OMT, while lower risk patients will be recommended to have OMT only. We expect that this recommended treatment will be beneficial for the patient's clinical outcomes, but the final decision is made by the attending medical doctor and the patient by shared decision-making. Randomisation will be stratified by centre.

The IMPROVE decision rule is designed to guide treatment decisions for all patients with symptomatic 30-99% ipsilateral carotid stenosis. Although it would be statistically more efficient to include only those patients for whom the IMPROVE decision rule changes the treatment advice compared to current clinical guidelines, this approach would not allow a valid assessment of the full clinical implementation of the IMPROVE decision rule. The IMPROVE decision rule is intended for the entire population of patients with symptomatic carotid stenosis who are currently considered for revascularisation, since it integrates both clinical predictors and an imaging-based predictor for risk assessment into one decision pathway. Restricting inclusion to a preselected subgroup would prevent generalisable conclusions about the overall effectiveness, feasibility, and cost-effectiveness of the IMPROVE approach in daily clinical practice and would therefore not justify a potential change in clinical guidelines. Including all eligible patients thus ensures that the trial evaluates the real-world performance of the IMPROVE decision rule across the full target population and provides evidence suitable for future clinical implementation.

Clinical events including TIA, stroke, perioperative complications, myocardial infarction, and carotid revascularisation procedures (carotid endarterectomy or stenting) will be measured by means of patients records and verified/completed by telephonic/online follow-up with patients at set intervals (44 days, 1, 2, 3 and up to 5 years) (Figure 1). The EQ-5D-5L, IMTA Productivity Cost Questionnaire (iPCQ) and Medical Consumption Questionnaire (iMCQ) will measure Quality of Live, productivity and healthcare resource use 44 days, 1, 2, 3 and up to 5 years after inclusion.

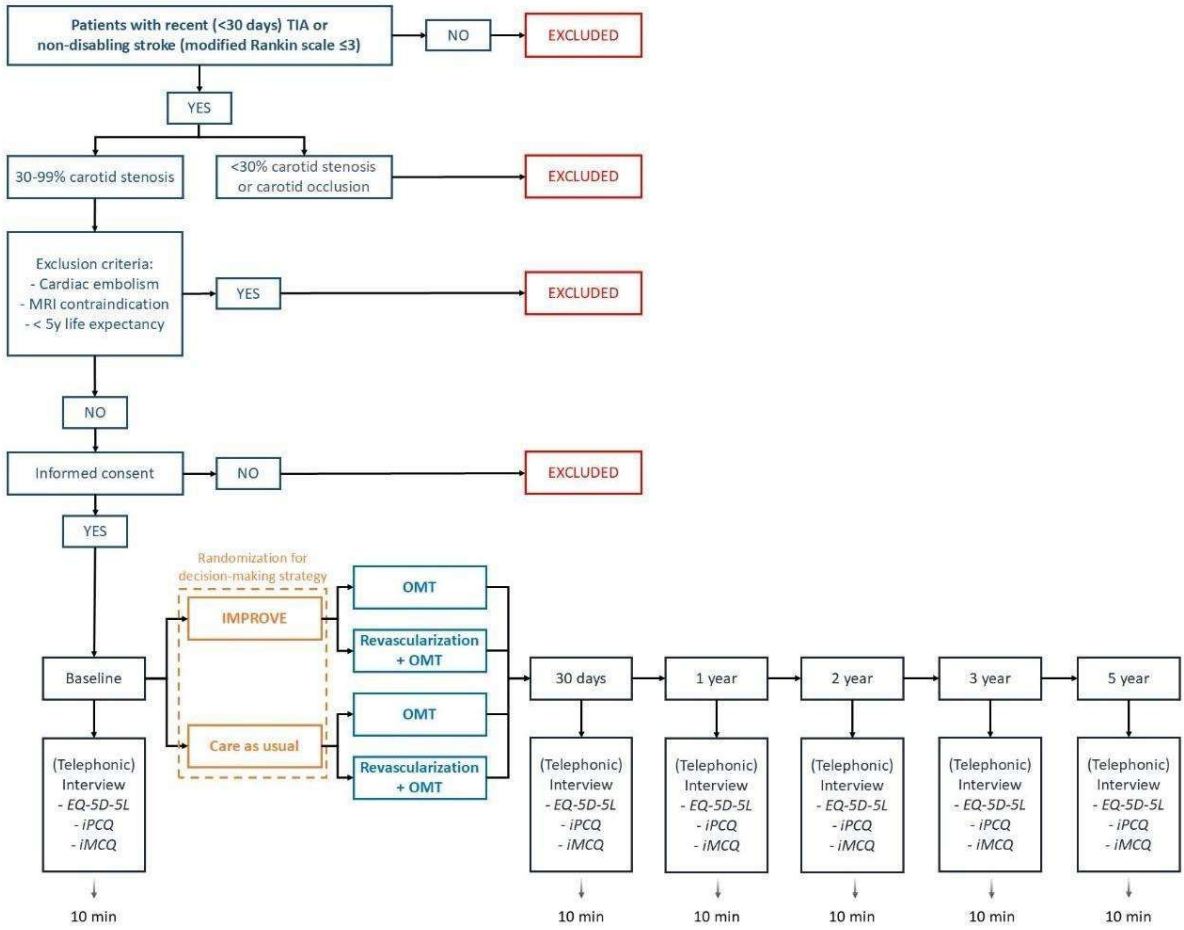

Figure 1. Flowchart of patient inclusion and follow-up during the IMPROVE study.
Patients with recent TIA or non-disabling ischemic stroke and ipsilateral 30-99% carotid stenosis will be included in the study after informed consent. Patients will be randomized for revascularization decision-making strategy (IMPROVE or care as usual (CAU). In the IMPROVE intervention patients with an IMPROVE risk for recurrent stroke ≥10% will be selected for revascularisation and OMT. Patients with a lower risk will be selected for OMT only. In the CAU arm, patients with ipsilateral 30-49% carotid stenosis will be selected for OMT only. In patients with ipsilateral 50-99% carotid stenosis, revascularisation is typically performed. Patients will be clinically followed for a minimum of 3 years and up to 5 years.

Clinical events including TIA, stroke, perioperative complications, myocardial infarction, and carotid revascularization procedures (carotid endarterectomy (CEA), Carotid Artery Stenting (CAS)) will be measured by means of patients records and verified/completed by telephonic/online follow-up with patients at set intervals (44 days, 1, 2, 3 and up to 5 years). The EQ-5D-5L, IMTA Productivity Cost Questionnaire (iPCQ) and Medical Consumption Questionnaire (iMCQ) will measure Quality of Live, productivity and healthcare resource use at baseline, 44days, 1, 2, 3 and up to 5 years after inclusion.

Filling in the questionnaires will take approximately 10 minutes per time point.

