指南

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欧洲中风组织 (ESO) 烟雾病血管病指南 血管欧洲参考认可网络 (VASCERN)

SAGE

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摘要

欧洲卒中组织(ESO)烟雾病(MMA)指南是根据 ESO 标准操作程序和推荐分级、评估、发展和评价(GRADE)方法制定的，旨在帮助临床医生管理 MMA 患者的决策。一个由神经学家、神经外科医生、遗传学家和方法学家组成的工作组确定了九个相关的临床问题，进行了系统的文献综述，并在可能的情况下进行了荟萃分析。 Quality assessment of the available evidence was made with specific recommendations. 在缺乏足够证据提出建议的情况下，拟订了专家协商一致声明。基于低品证据从一个 RCT，我们建议直接分流术手术在成人患者出血先露。对于缺血性成人和儿童，我们建议采用直接或联合技术而不是间接的血运重建手术，在存在血流动力学障碍的情况下，并在最后一次脑血管事件和手术之间间隔 6-12 周。在缺乏可靠试验的情况下，专家一致建议对非出血性 MMA 进行长期抗血小板疗法，因为它可能降低栓塞性卒中的风险。我们也同意在术前和术后进行血流动力学和大脑后动脉评估的实用性。没有足够的数据建议对 RNF213 p.R4810K 进行系统的变异筛查。此外，我们认为长期的 MMA 神经成像随访可以通过评估疾病进展来指导治疗决策。我们相信，这是欧洲第一个使用 GRADE 方法管理 MMA 的综合指南，将有助于临床医生选择最有效的 MMA 管理策略。

关键词

Moyamoya angiopathy, diagnosis, therapy, stroke, guidelines, systematic review

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更正(2023 年 3 月)文章已在线更新，将第 66 页第 38 行 PICO 5 上的“0.13-1.01”更正为“0.15-1.03”。

简介

烟雾病(Moyamoya angiopathy, MMA)是一种慢性脑血管病，其特征是进行性双侧锁骨上内颈动脉及其主要分支狭窄，脑深部出现脆弱血管的侧支网(日语称为“烟雾病”)的发育。[1,2] 尽管 MMA 在世界范围内的认知度越来越高，但它仍然被认为是一种罕见的疾病[3] 它在东亚国家更常见，特别是日本(发病率上至 0.54 / 10 万)，但在西方国家，这种疾病的发病率低 10 倍(0.047-0.086 / 10 万)。[4–7] However, MMA is probably underestimated outside East-Asia and may be an increasing health issue in Europe.[8] MMA 通常被归类为烟雾病疾病(MMD)，当它与遗传性疾病(如唐氏综合征、I 型神经纤维瘤病或镰状细胞病)或获得性疾病(如头部和颈放射疗法)相关时，则被归类为原发性疾病或烟雾病综合征(MMS)。[9–11] 最常见的临床特征是脑血管事件(短暂性缺血发作(TIA)、缺血性和出血性中风(缺血性和出血性中风)和蛛网膜下腔出血(SAH))，它们分别源于颅内 ICAs 分叉处狭窄闭塞过程和脆弱的侧支血管破裂。leptomeningeal anastomosis or associated saccular aneurysms.[9–13] 临床先露因年龄和种族不同而不同:成人可能出现短暂的或永久性的脑缺血事件和颅内出血，儿童主要出现缺血事件，而西方成人往往比东亚患者出现更低的出血率。[6,7,10–12,14–16] 认知缺陷、偏头痛样发作、精神和运动障碍也是常见的疾病特征。[11,13] 虽然疾病的临床表现在不同的病人之间有很大的差异，但是 MMA 可以有一个数发展导致严重的残疾，主要在儿科病例中，但也在成人中[10,17,18] 虽然血管生成因子的失调和遗传易感性被认为与 MMA 的病理生理学有关，但其发病机制尚不清楚。[9,10,19] 遗传因素的作用得到几个因素的支持，包括 MMA 与遗传性疾病的关系、东亚的高家族性发病率和该疾病的地理分布。[19–21] 特别是 RNF213 基因的一个变种，p.R4810K 具有很强的方正效应，在患有 MMA 的东亚人身上发现了，但在西方患者身上没有发现，而其他 RNF213 基因变种的作用[20,22] 显然与疾病的关系不大。[23–30] MMA 的诊断是根据所建立的血管造影诊断标准确定的，[31,32] 要求在 ICAs 终末部分和/或大脑前动脉和/或大脑中动脉近端部分存在双侧狭窄或闭合，并在闭塞或狭窄病变附近发育脆弱的侧支血管网络。[31,32] 在可变比例的 MMA 患者中，后循环(主要是可能累及大脑后动脉(pca)。虽然大脑 MRI 和 MRA 越来越多地用于识别 MMA 的主要神经放射学特征，但大脑数字减影血管造影(DSA)仍用于诊断确认，也用于评估经络和血管状态。Patient diagnostic work up usually includes haemodynamic assessment by transcranial ultrasound examination and perfusion imaging evaluation by perfusion CT or MRI with or without acetazolamide (ACZ) and/or ACZ single photon emission computed tomography (SPECT) or quantitative H2[15O] positron emission tomography (PET).[12,33,34] Although these techniques are currently used not only to assess the disease severity but also to establish indication to surgery, they are not validated, and no standardised indications are provided for pre-operative and outcome patient assessment.[35–37]

