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European Stroke Organisation (ESO) guidelines on treatment of patients with intracranial atherosclerotic disease (ICAD)

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Disclosures

Intellectual Disclosures: Juan F. Arenillas is the PI of RICORS-ICTUS, PI of the IMMINENT project and of the FIS project. He is a member of the Spanish Research Network on Stroke.

Marios-Nikos Psychogios is the Sponsor PI of the DISTAL and SPINNERS Study, He is the local PI for the ASSIST, SURF and ESCAPE-NEXT trials

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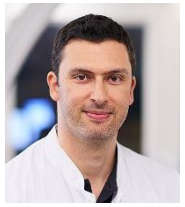

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Important definitions

- **Intracranial atherosclerotic disease (ICAD)**

Atherosclerotic plaques affecting major intracranial arteries in any stage of the disease, including non-stenotic ICAD

- **Intracranial artherostenosis (ICAS)**

Atherosclerotic plaque causing a significant luminal narrowing (> 50%); in case > 70% or associated with symptoms high-grade ICAS

- **Hemodynamic compromise:**

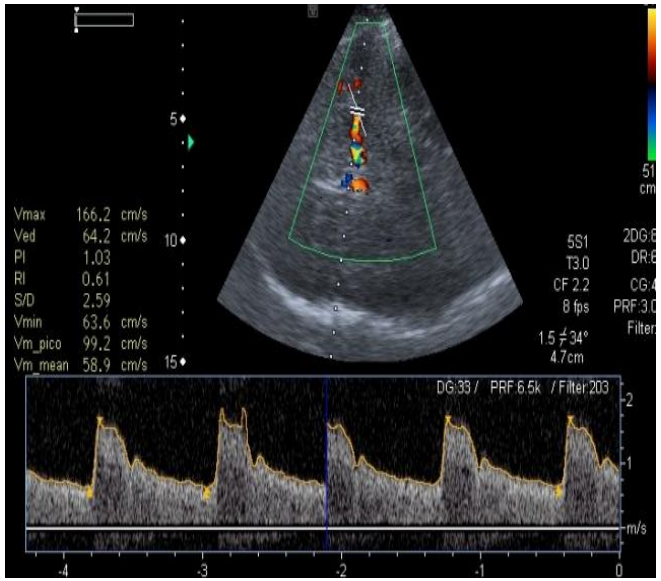
Significant reduction of anterograde flow in the downstream arterial territory

Epidemiology

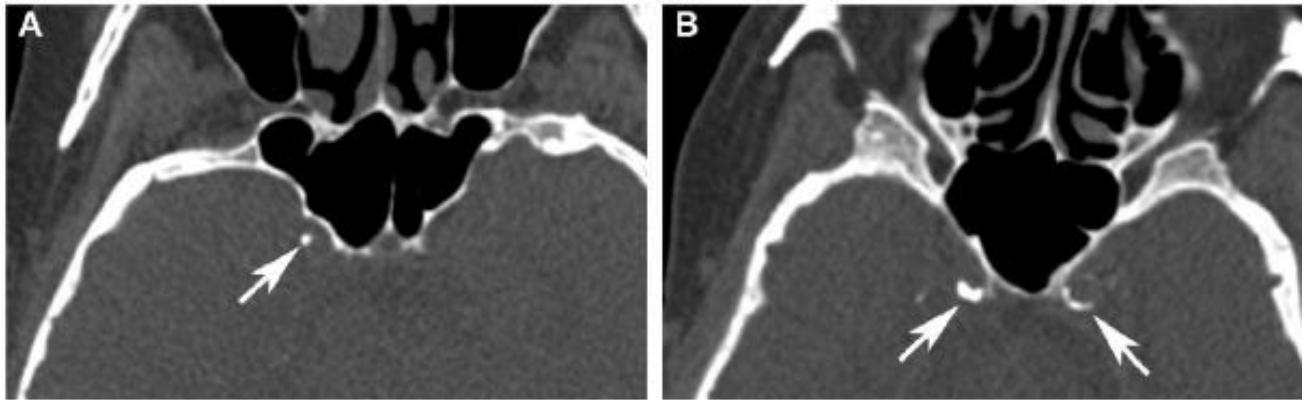
- Important reason for ischemic stroke
- Very prevalent in Asian populations; most prominent etiology of ischemic stroke and TIA (up to 40%)
- In Caucasians it may be responsible for up to 10% of ischemic strokes
- High risk for recurrent ischemic stroke

Outline of the Guideline

- Focus on three patient populations
  - I - Asymptomatic patients with no prior stroke / TIA (primary prevention)