4. STUDY POPULATION

4.1 Population (base)

Six hundred thirteen patients will be included from Maastricht UMC+, UMC Utrecht, Erasmus MC, Amsterdam UMC, Haaglanden MC, Albert Schweitzer Ziekenhuis, Zuyderland Ziekenhuis, Isala, Rijnstate and Radboud UMC. Neurologists, vascular surgeons and radiologists in all participating hospitals are willing to participate in this study. Inclusion will be done by the attending neurologist, a research nurse or a PhD candidate on site.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Mentally competent
- 18 years or older
- Recent (<30 days) stroke (modified Rankin scale ≤3) or TIA
- Ipsilateral 30-99% atheromatous stenosis at the carotid bifurcation assessed using non-invasive imaging according to NASCET criteria
- Life expectancy >5 years
- Patient and stenosis are suitable for carotid revascularisation
- Patient is agreeable to randomisation and willing to accept either IMPROVE-based or CAU-based selection method for carotid revascularisation

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Cardiac source of embolism
- Carotid stenosis caused by non-atherosclerotic disease e.g. dissection, fibromuscular disease or neck radiotherapy.
- MRI contra-indications
- Pregnancy

4.4 Sample size calculation

Based on our decision-analytic study, we estimate an incidence of the composite primary outcome of 2.8% in the intervention group versus 4.3% in the CAU group

[Nies, 2025b]. To be able to demonstrate non-inferiority (one-sided alpha of 5%, 80% power, and non-inferiority margin 2.5%), 530 patients are required. These assumptions are consistent with those employed in a prior large cardiovascular intervention trial with a similar design and outcome

incidence [von Birgelen, 2018]. Allowing for 7% non-compliance and 7% dropout, we will recruit 613 patients. This margin was chosen based on the previous ECST trial, where non- compliance and drop-out were 6% and 2%, respectively [European Carotid Surgery Trialists' Collaborative Group, 1998]. A slightly higher estimate of 7% was applied to ensure adequate power without inflating the sample size unnecessarily. Although we do expect fewer strokes in the intervention group, non-inferiority is sufficient to demonstrate cost-effectiveness due to anticipated cost reductions.

Feasibility of recruitment

Recruitment feasibility has been extensively evaluated through structured interviews with neurologists, vascular surgeons, and radiologists from the ten participating centres (five university and five non-university hospitals). All centres confirmed commitment and logistical feasibility, including MRI capacity for the additional scans [Bierens, 2025].

Together, these ten Dutch centres treat approximately 1,100 eligible patients with symptomatic carotid stenosis per year. Based on previous stroke trials, a 70% participation rate is realistic, whereas only ~23% participation is needed to reach the target of 613 participants within 2 years and 5 months. This makes completion within 2 years and 5 months feasible.

The expected contribution per centre is: Maastricht UMC (n=37), Amsterdam UMC (n=54), UMC Utrecht (n=72), Erasmus MC (n=72), Haaglanden MC (n=55), Albert Schweitzer (n=54), Zuyderland (n=68), Isala (n=106), Rijnstate (n=41), and Radboud UMC (n=54).

To ensure flexibility, a fixed inclusion fee per patient allows for expansion of the number of centres, if necessary. Several additional hospitals have already expressed interest in participating. Recruitment progress will be monitored, and corrective measures (e.g. temporary inclusion extension in certain centres or addition of sites) will be implemented, if needed.

Given the fixed project budget and predefined funding per participant, increasing total recruitment beyond 613 patients would not be feasible. Methodologically, a larger sample size could be desirable to allow a narrower non-inferiority margin and more precise effect estimates. However, the current sample size and current non-inferiority

margin represent the maximum achievable sample size within available resources and feasibility while maintaining adequate statistical power for non-inferiority testing and safeguarding clinical relevance.

5. TREATMENT OF SUBJECTS

< This chapter is only applicable for intervention studies>

5.1 Investigational product/treatment

The IMPROVE risk score will be provided as additional information for clinical decision-making on patient stratification for carotid revascularisation plus OMT versus OMT-only. A

revascularization procedure in combination with OMT will be advised for patients at high ipsilateral stroke risk (≥10% within 3 years) according to the IMPROVE score, while OMT-only is advised to patients with lower risk scores. Clinicians can decide whether to perform CEA or CAS when carotid revascularization is indicated. The ESVS guidelines recommend CEA as the primary intervention. CAS can be considered when a patient is younger than 70 years old or in cases of extreme comorbidity [Naylor, 2023].

5.2 Use of co-intervention (if applicable)

All participants in the intervention and control arm will receive OMT in line with current European and Dutch guidelines and clinical practice:

Antithrombotic Therapy: Antiplatelet therapy will be used unless anticoagulation is indicated (e.g. for atrial fibrillation), in which case appropriate anticoagulant therapy will be given. According to the Dutch guidelines (NVN), clopidogrel is recommended as first-line antiplatelet therapy. Alternatively, aspirin combined with dipyridamole or aspirin monotherapy may be used. Short-term dual antiplatelet therapy (aspirin plus clopidogrel) can be considered for up to 3 weeks in patients with a minor stroke or TIA. In case of CAS, dual antiplatelet therapy (aspirin plus clopidogrel) is prescribed for 3 months. Oral anticoagulation (DOAC preferred; VKA as second-line) will be administered, if indicated.

Lipid Management: Statin-based therapy will be initiated to achieve LDL <1.8 mmol/L. Treatment may be intensified to high-intensity statins (atorvastatin or rosuvastatin) and/or ezetimibe if targets are not met. Non- HDL cholesterol and total cholesterol (<4.0 mmol/L) will also be monitored. A low-cholesterol diet will be advised.

Blood Pressure Control: Antihypertensive therapy will be initiated or intensified once

the patient is neurologically stable and oral administration is possible. The target blood pressure is <140/90 mmHg in clinic and <135/85 mmHg for home measurements. Preferred combinations include a thiazide diuretic with an ACE inhibitor or ARB. Calcium channel blocker–based combinations are acceptable alternatives. Higher targets may be considered in elderly or intolerant patients.

Lifestyle Modification: Structured support will be provided for smoking cessation, weight management, and glycaemic control, if relevant.

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Not applicable

6.2 Summary of findings from non-clinical studies

Not applicable

6.3 Summary of findings from clinical studies

Not applicable

6.4 Summary of known and potential risks and benefits

Not applicable

6.5 Description and justification of route of administration and dosage

Not applicable

6.6 Dosages, dosage modifications and method of administration

Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

Not applicable

7.2 Summary of findings from non-clinical studies

Not applicable

7.3 Summary of findings from clinical studies

Not applicable

7.4 Summary of known and potential risks and benefits

Not applicable

7.5 Description and justification of route of administration and dosage

Not applicable

7.6 Dosages, dosage modifications and method of administration

Not applicable

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable

7.8 Drug accountability

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary outcome of the study is the composite of any stroke or death within 44 days after randomisation or ipsilateral ischemic stroke at any time during subsequent follow-up.