To date, no treatment limiting the progression of the occlusive arterial lesions is available for MMA patients and strategies aiming at reducing the risk of further cerebrovascular events employ surgical revascularization techniques.[38–40] The surgical methods are mainly divided into direct revascularization, in which the superficial temporal artery (STA) – a branch of the external carotid artery (ECA) – is directly anastomosed with the middle cerebral artery (MCA) or the anterior cerebral artery (ACA), and indirect revascularization (synangiosis procedures) in which tissues encompassing ECA branches (dura mater, temporal muscle, galeal tissue, or superficial temporal artery) are placed in contact with the surface of the ischaemic brain.Potential indications for revascularization surgery include ischaemic symptoms, a decreased regional cerebral blood flow or a cerebrovascular reserve (CVR) decrease on perfusion imaging.[41–44] Moreover, although recent meta-analyses suggest the efficacy of surgical revascularization in symptomatic MMA patients, the optimal surgical procedure as well as the timing of surgery remain controversial.Usually, decisions on the surgical approach depend on the neurosur- geon’s expertise and on the condition of the donor and recipient arteries.[35,45] 因此，尽管已经提出了一些治疗途径，[42] 对于 MMA 的管理和治疗，特别是在欧洲患者中，一直没有达成共识。

The aim of this guideline is to provide recommendations guiding stroke clinicians and researchers to ensure the best diagnostic and therapeutic management strategies when assessing patients with a diagnosis of MMA, with the final objective of reducing the risk of stroke recurrence and long-term disability.

方法

模块工作组的组成和核准

这些指南是由欧洲中风组织(ESO)发起的。两名主席(AB 和 DH)

被选中来组装和协调指导方针模块工作组(MWG)。最后一组包括 10 位专家(AB、NK、BF、FA、IC、ETL、PV、MZ、MK、DH)。这 10 位专家都是脑血管疾病方面的专家，对 MMA 有着特殊的兴趣。工作组包括 6 名血管神经学家，3 名神经外科医生和 1 名遗传学家。在 10 个工作组成员中，所有人都在欧洲工作。Two methodologists (SH, SL) supported the literature search as well as performed data extraction, risk of bias assessment and meta-analyses independently.

ESO 指南董事会和执行委员会审查了工作组所有成员的知识产权和财务披露，并批准了工作组的组成。工作组所有成员的详细情况及其披露情况载于补充材料-表 1。

临床问题的开发和批准

本指南依据 ESO 标准操作程序(SOP)编制，[46] 它是根据“建议、评估、发展和评价的分级”(GRADE)框架制定的。[47] 工作组制定了一个主题清单和相应的问题，最大的临床利益。问题的格式采用 PICO 方法(人口、干预、比较国和结果)，并由两名外部审查人员以及 ESO 指南委员会和执行委员会成员进行审查。工作组的成员根据评级标准将结果分为:关键的、重要的或有限重要的。最终决定采用德尔菲法。每个 PICO 问题的结果评分结果包括在补充材料-表 2 中。

We considered as critical outcomes (defined as ‘critical for making decision’): any stroke (ischaemic or haemorrhagic), major stroke (resulting in moderate to severe disability defined by mRS 3-5) and disability.We identified as important outcomes (defined as ‘important but not critical for making the decision’): TIA, death and cognitive impairment.不良临床结果(UCO)包括所有关键和重要的结果。

诊断标准

For inclusion in the guidelines, MMD diagnosis should have been performed according to established angiographic diagnostic criteria[31,32] including the presence of stenosis or occlusion at the terminal portion of the ICAs or the proximal segment of the ACAs or MCAs and abnormal vascular networks in the arterial territories near the occlusive or stenotic lesions.Patients were considered symptomatic when presenting with TIA, ischaemic or haemorrhagic stroke, headache, movement disorders or cognitive disturbances.Unilateral presentation was considered only in syndromic cases (MMS).

人口选择、干预、比较和结果(PICO)。工作组制定了 9 个与 MMA 管理相关的 PICO 问题，其中几个子问题与上述 6 种不同结果(如适用)、不同的亚群体、(补充材料-表 2)。工作组决定主要侧重于三种类型的干预措施:影像学评估、基因检测以及内科和外科治疗。在 PICO5 和 PICO6 中，成人人群与儿童人群被区分开来，因为影响收益-风险平衡的关键因素在这两种情况下是不同的。事实上，MMA 的表达在儿童中主要是缺血性的，而在成人中它也以脑出血为特征。血管重建技术也因解剖因素的不同而有所不同，解剖因素与脑血管的大小和新生血管的潜力有关，新生血管在儿童中似乎更有效。对于 PICO8，为了避免任何潜在的误解，双方同意对问题的措词进行事后修改。该 PICO 的初始声明如下:“在 MMA 患者中，与早期和/或即刻手术相比，尊重从急性脑血管事件到血运重建手术的 8 周时间间隔，是否能降低不良临床结果的风险?”我们选择 8 周作为平均持续时间，而不是一个固定的标准，以选择所有比较早期/立即手术和较晚时间窗的研究。这一选择是在定义 PICO 过程的早期做出的，当时还没有进行文献搜索。在实践中，为了确保选择所有感兴趣的研究，我们没有将“8 周”作为文献搜索的标准。文献检索发现了比较延迟 6 周或 12 周后早期/即刻手术与晚期手术的研究。这个 6 或 12 周的延迟接近我们最初提议的 8 周的平均延迟，这就是为什么我们把这些研究包括在手稿中。The module working group agreed to change the wording of the PICO as follows: In patients with MMA, does respecting a 6- or 12-week minimum time interval from an acute cerebrovascular event to revascularization surgery compared to earlier and/or immediate surgery reduce the risk of an unfavourable clinical outcome?