Asymptomatic MCA stenosis
detected by TCCD



Intracranial calcification
detected by non contrast CT

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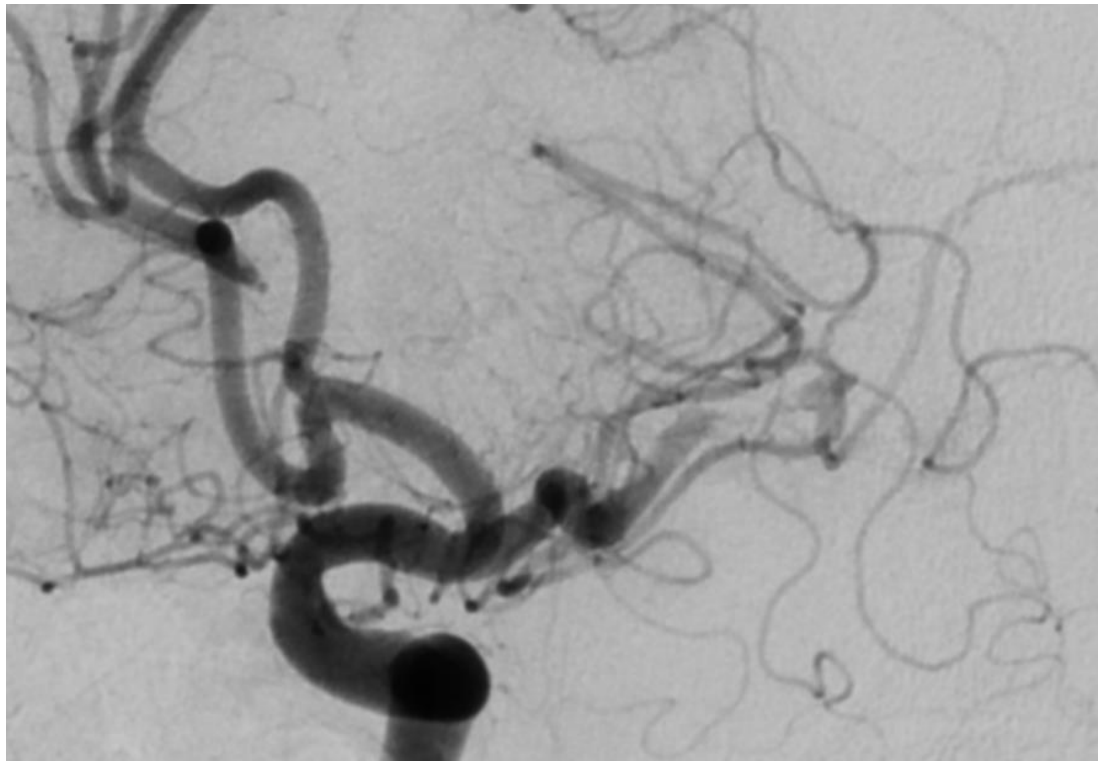
Outline of the Guideline

- Focus on three patient populations

  II - Patients with acute LVO-Stroke due to ICAD (hyperacute management)



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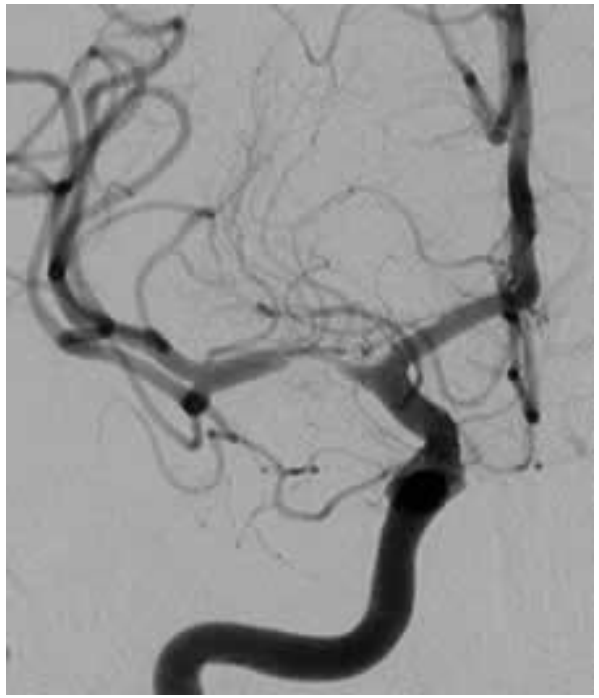
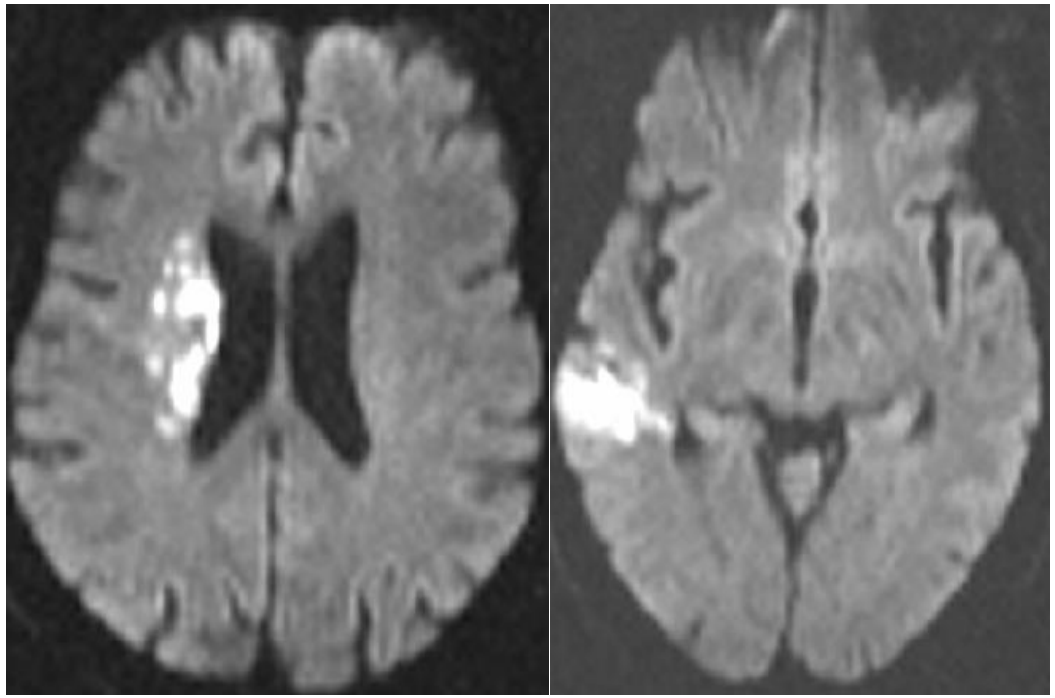
Outline of the Guideline