8.1.2 Secondary study parameters/endpoints (if applicable)

Secondary outcomes are:

- Incidence of other cardiovascular ischemic symptoms (any stroke, myocardial infarction, TIA)
- Quality of life questionnaire (EQ-5D-5L) questionnaire
- Functional outcome (mRS) at 44 days and 3 years after randomisation, assessed by telephone by a blinded researcher or research nurse

- Costs (iPCQ, iMCQ) questionnaires
- Incremental cost-effectiveness ratio (ICER; see economic analysis)
- Number of hospitalizations and carotid revascularisation procedures (CEA, CAS).

8.1.3 Other study parameters (if applicable)

- Clinical variables (age, sex, hypertension, current smoking, diabetes, hypercholesterolemia, BMI, ethnicity, family history of ischemic CVD, symptoms)
- Medication use (antithrombotics, antihypertensives, statins)
- Atherosclerotic plaque features on MRI or, if available, on CTA, or ultrasound
- Process variables

8.2 Randomisation, blinding and treatment allocation

We will carry out a randomized controlled trial with 10 centres. Patients will be randomized, stratified by centre, and allocated into the intervention group or control group directly after inclusion. Randomization will be concealed. Patients and clinicians cannot be blinded because approximately ~53% of the intervention group has to undergo an additional MRI scan while the control group does not and because patients and clinicians in the intervention arm receive advice for either revascularisation in combination with OMT or OMT-only based on the IMPROVE stroke risk.

8.3 Study procedures

The intervention consists of the use of the MRI-based IMPROVE risk score to select patients for carotid revascularization. Patients are screened, as part of usual care, with ultrasound and/or CTA for the presence of carotid stenosis. As indicated above, patients with 30-99% ipsilateral NASCET stenosis will be eligible for participation.
Participants in the intervention arm will undergo an additional MRI scan when the presence/absence of IPH can impact their risk categorization. ~53% of these patients need an extra MRI. In ~47% an MRI is unnecessary since, based on the other risk factors, the stroke risk is already high or low and the MRI result does not affect the risk category. All participating centres have confirmed the feasibility of scheduling these

MRIs in a timely manner. The IMPROVE score then stratifies patients based on a composite risk score incorporating plaque vulnerability (defined as the presence of IPH on MRI), degree of stenosis, type of most recent event (ocular vs. cerebral), age, and sex [Nies, 2025a].

Patients whose predicted 3-year risk of ipsilateral ischemic stroke is ≥10% are categorized as high-risk [Nies, 2025b]. This threshold has been shown to yield the greatest reduction in recurrent events (35%) and healthcare costs (€6101 saved per patient) [Nies, 2025b]. For high- risk patients in the intervention arm, carotid revascularization in combination with OMT is recommended. Patients below this threshold are advised to receive OMT alone. All treatment decisions are ultimately made through shared decision-making between the patient and the treating physician, with the IMPROVE score serving as a clinical decision support aid.

Patients in the control arm will receive standard care in accordance with Dutch clinical guidelines. Stenosis severity is assessed via ultrasound and/or CTA. Carotid revascularization is typically considered for patients with ipsilateral ≥ 50% stenosis. Risk stratification scores such as the CAR score may be used for patients with ipsilateral 50–69% stenosis, although these scores provide only an estimated 5-year stroke risk and do not offer treatment recommendations.

Carotid MR imaging for IPH identification

To identify IPH on carotid MRI, patients will undergo an MPRAGE (or equivalent) sequence using a standard neurovascular coil at 1.5 or 3.0 Tesla. The MPRAGE sequence (Magnetization Prepared Rapid Acquisition Gradient Echo) is a T1-weighted 3D gradient echo technique incorporating an inversion pulse, optimized for the detection of IPH within carotid artery plaques. This sequence provides high T1 contrast, whereby methaemoglobin (typically present in IPH) exhibits high signal intensity on MRI images relative to surrounding plaque components. MPRAGE does not require the administration of contrast agents.

In current clinical care, some of the patients with symptomatic carotid stenosis already undergo a brain MRI or carotid MRA. Acquisition of the carotid MPRAGE sequence takes approximately 5 minutes when added to a standard clinical MRI protocol. If this is not the case, the MPRAGE will be acquired during an additional MRI-scan, taking 15-20 minutes. The recommended MPRAGE protocol is provided in Section 15.

Follow-up procedure

Follow-up of study participants will be conducted both locally at the enrolling hospital and centrally by researchers from Maastricht University, primarily via telephone or online contact. Scheduled follow-up assessments will take place at day 44 after randomisation, and at 1, 2, and 3 years, with additional follow-up extending up to 5 years, allowing for long-term evaluation of clinical outcomes.

Clinical events, including transient ischemic attacks (TIA), ischemic or haemorrhagic strokes, perioperative complications, myocardial infarction, and carotid revascularisation procedures (carotid endarterectomy or stenting), will be systematically collected from patients' medical records and verified or supplemented through telephonic or online follow-up at these predefined intervals.

The primary outcome, the composite of any stroke or death within 44 days after randomisation or ipsilateral ischemic stroke during subsequent follow-up, will be adjudicated by an independent, blinded Event Adjudication Committee to ensure unbiased and standardized assessment across study sites.

In the event that contact with a participant is lost, the study team will verify vital status via the hospital's electronic patient record (e.g., discharge or death notifications). When necessary and legally permitted, mortality data will be obtained through national registries, including the Municipal Personal Records Database and the Statistics Netherlands cause-of-death registry. If participants relocate or transfer care to another hospital, relevant medical information will be requested from the new treating physician or hospital to maintain continuous follow-up.

Follow-up will continue for a minimum of 3 years, or until death or loss to follow-up. Most participants are expected to be monitored for more than 3 years (up to 5 years), allowing for comprehensive long-term outcome analysis and ensuring complete assessment of both clinical effectiveness and safety of the IMPROVE decision rule.

Measurement of primary outcome

Incidence of any stroke and death within 44 days of randomisation or ipsilateral ischemic stroke during subsequent follow-up will be measured by the means of hospital records and verified/completed during regular follow-up measurements with the patients (44 days, 1, 2, 3 years and up to 5 years).

Measurement of secondary outcomes

Quality of life will be measured by means of the EQ-5D-5L [Herdmann 2011]. The EQ-

5D-5L measures health-related quality of life on five dimensions of health: mobility, self- care, usual activities, pain/discomfort, and anxiety/depression. Its outcome will be valued using the Dutch tariff [Versteegh 2016]. The IMTA Productivity Cost Questionnaire (iPCQ) and the Medical Consumption Questionnaire (iMCQ) will be used to measure productivity and resource use, respectively.

The time span for which the iMCQ is validated is three months because patients will remember earlier healthcare consumption less precise. To cover full yearly periods, the costs for the time period of three months will be interpolated between measurements.

The questionnaires will be administered online, on paper, or through video call or telephone contact with the patient or their family, depending on the preference and abilities of the patient. Timing of the measurement is at baseline, 44 days after inclusion and randomisation, and at 1, 2, and 3 up to 5 years after inclusion. The questionnaires will take approximately 10 minutes per time point.