文献检索

对于每个 PICO 问题，搜索词都被开发、测试、精炼，并在总体工作组和指导方针方法学家(SL 和 SH)之间达成一致。当一个有效的搜索策略可用时，它被使用或调整。在最近对感兴趣的问题进行了有关的系统审查时，使用了相应的搜索策略和结果，并在必要时加以更新。搜索策略在补充材料-文件 1 中描述。我们对文献进行了系统的回顾，以收集证据来回答每个 PICO 问题。该搜索由 ESO 执行

指导方法学家。对于每一个 PICO 问题，我们搜索了以下数据库:PUBMED、EMBASE 和 Cochrane Library，从每个数据库成立到 2022 年 2 月。我们还搜索了评论文章的参考列表、作者的个人参考图书馆和先前的附加相关记录指南。搜索结果被加载到基于 web 的 Covidence 平台(健康创新，澳大利亚墨尔本)，由工作组进行评估。两名或两名以上的 MWG 成员被指派独立筛选在 Covidence 注册的出版物的标题和摘要，然后评估被确定可能相关的研究的全文。所有的分歧都通过两位审稿人或第三位 MWG 肢体的讨论得以解决。We prioritised randomised controlled trials (RCTs) but due to the limited data, we also considered health registry data analyses, large observational studies and systematic reviews or meta-analyses of observational studies.Only observational studies with more than 40 subjects for paediatric and more than 30 subjects for adult MMA were selected for evidence-based recommendation.定义这些不同的阈值是为了获得一个样本，其分布近似于在一般人群中观察到的(中心极限定理)，并尽可能地减少来自小样本容量的偏差。[48] 在 the pulse　把脉数据非常有限的情况下，对于 MMS 的同质样本，这个阈值被降低到 20 个参与者。我们只考虑了对人类的研究，以及有英文全文的地方。会议摘要(口头或海报)被排除在外。

数据分析

数据摘出术和分析由 ESO 方法学家(SH 和 SL)独立完成。采用 DerSimonian and Laird(随机效应)方法，使用 Review Manager (RevMan) 5.4.1 版本软件(Cochrane)进行 meta 分析。[49] 我们预期在人群特征、干预类型和设置方面有很高的异质性概率，因此，我们选择了随机效应模型而不是固定效应模型。荟萃分析的结果被总结为汇总效应估计和相关的 95%置信区间(CI)。使用 I^2 统计量，分类为中等(I^2 ⩾30%)，实质性的(I^2 ⩾50%)，或相当多(I^2⩾75%)。[50] 在适当的情况下，根据人群(缺血性或出血性烟雾病)和年龄组(成人或儿童)进行亚组分析。每个 PICO 的 MWG 成员独立评估每个元分析结果的有效性。

对证据品的评价
制定建议

偏倚风险由 Cochrane 协作偏倚风险工具的方法专家独立评估(RoB 2)用于随机试验，而 ROBINS-I 工具用于非随机研究。[51,52]

将数据分析结果导入 GRADEpro guidance Development Tool (McMaster University, 2015;由 Evidence Prime, Inc.开发)。对于每个 PICO 问题和每个结果，我们考虑以下因素:基于现有证据类型(随机或观察性研究)的偏倚风险;关于结果不一致性的思考;证据的间断性，结果的不精确性和其他可能的偏差。已编制了 GRADE 证据概况/调查结果表摘要，并用于拟订建议。[47] "基于证据的建议"是基于年级的方法。建议的方向、强度和配方是根据 GRADE 证据谱和 ESO-SOP 确定的。[46,47]

最后，当 PICO 组认为没有足够的证据来提供基于证据的建议，以及常规临床实践需要实际指导时，就添加专家共识声明。专家共识声明是基于工作组所有专家成员的投票。遗传学家 ETL，由于个人的专业经验，没有参与临床相关问题的投票。重要的是，这些专家共识声明不应被视为基于证据的建议。补充材料-表 3 总结了专家共识声明。

文件的起草、修改、批准

根据更新的 ESO SOP，每个 PICO 问题都在不同的部分中解决。[46] 首先，"当前证据分析"总结了当前的病理生理学考虑，然后对确定的随机对照试验和其他研究的结果进行了总结和讨论。第二，当需要对第一部分中提到的研究提供更多详细信息，以提供被纳入研究的关键亚组分析、正在进行或未来的随机对照试验以及可以提供重要临床指导的其他研究的信息时，添加了"附加信息"。Third, an 'Expert consensus statement' paragraph was added whenever the MWG considered that insufficient evidence was available to provide evidence-based recommendations for situations in which practical guidance is needed for everyday clinical practice.概要表(表 1)包括所有建议和专家共识声明。The Guideline document was reviewed several times by all MWG members and recommendations and consensus expert statement wording was modified using a Delphi approach until agreement was reached.The final submitted document was peer-reviewed by two external reviewers, two members of the ESO Guideline Board and one member of the Executive Committee.