- Focus on three patient populations

  III - Patients with stroke/TIA due to ICAD (secondary prevention)





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Primary prevention of ICAD

PICO 1:

In adult stroke-free subjects, is screening compared to no-screening for intracranial atherosclerosis beneficial for the prevention of Major Adverse Cardiovascular Events (MACE) including ischemic stroke?

Evidence-based Recommendation

In adult stroke-free subjects, the benefits of screening programs to detect the presence of asymptomatic intracranial atherosclerosis are uncertain and therefore we cannot make a recommendation regarding routine screening for ICAD.

Quality of evidence: **Low** ⊕⊕

Strength of recommendation: **-**

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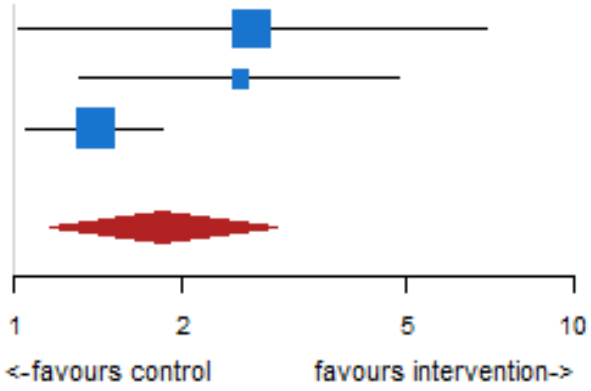
Strong association between asymptomatic ICAD and risk of stroke

PICO 1 - Association between asymptomatic ICAD and risk of future stroke

Study	*n(I)*	*N(I)*	*n(C)*	*N(C)*	*weight*	*HR(95%CI)*
Planas-Bellve 2019	6	31	44	853	17.4%	2.66 (1.02-6.94)
Wang 2016	NA.	NA.	NA.	NA.	28.7%	2.53 (1.31-4.87)
Duan 2014	64	272	289	1925	54.0%	1.40 (1.05-1.84)
Total	**70***	**303***	**333***	**2778***	**100.0%**	**1.85 (1.17-2.95)**

I^2=48%, p=0.15



*Data from Wang 2016 missing from totals

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Expert Consensus Statement PICO 1

Screening for asymptomatic ICAD in stroke-free individuals to help assess their vascular risk is not suggested as a prevention strategy. However, the detection of asymptomatic intracranial atherosclerosis or calcification as an incidental finding on neuroimaging exams implies a significantly higher risk for future major vascular events including stroke. Therefore, patients with asymptomatic intracranial atherosclerosis or calcification, may need to be recognized as harboring a high vascular risk.

Voting results: 11 agree / 1 disagree

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Primary prevention of ICAD

PICO 2:

In subjects with asymptomatic intracranial atherosclerosis, does antiplatelet treatment compared with no antiplatelet treatment lower the risk of MACE including ischemic stroke?

Evidence-based Recommendation

In subjects with asymptomatic intracranial atherosclerosis, whether antiplatelet treatment lowers the risk of MACE including ischemic stroke is still uncertain. Therefore, we cannot make a recommendation regarding antiplatelet therapy.

Quality of evidence: -

Strength of recommendation: -

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Expert Consensus Statement PICO 2

We suggest antiplatelet treatment in subjects with asymptomatic intracranial atherosclerosis after appropriate assessment of the benefit/risk profile on an individual basis. As factors favoring the indication of antiplatelet therapy, we suggest to consider: high or very high vascular risk, presence of severe and/or multiple intracranial stenosis, progression of ICAD, and detection of covert infarctions within the brain territory distal to an intracranial stenosis. As factors against, we suggest to consider those associated with an increased systemic and/or intracranial bleeding risk under antiplatelet therapy.

Voting results: 7 agree / 5 disagree

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Hyperacute management of ICAD related Stroke

A high probability of an ICAD-related LVO is assumed if all or most of the following criteria are fulfilled:

(1) absence of atrial fibrillation,

(2) absence of CT hyperdense sign or MRI susceptibility sign,

(3) watershed infarction,

(4) truncal-type occlusion,

(5) residual stenosis on DSA when stent is open or after three stent-retriever passes or

(6) early reocclusion.