In order not to miss any major health events, related or unrelated to ipsilateral carotid stenosis, a phone call will be made with each patient (or their relatives) at each measurement moment, irrespective of their individual choice concerning the means of data provision. In case a major health event is reported, medical files will be checked and the patient's neurologist and, if needed, general practitioner will be contacted for full details. Major health events include TIA, stroke, and other cardiovascular events.

If a participant becomes unable to complete questionnaires or interviews (e.g., due to stroke- related disability), follow-up will continue through a close caregiver or healthcare provider, who may complete the assessments on behalf of the participant. This approach ensures follow-up of all participants, including those with severe disability, which is essential for unbiased outcome evaluation.

Measurement of process variables

Process variables will be measured for the purpose of facilitating further implementation. These process variables are measured in the intervention group and include: emergency revascularisation before decision rule could be utilised (+ reasons); no MRI or other input data available (+ specification and reasons); elective revascularisation in low-risk patient (+ reasons); risk-based recommendation otherwise not followed by clinicians (+ reasons); not able to apply decision rule (+ specification). The Data Safety Monitoring Board (DSMB) will review predefined process and cost-related indicators during the interim analysis to evaluate study feasibility and interpretability. The DSMB will monitor (i) adherence to the IMPROVE-

based recommendations (revascularisation vs. optimized medical management-only) for each stenosis subgroup (30–49%, 50–69%, ≥70%) and (ii) the associated cost implications (per stenosis subgroup).
These variables will be documented during routine use of the IMPROVE decision rule. For cases where the rule was not used, healthcare providers will be contacted four weeks post- inclusion to report reasons for non-utilization.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

A drop-out rate of 10% has been taken into account.

8.6 Follow-up of subjects withdrawn from treatment

All randomized patients will remain in follow-up, regardless of whether the intervention was performed according to protocol. This means that patients who do not complete the intervention will still be followed up for all primary and secondary outcomes.

In cases of patients that are lost to follow-up, all reasonable efforts will be made to collect the required outcome data. This includes consulting medical records, and, if necessary, querying national registries for vital status. The aim is to minimise missing data and ensure the integrity of the dataset.

In case a patient withdraws from the study, all data up to that point will still be used for analysis, although incomplete.

8.7 Premature termination of the study

The study may be terminated prematurely in accordance with the provisions outlined in Article 11 of the Clinical Trial Agreement (CTA) between the Sponsor (Maastricht University) and the participating study sites.

Specifically, premature termination may occur if:

- ethical approval is not granted or irrevocably revoked;
- continuation of the study is deemed to pose risks to participants' health or is no

longer scientifically justified;

- one of the parties fails to comply with contractual obligations or becomes insolvent;
- circumstances beyond the control of the parties render continuation unreasonable;
- or if the Principal Investigator can no longer fulfil their role and no suitable replacement can be found.

The Sponsor may also terminate the study or participation of a site in case of insufficient recruitment or other justified reasons, provided this does not affect the overall execution of the study.

In case of premature termination, the Sponsor will promptly inform the METC and relevant authorities, and appropriate measures will be taken to ensure participant safety and data integrity.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance with section 10, subsection 4 of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any cardiovascular undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.
The investigator will report all SAEs that result in death or are life threatening to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal Onderzoeksportaal to the review committee that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum 8 days to complete the initial preliminary report.

All other (non-fatal or not life threatening) SAEs will be assessed for their potential relationship to the study procedures by the local principal investigator in consultation with the sponsor. A study-related SAE is defined as a SAE for which a causal relationship with study procedures (e.g. related to the carotid MRI or clinical management of carotid stenosis) cannot be excluded based on clinical judgement. These study-related SAEs will also be reported within 15 days of first knowledge. Non-study-related non-fatal or not life threatening SAEs will not be reported individually but will be submitted to the METC in a yearly line-listing.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported until the end of study within the Netherlands, as defined in the protocol.

9.4 Data Safety Monitoring Board (DSMB) / Safety Committee

The trial will be monitored by a DSMB, that will include a vascular neurologist, vascular surgeon and an independent methodologist/statistician. The role of the DSMB is to monitor the safety of the trial and to provide the steering committee with recommendations on the continuation or termination of the trial. The objectives of the DSMB are:

- To monitor the safety data of the included patients
- To analyse efficacy data in both arms of the trial
- To evaluate the overall conduct of the trial, protocol violations, compliance to previous DSMB recommendations, recruitment rates, losses to follow up, and trial monitoring

The DSMB will meet once before the first inclusion and thereafter twice a year during the patient recruitment phase. An efficacy interim analysis will be performed after 306 included patients have reached their one-year follow-up. For the efficacy interim analysis, the DSMB will analyse the incidence of the primary outcome (composite of any stroke or death within 44 days after randomisation or ipsilateral ischemic stroke at any time during subsequent follow- up) in both arms. The Haybittle-Peto boundary rule for premature termination of the trial will be applied.

For the safety interim analyses, the DSMB will evaluate the incidence of primary endpoints (composite of any stroke or death within 44 days after randomisation or ipsilateral ischemic stroke at any time during subsequent follow-up) and secondary endpoints. In the light of these analyses, the DSMB will advise the principal investigator if, in their view, the randomized comparisons in the trial have provided

both (i) "proof beyond reasonable doubt" that for all, or for some specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, and (ii) evidence that might reasonably be expected to influence materially patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a safety endpoint may be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the trial committee decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

Between-group differences in baseline characteristics will be described by differences in percentages or means but will not be statistically tested.

Missing values will be imputed by means of multiple imputation with conditional specification. M will be set to the percentage of incomplete records, and imputations for continuous variables will be drawn using predictive mean matching.

Randomisation is stratified by participating centre (see section 8.2). To account for potential systematic differences between centres and maintain consistency with the randomisation approach, the primary analysis model will include centre as a fixed-effect covariate. Specifically, indicator variables for each centre will be incorporated in the Cox proportional hazards model to adjust the treatment effect estimates for centre-related differences in case- mix and practice patterns.

Non-inferiority will be evaluated by means of comparing the least favourable limit of the 95%- confidence interval around the attributable risk with the non-inferiority margin (2.5%), after three years of follow-up. A non-inferiority design is justified because the IMPROVE decision rule is expected to maintain at least equal effectiveness (combined primary endpoint any stroke or death within 44 days after randomization or ipsilateral stroke during subsequent follow-up) while substantially reducing revascularizations and healthcare costs. Our decision-analytic study predicted ≈20% fewer

revascularizations and ≈35% fewer ipsilateral strokes and perioperative strokes and deaths, resulting in overall cost savings despite the additional MRI scans. A superiority or stepped-wedge design would require >2,000 participants and exceeds both the feasible timeframe and available budget. With a non-inferiority design, the study remains adequately powered (80% power, one-sided α=0.05) with 613 patients, enabling efficient evaluation within realistic limits.