表 1。所有建议和专家一致意见的概要骨板。

推荐信	专家共识声明
在烟雾病血管病(MMA)患者中，与不进行血流动力学评估相比，血流动力学评估(通过计算机断层摄影、MRI、SPECT、PET 和超声)是否能提高患者的不良预后风险? 循证推荐专家共识声明 ?MMA 患者是否存在持续的不确定性?对于所有 MMA 患者，我们建议在进行诊断性检查的优缺点中进行血流动力学评估，以帮助决策。由于缺乏特效药进一步分析，收集这些数据进行血流动力学评估可能有助于指导对这种罕见疾病的未来决策。投 9/9 票。比较研究和异质人群?无症状 MMA 患者和无症状患者(即手术和未手术患者;与血流动力学触发因素明显相关的不同，血流动力学评估方法适用于评估;等等)。应进行手术以识别有中风风险的大脑半球。投 9/9 票。证据质量:- 推荐强度:-	?For patients with clear haemodynamic triggered TIAs or watershed stroke in one cerebral artery territory, perfusion studies should be considered to identify other haemodynamically compromised yet asymptomatic brain territories.投 9/9 票。 ?For all patients in whom cerebral perfusion will be performed, we suggest using those imaging methods most familiar and available depending on individual institutions.投 9/9 票。
PICO 2 In patients with moyamoya angiopathy (MMA) does the assessment of involvement of posterior circulation compared with no assessment improve the identification of patients at higher risk of unfavourable outcome? 循证推荐 ?In patients with MMA there is a continuous uncertainty over the advantages and disadvantages of performing PCA assessment, based on current evidence, due to the lack of specific comparative studies and to the heterogenous populations (i.e. operated and not operated patients;评估所用的不同方法;等等)。 证据质量:- 推荐强度:-	专家共识声明 ?在所有的儿科 MMA 患者中，我们建议评估 PCA 或后循环累及(尤其是 5 岁以下儿童)，以确定卒中和认知障碍高风险患者。投 9/9 票。 ?In adult MMA patients, we suggest assessment of PCA or posterior circulation involvement to identify patients at risk of ischaemic or haemorrhagic stroke.投 9/9 票。
皮科 3 烟雾病血管病患者 RNF213 易感性变异型基因检测与无基因化验相比，是否能提高患者的不良预后风险? 循证推荐 ?There is continued uncertainty over the advantages and disadvantages of performing variant screening of RNF213 p.R4810K, due to the lack of specific comparative studies 以及数据的缺乏，这些数据大多来自欧洲患者。 证据质量:- 推荐强度:-	专家共识声明 ?在 MMA 患者中，无论种族，我们建议反对对 RNF213 p.R4810K 进行系统性变异筛查。投票 8/10。
PICO 4 In patients with moyamoya angiopathy, does antiplatelet therapy (any possible regimen) compared with no antiplatelet therapy reduce the risk of an unfavourable clinical outcome? 循证推荐 ?在 MMA 患者中，长期抗血小板疗法的益处和风险始终存在不确定性。证据质量很低 推荐强度:-	专家共识声明 ?在非出血性 MMA 患者中，我们建议使用长期抗血小板疗法，以减少栓塞性中风的风险，但不增加出血性中风的风险。投 9/9 票。
PICO 5 在烟雾病血管病患者中，血运重建手术与不手术相比是否降低了不良临床结局的风险? **循证推荐** *成人患者* ?在成人 MMA 出血性先露患者中，我们建议在出现脑血流动力学障碍和脉络膜络脉存在的情况下进行血运重建手术(仅针对直接 STA-MCA 分流术的证据)。证据质量:低⊕⊕ 推荐力度:弱为干预↑??在成人 MMA 患者的缺血性先露，有持续的不确定性的风险和好处，大脑血运重建。 证据质量:低可信度 推荐强度:- ?在成人无症状 MMA 患者中，对于脑血运重建的风险和益处存在持续的不确定性。 证据质量:低可信度 推荐强度:- *儿科病人* ?In paediatric patients, there is continuous uncertainty over the risks and benefits of cerebral revascularization.证据质量:低可信度 推荐强度:-	**专家共识声明** *成人患者* ?In adult MMA patients with ischaemic presentation, we suggest that revascularization surgery should be considered in case of clinical symptoms and/ or imaging markers of haemodynamic impairment.投 9/9 票。 ?In adult MMA asymptomatic patients, we suggest considering conservative treatment except in patients with both cerebral haemodynamic impairment and silent ischaemic lesions in the same cerebral region.投 9/9 票。 ?In symptomatic and asymptomatic adult MMA patients, we suggest that surgical revascularization is performed in a referral centre and by a neurosurgeon with significant experience in surgical revascularization techniques.投 9/9 票。*儿科病人* ?In paediatric MMA patients, we suggest revascularization surgery where there is evidence of ongoing ischaemic symptoms or cerebral haemodynamic impairment.投 9/9 票。 ?In paediatric MMA patients with recurrent TIA or recurrent ischaemic strokes, we suggest early revascularization surgery except in case of large territorial ischaemic lesion.投 9/9 票。 ?In paediatric MMA patients we suggest that surgical revascularization is performed in a referral centre and by neurosurgeons with significant experience in surgical revascularization techniques.投 9/9 票。