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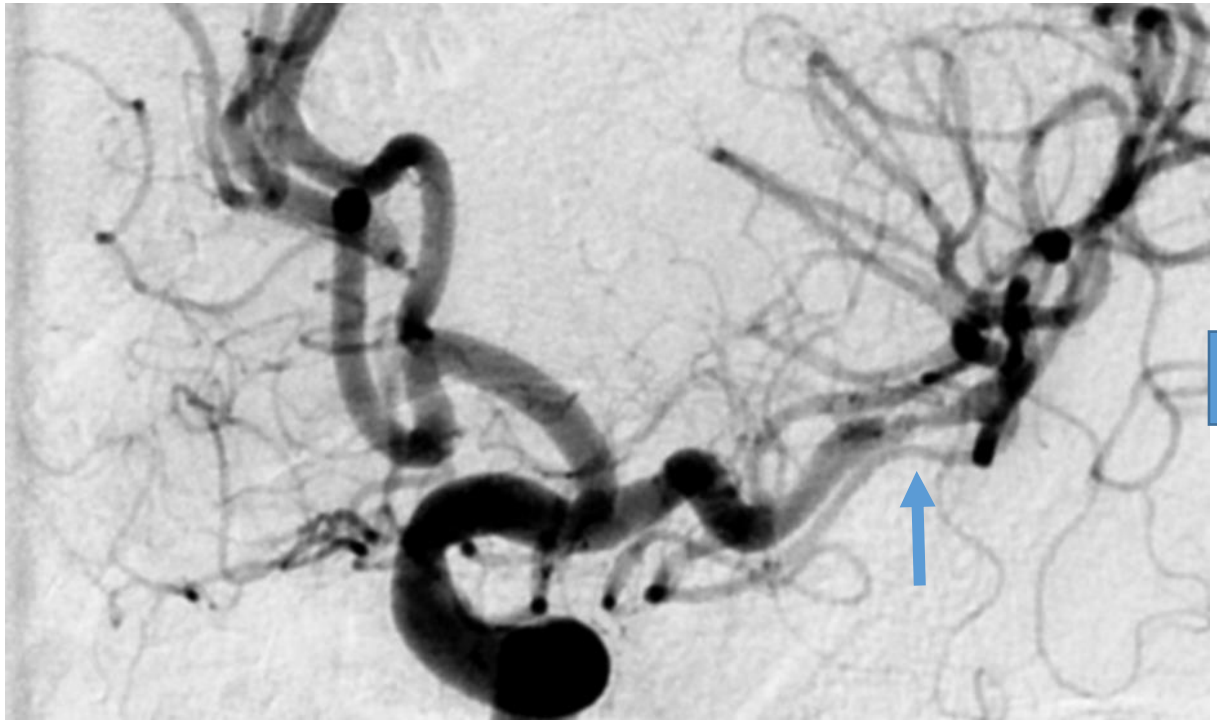
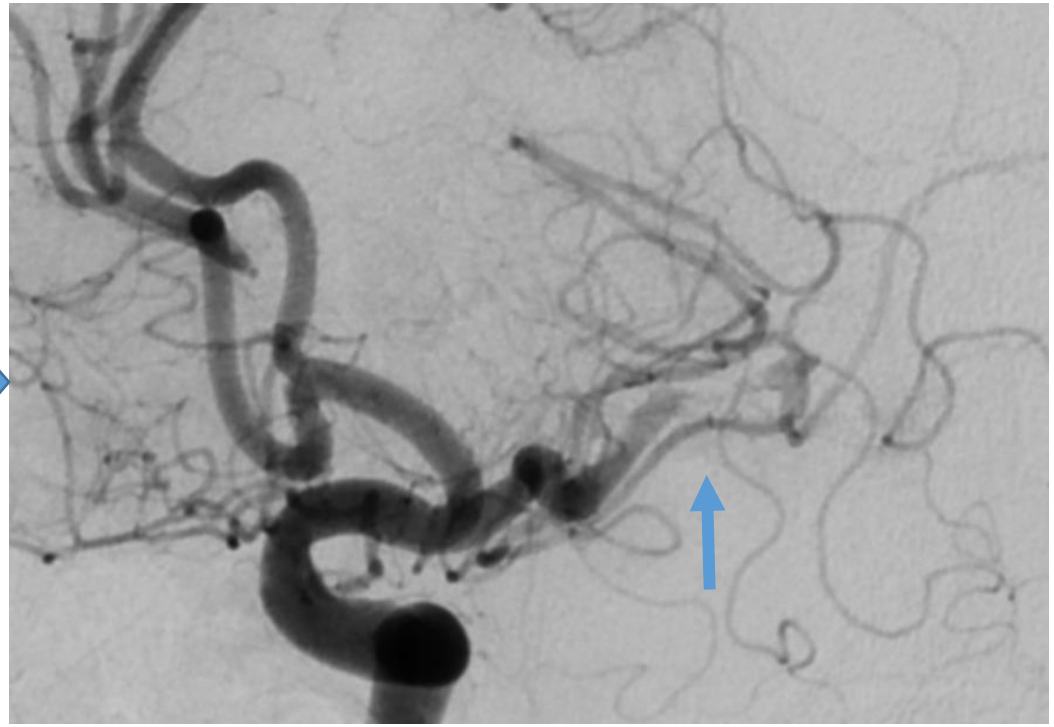
Hyperacute management of ICAD related Stroke