The absolute non-inferiority margin of 2.5% corresponds to a relative increase of ~58% given an expected 4.3% event rate in the care-as-usual group. This margin reflects the maximum clinically acceptable difference, as applied in comparable large cardiovascular trials with similar event rates and risk-benefit profiles (e.g., Von Birgelen et al., 2018). Lowering the margin would substantially increase the required sample size beyond the logistical and financial feasibility of this multicentre trial. Moreover, the intervention is expected to reduce the primary clinical outcomes rather than increase them (composite of any stroke or death within 44 days after randomisation or ipsilateral ischemic stroke at any time during subsequent follow up: 2.8% (IMPROVE) vs. 4.3% (care-as-usual)) in our decision-analytic study), making the 2.5% threshold a boundary that safeguards both clinical relevance and feasibility. Survival (i.e. not having experienced the outcome event) will be analysed by means of Kaplan- Meier analysis and the 95%-CI around the attributable risk at 3 years (and other follow-up times) will be estimated by use of Greenwood's formula. The start of follow-up for all time-to-event analyses will be the date of randomisation, ensuring identical time origins between study arms. All outcome events occurring after randomisation, including any strokes and deaths within 44 days of randomisation and ipsilateral strokes during subsequent follow-up, will be included in the survival analyses. In case of any meaningful baseline difference in a prognostically important parameter, adjustment will be done for that parameter by means of Cox proportional hazards modelling. Next to non-inferiority, superiority will be evaluated.

Primary analyses will be done according to intention to treat. In case of a meaningful number of protocol violations, a per-protocol analysis will be carried out for valid inference regarding non-inferiority. The intention-to-treat (ITT) analysis set includes all randomised participants, analysed according to their assigned study arm, regardless of adherence to the intervention protocol. This set will serve as the primary analysis population for evaluating non-inferiority. We expect that the loss-to-follow-up for the primary outcome parameter will be close to zero by means of collecting mortality data through national registries, including the Municipal Personal Records Database and

the Statistics Netherlands cause-of-death registry in case that contact with a participant is lost. To address potential loss to follow-up for primary outcome events, multiple imputation with conditional specification will be applied, using relevant covariates, under the assumption that data are missing at random. In addition, sensitivity analyses, including best-case and worst-case scenarios, will be performed to assess the robustness of the primary outcome results under different assumptions about missing data.

The per-protocol (PP) analysis set will consist of participants who fully adhered to the allocated study procedure and did not have major protocol deviations (e.g., unplanned crossovers or missing follow-up). PP analyses will be performed as a sensitivity check, since they provide supportive evidence in non-inferiority designs.

Patients may choose not to participate because of the required time and effort involved in providing data. This mechanism is not expected to cause bias, although it may lead to differences between the study population and the target population, which have to be addressed in the inferential phase. Patients may also not consent to undergoing the MRI needed for risk prediction. Our experience, however, is that the preparedness of patients to undergo MRI in trials is high. Some patients may not participate because of (back) ache, which can be uncomfortable in the MRI scanner, but non-participation for this reason is not likely to cause bias.

10.2 Secondary study parameter(s)

Secondary clinical outcomes

Secondary outcome measures (any stroke, myocardial infarction, TIA, functional outcome, QoL, number of revascularisations, number of hospitalisations) will be analysed using effect analyses similar to those applied to the primary outcome. Depending on the type of data, appropriate

regression models will be applied: Cox proportional hazards models for time-to-event outcomes, logistic regression for dichotomous outcomes, and linear or ordinal regression for continuous or ordinal outcomes. All analyses will be adjusted, where necessary, for relevant baseline covariates, including age, sex, degree of stenosis and study centre. The focus will be on estimating effect sizes and 95% confidence intervals, enabling interpretation of results in their clinical context.

Cost and cost-effectiveness assessment

Costs include all health care and patient and family costs and cost in other sectors (e.g.

productivity loss) and will be measured using the CRFs and the iMCQ. Impactful resource consumption such as treatment (revascularisation), admission to a hospital, nursing home rehabilitation clinic will be based on the CRFs. Productivity losses are measured using the iPCQ and valued based on friction costs. Cost calculation and prices will be based on the Dutch Guideline for Cost Analysis (‘Kostenhandleiding’). If cost prices are not available, we will use tariffs or market prices. We will interpolate the data obtained with the questionnaires and explore the impact of different interpolation methods in scenario analyses. We will use the price level of the year of reporting and adjust prices, if necessary.

QALYs of the intervention and control group will be calculated based on the EQ-5D-5L responses, and the Dutch tariff and survival as observed in the study. For QALYs, resource use and cost data we will follow the same analysis plan as for the primary outcome, taking into account the possibly skewed nature of this data. Missing data will be completed by multiple imputation with fully conditional specification.

We will perform a cost-utility analysis from a societal perspective for a time horizon of 3 years based on the study data, and with a lifetime horizon based on modelling, additionally informed by literature. We will discount costs with 4% and effects with 1.5%, in line with the Dutch guideline. Bootstrapping will be used to estimate the confidence interval of the ICER for the short-term economic evaluation and to construct a cost-effectiveness plane and acceptability curve. Uncertainty analyses will be presented in Tornado diagrams. Scenario analyses will be used to explore other uncertainties, for instance regarding the perspective of the analysis (societal, health care, patient and family) in a series of what-if analyses. We will use the BIA tool to perform a budget impact analysis from a societal, health care and payer perspective, and in line with health economic Dutch guidelines. Scenarios for budget impact will be based on interviews with stakeholders. We will analyse which parties will reap benefits/savings and which will incur additional costs. We will also specifically analyse impact on the workforce for different sectors, (types of) health care organisations and professionals. This information will be fed into the implementation plan.

In sum, to support the economic evaluation, participants will complete the EQ-5D-5L, iPCQ and iMCQ questionnaires. Each of these surveys serves a specific and essential role in estimating costs and QALYs. The EQ-5D-5L (5 items) is used to calculate health-related quality of life and QALYs. The iPCQ and iMCQ, measure productivity losses and medical consumption, respectively. Importantly, these questionnaires are designed using a branching structure: participants only receive additional questions if they report

relevant healthcare use or productivity loss. As a result, the total number of items completed per participant is limited, thereby minimizing respondent burden while maintaining sufficient data quality for cost- effectiveness and budget impact analysis.

In some cases, participants may have neurological deficits that make it difficult to complete the questionnaires independently. In these instances, a close relative may assist or complete the questionnaires as a proxy respondent. To address potential bias introduced by proxy responses, the identity of the respondent (patient vs. proxy) will be recorded for each questionnaire. Sensitivity analyses will be performed to evaluate the potential impact of proxy data by comparing analyses with and without these responses. For the EQ-5D-5L, the proxy estimates the patient's perceived health status. For the iPCQ and iMCQ, the risk of bias is expected to be minimal, as these primarily concern factual data such as work absence and healthcare utilization.

Subgroup analysis

Subgroup analyses and equity analyses will assess cost-effectiveness and fairness of the intervention across socioeconomic groups, ethnic backgrounds, sex, and comorbidities [Wilson, 2019]. In addition, exploratory subgroup analyses (regarding primary endpoints and cost- effectiveness) will compare patients with the largest expected differences between IMPROVE and CAU. Specifically, these include (1) patients who would not undergo revascularization under CAU but would under IMPROVE, and (2) patients who would undergo revascularization under CAU but not under IMPROVE.