(续)

表 1。(续)

推荐信	专家共识声明
PICO 6 In patients with moyamoya angiopathy, does direct or combined revascularization techniques compared with indirect revascularization alone reduce the risk of an unfavourable clinical outcome? 循证推荐专家共识声明 *成人患者* ?In adult MMA patients with ischaemic presentation, there is continued uncertainty over the superiority of combined indirect strategies for reducing risk of stroke. 证据质量:非常低的⊕ 推荐强度:-	?In adult MMA patients, we suggest direct/combined revascularization instead of over indirect cerebral revascularization strategies. 儿科患者 ?In paediatric MMA patients, we suggest combined revascularization instead of 在技术上可能的情况下采取间接策略，以降低短期风险中风
儿科病人 ?In paediatric MMA patients, there is continuous uncertainty on the superiority of combined cerebral revascularization over indirect revascularization 证据质量:低可信度 推荐强度:-	
PICO 7 In patients with moyamoya angiopathy, does the discontinuation compared with the continuation of antiplatelet therapy during the revascularization procedure increase the risk of an unfavourable clinical outcome? 循证推荐专家共识声明 ?MMA 患者接受血运重建手术?对于 MMA 患者，我们建议，在继续分流术手术期间，抗血小板治疗作为单一疗法(阿司匹林)是否安全仍存在不确定性。然而，在围手术期抗血小板疗法。停药后，我们建议术后 1-7 天重新开始抗血小板疗法，证据质量:取决于术后计算机断层摄影扫描。投 9/9 票。 推荐强度:-	?In case of dual antiplatelet therapy (aspirin + clopidogrel or other antiplatelets), we suggest stopping clopidogrel, or the other second antiplatelet therapy, for 7 days before surgery.投 9/9 票。
PICO 8 In patients with MMA, does respecting a 6- or 12-week minimum time interval from an acute cerebrovascular event to revascularization surgery compared to earlier and/or immediate surgery reduce the risk of an unfavourable clinical outcome?循证推荐专家共识声明 对其好处一直存在不确定性。In patients with MMA, we suggest waiting 6–12 weeks from an acute cerebrovascular event before performing surgery for MMA patients, to reduce the risks of early or delayed surgery, due to the lack of specific comparative studies and to the heterogeneous population the rate of postoperative complications.投 9/9 票。 学习。?In patients with MMA, we suggest avoiding trigger factors such as dehydration, fever, and hyperventilation as well as hypotension when waiting for surgery.推荐票数:- 9/9。	?对于 MMA 患者，我们建议在儿童等待手术时，应平衡进一步卒中的风险。投 9/9 票。 ?In patients with MMA, we suggest that early surgery could be considered in paediatric patients especially those with recurrent TIAs, single or recurrent ischaemic strokes with rapid and complete clinical recovery.投 9/9 票。
PICO 9 In patients with moyamoya angiopathy both after surgery and in conservative patients, does long term follow-up neuroimaging assessment compared to no follow up assessment modify the clinical practice in term of medical or surgical treatment? 循证推荐 There is continuous uncertainty over the advantages and disadvantages of providing systematic follow up assessment, based on current evidence 证据质量:- 推荐强度:-	专家共识声明 ?In patients with MMA, we suggest that neuroimaging follow-up should not only be limited to post-operative evaluations of surgical efficacy but should include long-term follow-up to evaluate progression of angiopathy.投 9/9 票。 ?In patients with initially diagnosed unilateral MMA, neuroimaging assessments should be carried out for early detection of progression.投 9/9 票。 ?In conservatively managed patients with MMA (asymptomatic and symptomatic patients with or without haemodynamic impairment), neuroimaging assessments should be carried out.投 9/9 票。 ?In patients with MMA, the neuroimaging follow-up should include at least MRI- MRA and haemodynamic evaluation (MR perfusion, PET, SPECT).在有经验的人看来，经颅双工超声可能是有用的。投 9/9 票。 ?对于 MMA 患者，当怀疑有血管改变，需要做出治疗决定或非侵入性技术不能确定时，应优先进行 DSA。投 9/9 票。 ?后续评估的时间不能严格规定，而且应该因人而异。投 9/9 票。

结果

PICO 1: In patients with MMA, does haemodynamic assessment by (CT, MRI, SPECT, PET and ultrasound) compared with no haemodynamic assessment improve the identification of patients at higher risk of unfavourable outcome?