Residual stenosis after thrombectomy



Early arterial reocclusion

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Hyperacute management of ICAD

PICO 3:

In patients undergoing mechanical thrombectomy for an acute ischemic stroke due to an ICAD-related intracranial arterial occlusion, does infusion of glycoprotein IIb/IIIa inhibitors after initial mechanical thrombectomy, as compared with standard of care, improve functional outcome?

Evidence-based Recommendation

In patients undergoing mechanical thrombectomy for an acute ischemic stroke due to an ICAD-related intracranial arterial occlusion, the benefit of the additional infusion of glycoprotein IIb/IIIa inhibitors after initial mechanical thrombectomy remains uncertain. We suggest enrolling patients in a dedicated randomized-controlled clinical trial.

Quality of evidence: **Very low** ⊕

Strength of recommendation: **-**

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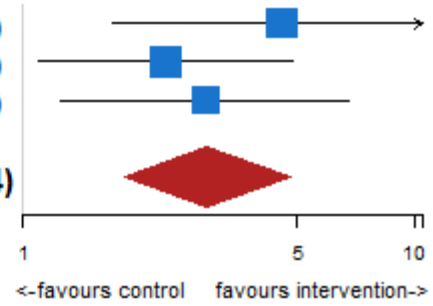
Additional information PICO 3

PICO 3 - Association between infusion of glycoprotein IIb/IIIa inhibitors after mechanical thrombectomy, compared to standard of care, and good functional outcome (mRS0-2) at 90 days, in observational studies

Study	*n(I)*	*N(I)*	*n(C)*	*N(C)*	*weight*	*OR(95%CI)*
Baek 2021	55	84	7	24	24.4%	4.61 (1.71-12.38)
Kim 2020	31	59	19	59	42.6%	2.33 (1.10-4.92)
Yan 2020	27	48	14	46	33.1%	2.94 (1.26-6.86)
Total	**113**	**191**	**40**	**129**	**100.0%**	**2.97 (1.82-4.84)**

I^2=0%, p=0.56



OR reported for the studies are crude OR calculated by authors based on the raw numbers reported in the articles

- All studies were **retrospective**
- Unclear patient selection criteria
- High heterogeneity regarding concomitant treatment
- Very large 95%-CI indicates high level of uncertainty

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Expert Consensus Statement PICO 3

We suggest that if inclusion in a dedicated randomized-controlled clinical trial is not possible, glycoprotein IIb/IIIa inhibitors may be used as a rescue strategy after assessing the bleeding risk for patients with an acute ischemic stroke suspected to be caused by an underlying ICAD in case of unsuccessful mechanical thrombectomy.

Voting results: 10 agree / 2 disagree

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Hyperacute management of ICAD

PICO 4:

In patients undergoing mechanical thrombectomy for an acute ischemic stroke due to an ICAD-related intracranial arterial occlusion, does angioplasty and/or stenting plus best medical treatment (BMT) after initial mechanical thrombectomy, as compared to BMT alone, improve functional outcome?

Evidence-based Recommendation

In patients undergoing mechanical thrombectomy for an acute ischemic stroke due to an ICAD-related intracranial arterial occlusion, whether angioplasty and/or stenting after initial mechanical thrombectomy improves outcome, remains unknown. We suggest enrolling patients in a dedicated randomized-controlled clinical trial whenever possible.

Quality of evidence: **Very low ⊕**

Strength of recommendation: **-**

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Expert Consensus Statement PICO 4

We suggest that if inclusion in a dedicated randomized-controlled clinical trial is not possible, angioplasty and/or stenting may be used as a rescue therapy after unsuccessful mechanical thrombectomy in patients with an acute ischemic stroke suspected to be caused by underlying ICAD. This suggestion needs to be considered with caution, since the referred studies with angioplasty and/or stenting in ICAD-related LVO were focused mainly on Asian patients and their results might not necessarily be generalizable to other populations.

Voting results: 8 agree / 4 disagree

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Hyperacute management of ICAD

PICO 5:

In patients with an acute ischemic stroke or transient ischemic attack related to a high-grade intracranial atherosclerosis causing hemodynamic compromise, does permissive or induced hypertension, as compared to conventional blood pressure (BP) management (targeting normotension), during the acute phase, improve outcome?

Evidence-based Recommendation

In patients with an acute ischemic stroke or transient ischemic attack related to high-grade intracranial atherosclerosis causing severe hemodynamic compromise, we cannot make a recommendation regarding the use of permissive or induced hypertension over conventional blood pressure management (target normotension) during the acute phase, based on current evidence.