10.3 Other study parameters

Not applicable

10.4 Interim analysis (if applicable)

See 9.4

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (75th WMA General Assembly, Helsinki, Finland, October 2024) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

Eligible patients will be approached by their treating physician (neurologist, nurse specialist, or resident physician) during hospital admission or TIA outpatient evaluation. The treating physician will briefly and verbally inform the patient about the study and, if the patient expresses interest, notify the local study investigator or research nurse. The study investigator or research nurse will then contact the patient and provide a detailed oral (possibly by telephone) and written explanation of the study objectives, procedures, potential risks and benefits, and answer any initial questions.

Participants will be clearly informed that the study involves the use of the IMPROVE clinical decision rule, which aims to enhance clinical decision-making regarding carotid revascularization. The IMPROVE risk score estimates the individual risk of recurrent ischemic stroke with greater precision than current methods. While the IMPROVE decision rule has the potential to enhance the quality of treatment recommendations, its predictions are probabilistic in nature and should not be considered definitive. Patients will be explicitly reassured that participation in the study will not compromise the quality of their medical care in any way.

Patients will be asked to provide written informed consent after a minimum of 24 hours has passed since the first explanation, allowing time to consider participation and to discuss the study with family or advisors. The local study investigator from the participating hospital will then meet the patient in the hospital to complete the informed consent procedure. During this meeting with the local researcher, the patient can ask any additional questions and can sign the ICF in the presence of the local investigator at the hospital.

Given the time-critical nature of stroke treatment, it is essential to initiate clinical decision- making promptly after diagnosis. According to Dutch guidelines (Naar passende oncologische- en vaatchirurgische zorg 25-03-2025) established by Zorginstituut Nederland and the Dutch Audit for Carotid Interventions (DACI), at least 80% of symptomatic patients should undergo revascularization within two weeks after their first clinical symptoms. However, typically revascularization is performed within one week to prevent recurrent stroke while the patient is waiting to undergo revascularization. Therefore, eligible patients will be given a 24-hour window to consider participation in the IMPROVE study, ensuring both informed decision-making and timely clinical decision-making and care. A longer reflection period (the standard seven days) is not feasible in this clinical context, as treatment decisions for carotid revascularization must be made within an extremely short timeframe after symptom

onset to avoid delaying potentially beneficial carotid revascularisation. Moreover, if the patient is randomized to the IMPROVE arm, an additional MRI scan may need to be scheduled within this short time window and, subsequently, the patient needs to be discussed in an interdisciplinary meeting (MDO). Therefore, a more than 24-hour reflection period would be clinically and logistically impossible, as it would preclude timely MRI (if required), MDO discussion, and adequate acute care.

The 24-hour period is considered sufficient for patients and their families to discuss participation, as they receive both verbal and written information from a trained investigator and can ask follow-up questions before providing consent. Voluntary participation is safeguarded by the clear oral explanation of the study provided on the first day, the written Participant Information Form, and the opportunity to ask questions at the hospital before signing the informed consent. Therefore, this timeframe reflects a careful balance between respecting patients' autonomy and maintaining clinical safety and feasibility in the acute stroke and TIA setting.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

11.4 Benefits and risks assessment, group relatedness

With the IMPROVE risk score, it is possible to determine the risk of having a stroke much better than before, and therefore we expect that better advice can be given on whether or not the patient should undergo carotid revascularization. This is expected to lower the risk for a recurrent ipsilateral ischemic stroke. Participation will help improve the care of patients with carotid artery disease, which will benefit future patients.

Patients in the intervention group will receive an extra MRI when the result of the MRI scan can affect their risk category. Our intervention will result in an extra MRI scan in ~53% of patients in the intervention group [Nies, 2025b]. In ~47% an MRI is unnecessary since, based on the other risk factors, the stroke risk is already high or low and the MRI result does not affect the risk category. In current clinical care, some of the patients with symptomatic carotid stenosis already undergo a brain MRI. When an MRI is part of clinical practice, a carotid MRI can be added to the brain scan since it can be performed with a standard neurovascular MRI coil, without the use of a contrast medium and only requires an additional 5-minute MRI sequence. If this is not the case, an additional MRI-scan has to be conducted. All centres confirm the feasibility of an additional timely MRI.

Current clinical guidelines recommend carotid revascularisation for all patients with ipsilateral ≥70% carotid stenosis, suggest consideration of revascularization for those with ipsilateral 50– 69% stenosis, and advise against it for patients with ipsilateral 30–49% stenosis [Naylor, 2023]. However, this stenosis-based approach can lead to both under-treatment and over-treatment: some high-risk patients are denied revascularization despite potential benefit, while others undergo unnecessary procedures despite being adequately managed with medication alone.

Our aim is to improve patient selection by stratifying individuals into low- and high-risk categories for recurrent stroke, thereby enabling truly high-risk patients to receive the benefits of revascularization while sparing low-risk individuals from unnecessary surgical intervention and its associated risks. Using a decision-analytic model, we found that 28% of patients could be more accurately classified with the IMPROVE strategy: 18% of patients with 30–49% stenosis (currently not considered for intervention) were identified as high risk and would likely benefit from revascularization. Conversely, revascularization could be safely avoided in 53% of patients with 50–69% stenosis and 16% with 70–99% stenosis, who are typically revascularized in current practice [Nies, 2025b]. As such IMPROVE will deliver an individualised selection method offering the optimal therapy on a personalised level. Given the limited additional burden (an extra ~5- minute MRI in ≈53% of intervention patients), expected clinical and economic benefits outweigh the modest and manageable risks.

Carotid plaque imaging using MRI is a safe and extensively validated technique for assessing atherosclerotic plaque vulnerability [Schindler 2020; van Dam-Nolen 2022]. Our recent meta- analysis demonstrated that IPH on MRI is a powerful, independent predictor of ipsilateral ischemic stroke (hazard ratio: 11.0), a stronger predictor than any clinical risk factor, including the degree of stenosis (hazard ratio: 3.3) [Schindler 2020]. Currently, three clinical models aim to predict long-term (>90 days) stroke risk in patients with symptomatic carotid stenosis: the ECST (European Carotid Surgery Trial) medical model and its derivative, the CAR score, the SCAIL score (Symptomatic Carotid Atheroma Inflammation Lumen Stenosis) and the CaroTID-VasC score [Rothwell 2005; Kelly 2020; Kumar 2023]. However, critical appraisal has revealed significant methodological limitations in these models [Nies 2021].

To date, no other model provides a robust and reliable prediction of stroke risk tailored to today’s patient population. The IMPROVE prediction model is, to our knowledge, the first risk model that reflects contemporary stroke risk and is developed from a sufficiently large and relevant patient cohort. To our knowledge, the IMPROVE prediction model is

the most complete and robust model currently available. It has a higher number of events per variable, is fully based on contemporary cohorts, and incorporates MRI-based plaque vulnerability alongside key clinical variables, thereby enhancing individual stroke risk prediction. In our decision-analytic impact study, implementation of the IMPROVE tool is projected to reduce ischemic strokes by 35% over three years, with an associated annual reduction in Dutch societal healthcare costs of €18 million [Nies 2025b].