*对现有证据的分析。*The literature search identified no RCT and no comparative studies specifically evaluating the effectiveness of the assessment versus no assessment of haemodynamic status (by CT perfusion, MRI perfusion, PET, SPECT or Doppler sonography) in identifying patients at higher risk of unfavourable clinical outcome
(uco)。

*附加信息。*有关综合格斗自然过程的科学数据在东亚人中很少见，在高加索人中更少见，尤其是在欧洲人中。之前来自美国和德国的回顾性研究表明，首次卒中后 5 年内发生反复发作脑血管事件的风险为 80%-82%[53,54] 在一项对 49 名成人患者进行的前瞻性研究中，这一数值在 3.7 年的时间框架中仅为 10.2%，其中一半以上的患者在基线时患有中风。[55] 在许多回顾性研究中，灌注研究已被证明可识别 MMA 患者的血流动力学卒中风险。[56–61] Hervé 等前瞻性随访了 90 例经保守治疗的多民族烟雾病和 MMS 患者，为期 42.8 个月。[43] 在这些患者中，乙酰唑胺- 99mtc - hmpao - spect 评估的 CVR 损伤，以及东亚起源和 TIA 史，被确定为卒中的独立预测因素，卒中或无症状缺血性或出血性病变的年风险从 0.5%增加到 20%。[43] 其他回顾性数据表明，即使没有症状或血流动力学损害的影像学标记，脑灌注成像也可用于识别有卒中风险的患者，这些患者仅表现为头痛或分水岭以外的缺血性病变。[62–65]

Regarding asymptomatic MMA, natural history data are available from only few studies and biased by inconsistent definition of ‘asymptomatic’ and short follow up periods.[66] In a small cohort study of 40 East Asian asymptomatic patients, perfusion studies (Xenon CT, SPECT, PET) detected cerebral haemodynamic impairment in 40% of hemispheres but it was not related to disease progression in conservatively treated patients.[67] Another study on East Asian ‘asymptomatic’ subjects (defined as without ischae- mic event or cerebral lesion) found a significant association between TIA and decreased CVR ($p < 0.001$, log-rank test) on 99mTc-HMPAO-SPECT[66] 而 Yang 等人。[62] found a significant relationship between initial CVR decrease and disease progression ($p = 0.05$) in 42 asymptomatic MMD 平均随访时间为 37.3 个月。Disease progression was defined in this study as the occurrence of any neurological symptom or silent lesions on MRI or CVR worsening during the follow-up.

MMA 也是出血性中风的原因。In a cohort of 200 Caucasian European patients, 9.5% of the patients had an haemorrhagic presentation.[14] CVR decrease on SPECT was prospectively found to be an independent risk factor (HR 5.37, 95% CI 1.07–27.02) for subsequent haemorrhage in a supplementary analysis of the Japan Adult Moyamoya (JAM) trial.[61] In East Asia, bleeding risk recurrence was also found to be associated with decreased basal perfusion measured by 99mTc- HMPAO-SPECT.[68] 然而，由于 MMA 中的出血主要是由脆弱的侧支系统引起的，仅进行灌注研究并不总是可靠的预后指标

Regarding the impact of haemodynamic impairment on cognition, long-standing hypoperfusion in specific brain regions measured by SPECT was found to be associated with impairment of several cognitive domains ($p < 0.01$) in 53 Japanese patients.[71] Roder 等在欧洲高加索患者中发现，双性-厄瓜多尔认知综合征与在 H215OPET 和 ACZ 挑战中检测到的 CVR 损伤存在显著相关性。[72] 在主要的欧洲高加索患者中，症状检查表-90- r 评估的精神质在左(0.0124)MCA 区或右($p = 0.0145$) MCA 区观察到 PET 显像灌注不足的患者中显著更频繁。[73]

Numerous studies demonstrated improvement of perfusion assessments after bypass surgery for almost all methods of haemodynamic assessment including CT perfusion, Xenon CT, perfusion-weighted imaging (PWI), Acetazolamide-99mTc-HMPAO-SPECT and PET with ACZ challenge, both in East Asian and Caucasian patients.[57,58,74–77] Transcranial Doppler sonography with inhalation of hypercapnic normoxic gas to assess vasomotor reactivity is also known to reflect CVR, allowing pre- and postoperative haemodynamic assessment in MMA.[54,57,78]

Overall, based on current literature, it is not yet possible to identify the best haemodynamic evaluation technique for MMA risk stratification and each available perfusion imaging modality has its strengths and weakness.PET 使用 H215O，$^{15}o_2$ 或 $C^{15}o_2$ as tracers, seems to have greatest clinical utility as it allows quantitative assessment and could be used to evaluate oxygen extraction fraction (OEF), cerebral metabolic rate of oxygen (CMRO2) and CVR capacity.[79–81] 这种方法的常规和广泛应用受到硬件可用性、高成本和测量时间长的限制。SPECT using 99mTc-ECD, 99mTc-HMPAO and 123I-IMP as tracers is also considered as a reference standard technique to assess the regional CBF and the CVR capacity to CO_2 or acetazolamide challenge but this perfusion modality was found,

在一项研究中，它在检测受损 CVR 方面不如 PET 有效。[56] The other perfusion imaging modalities used in the management of MMD such as ASL, CT perfusion, PWI, resting-state fMRI, and transcranial doppler ultrasound are more available.Even where they have been compared to SPECT and PET, their predictive value regarding the clinical course of the disease have not yet been prospectively verified.[82–85]

循证推荐

In patients with MMA, there is continuing uncertainty over the advantages and disadvantages of performing haemodynamic assessment, due to the lack of specific comparative studies and to the heterogeneous populations (i.e. operated and not operated patients;评估所用的不同方法;等等)。证据质量:-
推荐强度:-

专家共识声明

对于所有 MMA 患者，我们建议在诊断检查期间进行血流动力学评估，以帮助决策。Collecting these data for further analysis may be useful in guiding future decisions in this rare disease.投 9/9 票。
对于无症状 MMA 患者，以及那些症状与血流动力学触发因素不明显相关的患者，应进行血流动力学评估，以确定有卒中风险的大脑半球。投 9/9 票。For patients with clear haemodynamic triggered TIAs or watershed stroke in one cerebral artery territory, perfusion studies should be considered to identify other haemodynamically compromised yet asymptomatic brain territories.投 9/9 票。
For all patients in whom cerebral perfusion will be performed, we suggest using those imaging methods most familiar and available depending on individual institutions.投 9/9 票。

PICO 2:在 MMA 患者中，与未进行评估相比，对后循环介入的评估是否能提高对不良预后高风险患者的识别?