Quality of evidence: **Moderate** ⊕⊕⊕

Strength of recommendation: **-**

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Expert Consensus Statement PICO 5

In patients with high-grade symptomatic intracranial stenosis and clinical or imaging signs of hemodynamic compromise we suggest considering induced arterial hypertension as a rescue treatment option, only after other more conservative measures to improve cerebral hemodynamics have been tried.

Voting results: 8 agree / 4 disagree

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Management of patients with symptomatic ICAD

PICO 6:

In patients with an ischemic stroke or transient ischemic attack related to a high-grade stenosis related to ICAD and without any formal indication for anticoagulation, does anticoagulant therapy, as compared to antiplatelet therapy, improve outcome?

Evidence-based Recommendation

In patients with an ischemic stroke or transient ischemic attack due to high-grade stenosis related to ICAD we recommend against oral anticoagulation over aspirin unless there is another formal indication for it.

Quality of evidence: **Moderate** ⊕⊕⊕

Strength of recommendation: **Strong against intervention** ↓↓

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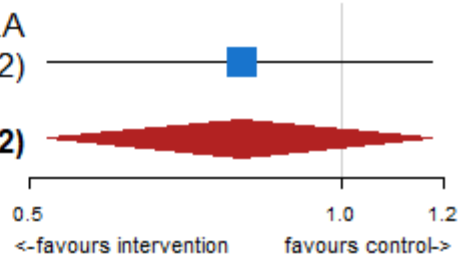
Additional information PICO 6

PICO 6 - Association between anticoagulation therapy compared to antiplatelet therapy and risk of long term recurrence of IS in RCT

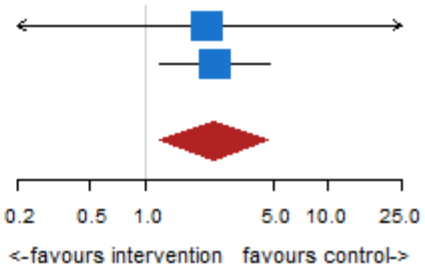
Study	*n(I)*	*N(I)*	*n(C)*	*N(C)*	*weight*	*OR(95%CI)*
Marti-Fabregas 2006	0	14	0	14	0.0%	N.A
Chimowitz 2005	49	289	57	280	100.0%	0.80 (0.52-1.22)
Total	**49**	**303**	**57**	**294**	**100.0%**	**0.80 (0.52-1.22)**



PICO 6 - Association between anticoagulation therapy compared to antiplatelet therapy and mortality in RCT

Study	*n(I)*	*N(I)*	*n(C)*	*N(C)*	*weight*	*OR(95%CI)*
Marti-Fabregas 2006	2	14	1	14	7.1%	2.17 (0.17-27.08)
Chimowitz 2005	28	289	12	280	92.9%	2.40 (1.19-4.81)
Total	**30**	**303**	**13**	**294**	**100.0%**	**2.38 (1.21-4.66)**

I^2=0%, p=0.94



- Data from two RCTs
- Effects primary driven by WASID trial
- No effect on risk of long-term recurrence of IS
- Higher risk of mortality and major bleeding
- No trials on NOACs

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Management of patients with symptomatic ICAD

PICO 7:

In patients with an ischemic stroke or transient ischemic attack related to intracranial stenosis related to ICAD, does dual antiplatelet therapy, as compared to single antiplatelet therapy, improve outcome?

Evidence-based Recommendation

In patients with an ischemic stroke or transient ischemic attack related to intracranial stenosis due to ICAD we suggest dual antiplatelet therapy over single antiplatelet therapy. Regarding the duration of the dual antiplatelet therapy, we refer to the additional information.

Quality of evidence: **Very low ⊕**

Strength of recommendation: **Weak for intervention ↑?**

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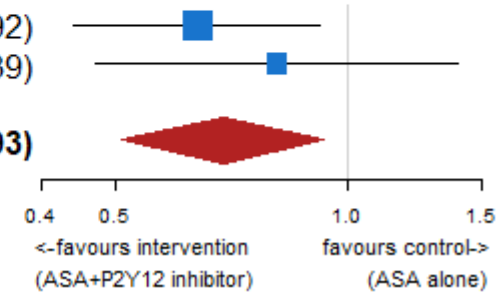
Additional information PICO 7

PICO 7 - Association between aspirin + P2Y12 inhibitor intake, compared to aspirin intake alone, and risk of recurrent IS or death in RCT

Study	*n(I)*	*N(I)*	*n(C)*	*N(C)*	*weight*	*OR(95%CI)*
Amarenco 2020	53	516	85	558	68.9%	0.64 (0.44-0.92)
Liu 2015	26	231	34	250	31.1%	0.81 (0.47-1.39)
Total	**79**	**747**	**119**	**808**	**100.0%**	**0.69 (0.51-0.93)**

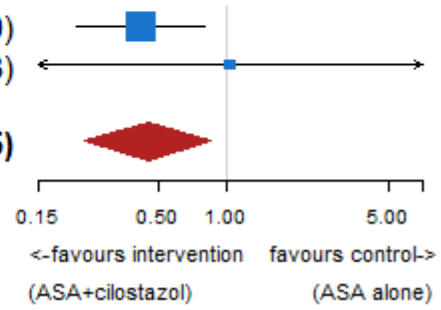
I²=0%, p=0.48



PICO 7 - Association between aspirin + cilostazol intake, compared to aspirin intake alone, and risk of MACE in RCT