We performed a systematic literature search to investigate whether there are any studies (performed in the past, or underway) that resemble the IMPROVE trial. Therefore, we systematically searched for randomised controlled or stepped-wedge trials, before-after comparisons, cost-effectiveness studies and impact studies on MRI-based risk assessment and risk-based treatment selection in recent TIA or minor stroke patients with ipsilateral carotid artery stenosis. We identified 2 articles with moderate relevance for our review research question: Gupta et al [Gupta 2015] and Timmerman et al. [Timmerman 2020]. From a Clinical Trials.gov yield, one study was identified with moderate relevance. The study by Gupta et al [Gupta 2015] is a cost-effectiveness model-based analysis in a simulated patient population comparing two strategies: acquiring an MRI examination of the carotid plaque and performing carotid endarterectomy when intraplaque haemorrhage (IPH) is identified, versus intensive medical therapy. The medical therapy-based strategy had a lower life expectancy (12.65 years vs 12.95 years), lower lifetime QALYs (9.96 years vs 10.05 years), and lower lifetime costs ($13 699 vs $15 297) when compared with the MR imaging IPH-based strategy. These results are in the expected direction. There are, however, three important differences of this study with the IMPROVE trial: first, the analysis was carried out for asymptomatic patients, who have a lower mean baseline stroke risk; second, the study is fully decision model based (non-empirical); and third, the care strategies were based on IPH only (not a prediction model incorporating multiple clinical risk factors like the IMPROVE decision rule).

The article by Timmerman et al [Timmerman 2020] is a protocol paper for a study aimed at developing a risk stratification model for cerebrovascular complications in patients with asymptomatic carotid artery stenosis (ACAS). The risk stratification model will comprise clinical, circulating, plaque and imaging biomarkers. The observational study will include 300 patients with 50-99% ACAS. The primary endpoint is the three-year incidence of cerebrovascular complications. Again, this study is aimed at asymptomatic patients whereas the IMPROVE trial focuses on symptomatic patients, who have

different characteristics and a higher mean baseline stroke risk. We found no evidence for an empirical impact study similar to ours being planned or carried out. In our search on Clinical Trials.gov, we found a study by the same group looking at outcomes among patients with carotid artery stenosis (both symptomatic and asymptomatic) who have either received surgery or optimal medical therapy on the basis of judgement of treating physicians of local institutes [Clinicaltrials.gov, TAXINOMISIS]. There was no systematic use of a prediction model in this study that started in 2018. There was neither randomization nor a comparison between risk-based care versus usual care. We found no publications of this study in PubMed. In conclusion, there are no studies (performed in the past, or underway) that resemble the IMPROVE trial.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Participants will receive reimbursement for travel and parking expenses incurred due to study participation. No fixed financial compensation will be provided.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All patient data will be confidentially treated in accordance with the General Data Protection Regulation (AVG) and the Dutch Implementation Act of the GDPR (UAVG). In collaboration with the Clinical Trial Centre Maastricht (CTCM), we will develop a CRF-based CASTOR database. The local investigators and the investigators of Maastricht University will collect the data and enter the data in the coded CASTOR database. All data entered in CASTOR will be automatically coded: each participant receives a unique study ID based on the centre and number of inclusion. The key linking this study ID to identifiable patient information will be securely stored locally at each participating centre, and during the duration of the study centrally at Maastricht University, under the responsibility of the local PI and the coordinating investigator and will not leave the local centre and the coordinating centre (Maastricht University). Only three coordinating investigators from Maastricht University have access to this key and

to directly identifiable data. Central storage of the keys at Maastricht University is necessary to facilitate central follow-up by the coordinating investigators. Central follow-up will ensure standardised surveys across all centres throughout the full study duration. Only the participant's name, phone number, email address and home address will be accessible to the coordinating researchers at Maastricht University, solely for the purpose of conducting the central follow-up. All other personal, medical and research data will not be accessible to these researchers.

Authorized monitors and inspectors from the Dutch Health and Youth Care Inspectorate (IGJ) may have access to the directly identifiable data for monitoring, auditing, and regulatory purposes. CTCM monitors will oversee data monitoring and quality control also requiring access to uncoded data.

All study data will be retained for a minimum of 15 years following completion of the IMPROVE trial. This applies both to the data collected for the current study and to data that may be used for future research in the line of the present project. With the explicit consent of the participant, data may also be preserved for future research in the line of this study. Reusable data will be stored in the Maastricht Data Repository with a persistent identifier and rich metadata, following FAIR principles and ZonMw regulations. All data that is acquired during this study may be shared with hospitals that participate in the IMPROVE study for their own additional research and analyses in the line of the present project. In addition, clinical information and follow-up data may be made available to these and other parties for research purposes. However, all data will be anonymized, so that none of the other institutions will receive information that can directly lead to the individual patient. Data transfer beyond the EU will only occur to countries recognized by the European Commission as providing an adequate level of data protection (e.g., the United Kingdom and Switzerland) or to institutions in the United States under EU

Standard Contractual Clauses with additional safeguards such as encryption and pseudonymisation, in accordance with the GDPR, the Dutch Data Protection Authority, and the EDPB guidance. Data stewards from CTCM and DataHub will provide ongoing support for data management.

All data collected in the IMPROVE study will primarily be stored and processed within the EU/EER. Any sharing of data with other institutions or parties outside the EU/EEA will only occur if it is necessary for research in the line of this study, and only after explicit consent from the participant. In such cases, all data will be pseudonymised or anonymised, and appropriate data transfer agreements and safeguards will be in place to comply with AVG/UAVG and international data protection standards.

12.2 Monitoring and Quality Assurance

To assess confirmation to the study protocol, a member of the CTCM (Clinical Trial Center Maastricht) will conduct a data quality monitoring in all centres after signing a Confidentiality Agreement. This monitoring will consist of a review of informed consent forms of all included study subjects. In addition, a more detailed review of the CRF and/or clinical records will be conducted in selected subjects.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report

with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

All results of this study will be offered to peer-reviewed scientific journal(s).

Publication and public disclosure will be conducted in accordance with the conditions set out in Article 10 of the Clinical Trial Agreement (CTA) and the "CCMO-statement Publicatiebeleid".

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

In the intervention group, patient selection for carotid revascularisation will be optimised by incorporating the IMPROVE score into shared decision-making between clinicians and patients.

A decision-analytic model, informed by complication risk estimates from the Dutch Audit of Carotid Interventions, demonstrated that the IMPROVE strategy enables substantially more accurate risk stratification. Specifically, 28% of patients would be reclassified compared to current practice: among patients with 30–49% stenosis, 18% were identified as high-risk candidates who are likely to benefit from revascularisation, despite being excluded from intervention under existing guidelines. Conversely, revascularisation could be avoided in 53% of patients with 50–69% stenosis and 16% with 70–99% stenosis, patient groups that typically undergo an intervention in routine care [Nies, 2025b].