*对现有证据的分析。*文献检索没有明确的比较研究来评估评估 MMA 患者后循环受累与未评估患者后循环受累的益处。

附加信息。 Although MMA is more often considered a disease of the anterior circulation, involvement of the posterior circulation, mainly posterior cerebral artery (PCA), has increasingly become a point of interest due to

它在脑血流动力学和临床结果方面的相关性。

后循环是 MMA 中一个重要的辅助通路，有助于补偿和供应流向前循环的血液。在本研究中，儿科和成人 MMA 分别讨论，以回顾已发表的关于后循环受累评估的数据，以及该特征对缺血性或出血性卒中结局的作用。根据预先定义的文献搜索，发现了六篇关于 PCA 在儿科人口中的参与的论文。[86–91]

在东亚的一组成人和儿科 MMA 患者中，PCA 的参与被发现对脑梗死有显著的预测作用。[90] 尤其是在较年轻的年龄组(<4 岁) PCA 的参与导致缺血性中风的高患病率。[89] Araki 等人。[86] 2021 年强调年龄(早发性烟雾病，年龄<5 岁)是早期卒中的独立风险因子。在这个年龄组中，经常观察到 PCA 累及的相关特征。

在一项主要针对欧洲儿科 MMA 队列的研究中，35%的病例存在 PCA。[88] Early age at symptom onset (<2 years of age) and PCA involvement was observed to be an important risk factor for a higher overall stroke burden with an unfavourable neurological and clinical outcome tested on the paediatric stroke outcome score and modified Rankin score (mRS).类似地，PCA 的参与也被证明是较差的非言语智商和处理速度的一个风险因子，在基线和术前通过一系列神经发育测试测量。[91] Additionally, long-term social outcome, that is testing for education and occupation history has also been shown to be unfavourable in patients with PCA involvement 10 years after revascularization surgery.[87]

出血性脑卒中在儿童中的发生率低于成人 MMA 患者(分别为 3%和 25%-60%)，但 PCA 的参与和脉络膜吻合的发育似乎是这些患者出血的主要原因。[92]

关于 PCA 参与成人人群的信息来自四篇论文。[44,60,93,94] Hishikawa 等。[44] compared long-term outcomes in adult patients with posterior circulation involvement versus those without, after cerebral revascularization.The prevalence of stroke presentation was significantly higher among patients with posterior circulation involvement than in patients without PCA involvement (67% vs 15%, p = 0.006).这些患者的 mRS 评分在术前和术后均显著升高。In another long-term (>5 years) follow up of MMA patients (62% adults) after combined direct and indirect surgery,[93] symptomatic disease progression affecting PCA occurred 0.5– 15 years after initial surgery (mean 5.4 ± 4.4 years) suggesting late disease progression and hence highlighting the need for longer follow up periods after bypass surgery.

In a retrospective analysis of 574 angiograms, PCA involvement was present in 30% of East Asian adult MMA patients with haemorrhage being the most common presentation.此外，与未接受 PCA 的患者相比，接受 PCA 的患者发生后循环梗死的风险明显更高。[94] Noh 等人。[60] evaluated 104 adult MMA patients with ischaemic stroke or TIA, followed up for a median 29 months.45 例患者行血管重建术。PCA stenosis (HR = 17.53, 95% CI 2.02–152.43) was identified as predictor of ischaemic stroke recurrence (1.6% in the first year and 11.8% in the fifth year) in non-surgically treated MMA patients, but not in the surgically treated MMA, suggesting a protective role of surgical revascularization.

此外，经发育脆弱的丘脑-穿支及脉络膜，前列腺癌的累及似乎是后出血的一个独立因子。[95] 此外，后路出血是 MMA 再出血的重要预测因素。[96] Funaki 等人。[97] JAM 试验对 75 例出血性脑半球患者的 75 例进行了补充分析，结果显示 24 例(32%)出血性脑半球存在 PCA，并在单变量和多变量分析中发现这一特征与后脑出血相关。In addition, the presence of choroidal anastomosis was associated with posterior haemorrhage, with a good topographical correspondence between bleeding points and the anatomical distribution of the choroidal arteries.