Study	*n(I)*	*N(I)*	*n(C)*	*N(C)*	*weight*	*OR(95%CI)*
Uchiyama 2021	14	275	31	272	90.2%	0.42 (0.22-0.80)
Kwon 2005	2	67	2	68	9.8%	1.02 (0.14-7.43)
Total	**16**	**342**	**33**	**340**	**100.0%**	**0.45 (0.24-0.85)**

I²=0%, p=0.40



- Data from subgroup analysis of 3 RCTs
- Not all outcomes reported in the trials
- Suggest lower risk of MACE and combination of recurrent IS or death

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Expert Consensus Statement PICO 7

In patients with symptomatic ICAD, the optimal duration of DAPT is not clear according to current evidence. We suggest prolonging DAPT up to day 90 after the index event.

Voting results: 12 agree / 0 disagree

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Management of patients with symptomatic ICAD

PICO 8:

In patients with an ischemic stroke (IS) or transient ischemic attack (TIA) related to a high-grade stenosis due to ICAD, does angioplasty and/or stenting plus BMT, as compared to BMT alone, improve outcome?

Evidence-based Recommendation

In patients with an ischemic stroke or transient ischemic attack related to a high-grade stenosis due to ICAD, we recommend against angioplasty and/or stenting added to best medical treatment as first-line treatment.

Quality of evidence: **Low** ⊕⊕

Strength of recommendation: **Strong against intervention** ↓↓

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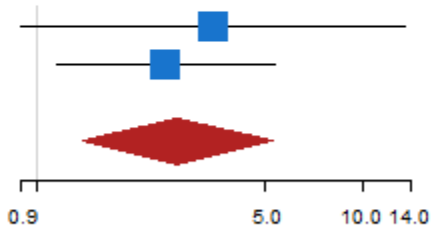
Additional information PICO 8

PICO 8 - Association between angioplasty and/or stenting + BMT compared to BMT and risk of recurrent IS at 30 days in RCT

Study	*n(I)*	*N(I)*	*n(C)*	*N(C)*	*weight*	*OR(95%CI)*
Zaidat 2015	10	58	3	53	24.4%	3.47 (0.90-13.39)
Derdeyn 2014	23	224	10	227	75.6%	2.48 (1.15-5.35)
Total	**33**	**282**	**13**	**280**	**100.0%**	**2.69 (1.38-5.25)**

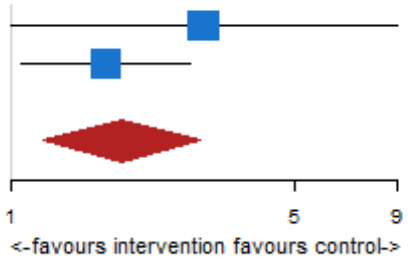
I²=0%, p=0.67



PICO 8 - Association between angioplasty and/or stenting + BMT compared to BMT and risk of MACE in RCT

Study	*n(I)*	*N(I)*	*n(C)*	*N(C)*	*weight*	*OR (95%CI)*
Zaidat 2015	14	58	5	53	13.3%	2.99 (1.00-8.96)
Derdeyn 2014	52	224	34	227	86.7%	1.72 (1.06-2.77)
Total	**66**	**282**	**39**	**280**	**100.0%**	**1.88 (1.21-2.92)**

I²=0%, p=0.35



- Data from two RCTs
- Effects driven by the SAMMPRIS trial (451 patients vs 112 patients)
- Both trials show worse outcomes in intervention arm
- However, new devices and more experienced interventionalists might offer more beneficial results

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Expert Consensus Statement PICO 8

We suggest considering endovascular treatment (angioplasty and/or stenting) as a rescue therapy in selected patients with symptomatic high-grade ICAS after clinical recurrence despite BMT.

Voting results: 11 agree / 1 disagree

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Management of patients with symptomatic ICAD

PICO 9:

In patients with an ischemic stroke or transient ischemic attack related to a high-grade stenosis due to ICAD do any neurosurgical intervention plus BMT, compared to BMT alone, improve outcome?

Evidence-based Recommendation

In patients with an ischemic stroke or transient ischemic attack related to a high-grade stenosis due to ICAD, we recommend against neurosurgical procedures.

Quality of evidence: **Low** ⊕⊕

Strength of recommendation: **Strong against intervention** ↓↓

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Additional information PICO 9

- Data from one RCT, the **EC-IC bypass study group trial**
- Published in 1985
- 1377 patients included; Increased rates of major stroke (7 vs 5%) and mortality (20 vs 17%) in surgical arm at end of the study
- Effects of Encephaloduroarteriosynangiosis (EDAS) still unclear
- Preliminary study suggests beneficial effects (IS or stroke rate of 9.6%)
- However, quality of data is low as patients were not randomized and compared to historical data

Management of patients with symptomatic ICAD

PICO 10:

In patients with an ischemic stroke or transient ischemic attack related to a high-grade intracranial atherostenosis, does remote ischemic pre-conditioning plus BMT, compared to BMT alone, improve outcome?