Importantly, our modelling indicates that clinical implementation of the IMPROVE score has the potential to reduce the incidence of ipsilateral stroke and perioperative stroke or death by 35% (2.8% with IMPROVE-guided care vs. 4.3% under current standard care), while simultaneously decreasing the number of revascularisation procedures by 20% [Nies, 2025b]. Even at the lower bound of the 95% confidence interval of the IMPROVE model, probabilistic analyses showed IMPROVE's superiority over standard care [Nies, 2025b].

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

See a.

c. Can the primary or secondary mechanism be induced in animals and/or in ex- vivo human cell material?

no

d. Selectivity of the mechanism to target tissue in animals and/or human beings

n/a

e. Analysis of potential effect
n/a

f. Pharmacokinetic considerations
n/a

g. Study population
We refer to chapter 4.

h. Interaction with other products
n/a

i. Predictability of effect
n/a

j. Can effects be managed?
n/a

13.2 Synthesis

With the IMPROVE risk score, it is possible to determine the risk of recurrent ipsilateral ischemic stroke much better than before, and therefore we expect that better advice can be given on whether or not the patient should undergo carotid revascularization. This is expected to lower the composite risk for a recurrent ipsilateral ischemic stroke during follow-up and perioperative stroke and death in the intervention arm.

14. REFERENCES

Bierens et al. IMPROVE Decision Rule for Carotid Revascularization: Clinician Perspectives on Acceptability and Implementation Barriers. Res Sq. 2025. doi.org/10.21203/rs.3.rs- 5917075/v1

Buisman et al. Cost-effectiveness of novel imaging tests to select patients for carotid endarterectomy. Health Policy and Technology 8.2 (2019): 111-117.

Cheng et al. Contemporary prevalence of carotid stenosis in patients presenting with ischaemic stroke. Br J Surg. 2019;106:872
Gupta et al. Cost-Effectiveness of Carotid Plaque MR Imaging as a Stroke Risk Stratification Tool in Asymptomatic Carotid Artery Stenosis. Radiology 277, 763–772 (2015).

Herdman et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res, 2011;20:1727

Johnson et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study (2016). Lancet Neurol. 2019, 18:439

Kumar et al. Simple CaroTID-VasC score to predict one-year risk of stroke in symptomatic carotid stenosis patients. J Neurol Sci. 2023 (446) 120578

Kelly et al. A Risk Score Including Carotid Plaque Inflammation and Stenosis Severity Improves Identification of Recurrent Stroke. Stroke 2020 (51) 838

Muller et al. Carotid artery stenting versus endarterectomy for treatment of carotid artery stenosis. Cochrane Database Syst Rev. 2020;2(2):CD000515.

Naylor et al. European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease. EJVES. 2023.
5(1), 7-111.

Nederkoorn & de Borst. The Second European Carotid Surgery Trial (ECST-2): Clinical Implications and Future Directions. EJVES. 2025. S1078-5884.

Nies et al. Emerging Role of Carotid MRI for Personalized Ischemic Stroke Risk Prediction in Patients With Carotid Artery Stenosis. Front Neurol. 2021;12:718438
Nies et al. Individualized MRI-Based Stroke Prediction Score Using Plaque Vulnerability for Symptomatic Carotid Artery Disease Patients (IMPROVE). Stroke. 2025a. Epub 8 May 2025.

Nies et al. Model-based cost-effectiveness of the IMPROVE score versus care as usual for risk-based selection of symptomatic patients for carotid revascularization. Res Sq. 2025b.
doi.org/10.21203/rs.3.rs-5876221/v1

Ogndimu et al. Adequate sample size for developing prediction models is not simply related to events per variable. Journal of Clinical Epidemiology. 2016. Volume 76, August 2016, Pages 175-182

Rothwell PM et al. Treating individuals 3: From subgroups to individuals: general principles and the example of carotid endarterectomy. Lancet. 2005;365:256–265.

Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). The Lancet 351, 1379–1387 (1998).

Schindler et al, Prediction of Stroke Risk by Detection of Hemorrhage in Carotid Plaques: Meta-Analysis of Individual Patient Data. JACC CVI. 2020;13:395

Timmerman et al. The TAXINOMISIS Project: A multidisciplinary approach for the development of a new risk stratification model for patients with asymptomatic carotid artery stenosis. Eur. J. Clin. Invest. 50, e13411 (2020).

van Dam-Nolen et al. Carotid Plaque Characteristics Predict Recurrent Ischemic Stroke and TIA: The PARISK (Plaque At RISK) Study. JACC CVI. 2022; 15:1715

von Birgelen et al. Thin composite wire strut, durable polymer-coated (Resolute Onyx) versus ultrathin cobalt–chromium strut, bioresorbable polymer-coated (Orsiro) drug-eluting stents in allcomers with coronary artery disease (BIONYX): an international, single-blind, randomised non-inferiority trial. The Lancet. 2018; 10154:1235

Versteegh et al. Dutch Tariff for the Five-Level Version of EQ-5D. Value in Health, 2016; 19:343.

Wilson et al, Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. Lancet Neurol. 18, 653–665 (2019).

15. RECOMMENDED MRI PROTOCOL

- To image IPH, a 3D or 2D MPRAGE sequence is necessary.
- Carotid or neurovascular coils are required for use with both protocols.
- It is possible to add an approximately 5-minute 3D MPRAGE sequence to routine clinical carotid MRA or neuro MRI protocol.

Table 1. Multisequence 3D or 2D non-contrast protocol for IPH identification.

Name	3D MPRAGE	2D MPRAGE
Plaque feature	Intraplaque hemorrhage	Intraplaque hemorrhage
Sequence names	IR-TFE/SPGR	IR-TFE/IR-FSPGR
Image mode	3D	3D
Scan plane	Coronal	Axial
TR (ms)	15	13
TE (ms)	Minimum	Minimum
FOV (cm)	16 × 16	16 × 16
Resolution (mm^2)	0.6 × 0.6 (carotid coil) 0.8 × 0.8 (neurovascular coil)	0.63 × 0.63
Slice thickness (mm)	0.6 (carotid coil) 0.8 (neurovascular coil)	2/−1
Blood suppression	None	None
Special parameters	Flip angle = 15°, turbo factor = 30, TI = 500 ms, IRTR = 800 ms	Flip angle = 15°, turbo factor = 30, TI = 500 ms, IRTR = 800 ms
Fat suppression	Yes (water excitation)	Yes (water excitation)
No. of Slices		40

- **Note:** SPGR indicates echo-spoiled gradient-echo; FFE, fast-field echo; IR-TFE, inversion recovery–turbo field echo; VFA, variable flip angle; IRTR, time interval between 2 consecutive IR pulses; MSDE, motion-sensitized driven equilibrium; FSD, flow-sensitized dephasing.
- Pulse gating not required for any sequence.