Evidence-based Recommendation

In patients with an ischemic stroke or transient ischemic attack related to a high-grade stenosis due to ICAD, we suggest ischemic pre-conditioning as an adjuvant to BMT. We suggest enrolling patients in a dedicated randomized-controlled clinical trial whenever possible.

Quality of evidence: **Low ⊕⊕**

Strength of recommendation: **Weak for intervention ↑?**

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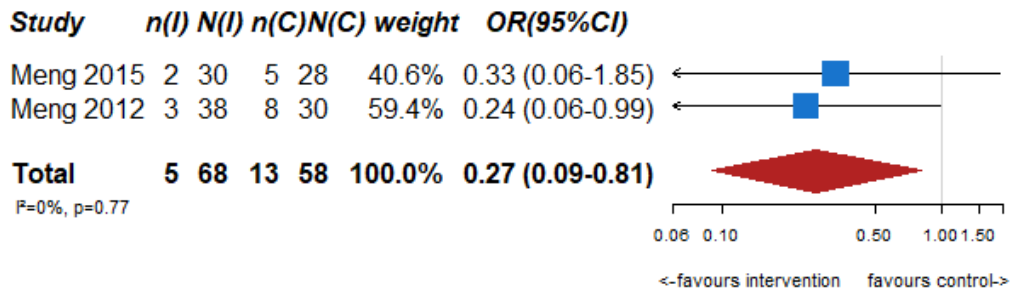
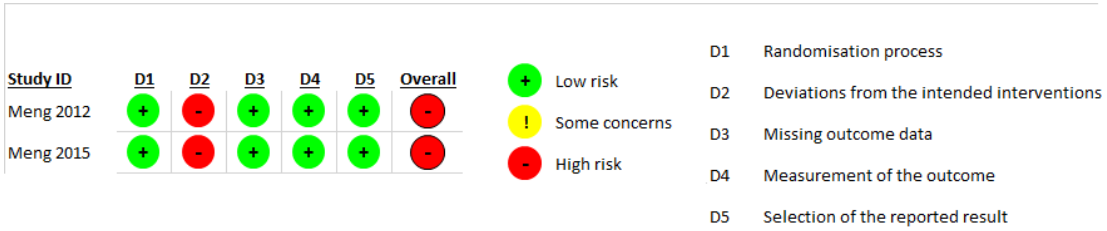
Additional information PICO 10

PICO 10 - Association between remote ischemic conditioning plus BMT compared to BMT alone and the risk of long term recurrence of IS in RCTs





- Data from two RCTs
- Different age groups in the trials (< 80 years and ≥ 80 years)
- However, high risk of bias due to absence of blinding and inappropriate analysis

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Management of patients with symptomatic ICAD

PICO 11:

In patients with an ischemic stroke or transient ischemic attack related to an intracranial atherostenosis, does aggressive vascular risk factor control, including lipid management, improve outcome?

Evidence-based Recommendation

In patients with an ischemic stroke or transient ischemic attack related to an intracranial atherostenosis, we suggest aggressive vascular risk factor control, including lipid management and lifestyle changes (i.e., increased physical activity), in order to improve outcomes, although uncertainty exists regarding target levels of BP and LDL in this specific population.

Quality of evidence: **Low ⊕⊕**

Strength of recommendation: **Weak for intervention ↑?**

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Expert Consensus Statement PICO 11

We suggest that patients with symptomatic ICAS should be considered as a very-high-risk population and target levels of LDL cholesterol should be achieved according to ESC/EAS guidelines (LDL <55 mg/dl).

Voting results: 11 agree / 1 disagree

We suggest that even in the subacute phase of stroke due to ICAS, strict BP control probably should be initiated to prevent recurrence and stenosis progression. Regarding the optimal BP target in ICAD patients, we refer the readers to ESO stroke secondary prevention guidelines, since there is no specific evidence-based recommendation for ICAD patients.

Voting results: 12 agree / 0 disagree

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Areas of future research

Primary prevention

- No data exists on screening
- Benefit/Risk of primary prevention with ASA should be explored in RCTs

Hyperacute management

- Retrospective data suggests potential beneficial effects of Glycoprotein IIb/IIIa inhibitors and/or stenting/angioplasty
- Well designed RCTs urgently needed

Secondary prevention

- Role of newer antiplatelets and anticoagulants
- Role of inflammation
- Identification of subgroups of patients which might benefit from interventional approaches
- Evaluation of new devices which might have better risk/benefit ratio
- Effect of life-style changes, and medication on recurrent IS or TIA should be investigated

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Conclusion

- Overall paucity of data on effective treatment approaches
- High risk for future strokes associated with asymptomatic ICAD but uncertain management
- Evidence-based recommendations in secondary prevention:
  - Antiplatelet vs. anticoagulants as antithrombotic (DAPT 90 days preferred)
  - Angioplasty-stenting not a first-line treatment
  - Neurosurgical procedures not a first-line treatment
  - Remote ischemic conditioning promising results in first RCTs
  - Importance of lifestyle changes and aggressive risk factor control
- RCTs highly warranted for hyperacute management of ICAD