In addition to being an important risk variable for stroke and poor clinical outcome at baseline, involvement of PCA is also important while planning revascularization surgery.Park et al. showed PCA involvement to be an independent risk factor for peri- and postoperative stroke (within 15 days of surgery) in adult patients who additionally had preoperative stroke and TIAs.[98] Muraoka 等人的研究表明，对儿童也是如此。[99]

循证推荐

在 MMA 患者中，由于缺乏特效药比较研究以及对异质性人群(即手术患者和未手术患者)，基于现有证据进行 PCA 评估的利弊仍存在不确定性;评估所用的不同方法;等等)。证据质量:-
推荐强度:-

专家共识声明

在所有的儿科 MMA 患者中，我们建议评估 PCA 或后循环受累(特别是 **5** 岁以下儿童 **)**，以确定后循环受累率较高的患者，以确定有风险的患者中风和认知障碍的风险。投 **9/9** 票。

在成人 **MMA** 患者中，我们建议对 **PCA** 或缺血性或出血性卒中进行评估。投 **9/9** 票。

PICO 3:在 MMA 患者中进行 RNF213 易感性变异的遗传检测，与未进行遗传化验的患者相比，可提高对高危患者的识别不利的结果?

*对现有证据的分析。*文献检索未发现任何研究专门比较 RNF213 基因变异的基因化验和无基因化验，以提高对 UCO 高危患者的识别。

*附加信息。*MMD 与 17q25.3 位点的关联[100]尤其是在日本患者中，RNF213 基因(p.R4810K 或 p.R4859K)中有一个单一的错义突变。[101] 这种 p.R4810K (c.14576G>A)变异在 95.1%的家族性烟雾病病例和 79.2%的散发性烟雾病病例中被检测到，OR 为 259 (p < 0.001)。[101] The exact pathophysiological mechanism by which the RNF213 gene is involved in MMA pathogenesis remains unknown.However, p.R4810K has been found also in about 20% of intracranial major artery stenosis as well as in 0.4%–2% of Japanese controls.[102] 以前的作者发现这种变异的纯合子携带者更频繁地早期发病，以梗死为初始先露，并随着 PCA 的参与而改变。[101] 在另一项研究中，这些患者也更频繁地有家族性 MMA 病史、早发(<5 年)、诊断为脑梗死以及 1 年随访时出现认知障碍。[103] 虽然我们没有发现评估基因检测可能益处的比较研究，但现有研究没有显示 RNF213 杂合 p.R4810K 变异与任何结果之间的任何关联。特别是，虽然对 3 篇论文进行了评价，但没有纳入分析范围。Hara 等人的第一篇论文研究了 prr - 4810k 变异在 129 名日本儿童发病型烟雾病(发病年龄?15 岁)患者的回顾性研究中的作用。[104] 近 80%的患者存在纯合或杂合或 RNF213 p.R4810K 变异。The authors did not find any significant association between heterozygous p. R4810K genotype and clinical surgical and non-surgical outcomes, after 1-year follow-up.与野生型相比，具有纯合性和杂合性的 prr - 4810k 变异的患者有更多的良好的手术结果，但差异不显著(90.9% vs 92.2% vs 76.5%;*P = 0.166)*。另一项回顾性队列研究对 94 名日本 MMD 患者进行了直接或联合分流术血运重建，评估了 p.R4810K 基因型与 100 个月(30 - 219 个月)随访结果之间的关系。[105] 在 94 例烟雾病患者中有 69 例(73.4%)检测到 p.R4810K (c.14429G>A) RNF213 基因变异。纯合子(A/A)和杂合子变异(A/G)分别在 5 例和 64 例患者中被发现。作者没有观察到两者之间的差异

genotype regarding baseline features except for a slightly higher frequency of TIA in A/G compared to G/G patients.All patients underwent surgical revascularization.There weren't significant differences among these genotypes in terms of perioperative and follow up stroke occurrence or in the stroke survival rate and frequency of poor functional condition.Finally, Wang et al., evaluated retrospectively the genotype of 2545 Chinese MMD patients treated with surgical revascularization (median of follow-up duration: 32 months).Of these 627 (24.63%) patients were GA and 10 (0.39%) patients were AA p.R4810K genotype.They did not find, using multivariate Cox analysis, any association between p.R4810K variant and stroke or poor neurologic outcome at the last follow-up visit.

在西方 MMA 患者中，p.R4810K RNF213 变异不存在，[102] 但其他位于 E3 连接酶域的 RNF213 易感性变异与 MMA 有关。它们的外显率是未知的，并且缺乏这些变异对临床结果影响的证据。However, de novo RNF213 gene mutations located in the E3 ligase have recently been reported in several severe infant onset MA cases.[27–29,106] Liver, kidney and skin clinical manifestations are often associated with cerebrovascular manifestations in those infants leading to diagnosis delay and unneeded investigations.

循证推荐
在 MMA 患者中，由于缺乏特效药比较研究，且数据主要来自欧洲患者，因此对于进行 RNF213 p.R4810K 变异筛选的优缺点一直存在不确定性。
证据质量:-
推荐强度:-

专家共识声明
在 MMA 患者中，无论种族，我们建议反对对 RNF213 p.R4810K 进行系统性变异筛查。投票 8/10。

PICO 4: In patients with MMA, does antiplatelet therapy (any possible regimen) compared with no antiplatelet therapy reduce the risk of an unfavourable clinical outcome?

对现有证据的分析。 The literature search identified no RCT specifically analysing the effects of antiplatelet therapy compared with no antiplatelets.然而，我们发现观察性研究为该 PICO 提供了相关信息。

在 MMA 中，抗血小板通常用于两种情况:用于非手术的 MMA 患者，目的是减少缺血事件;用于手术治疗的患者，目的是减少围手术期的潜在风险

complications as well as ischaemic strokes in the long-term follow-up.然而，国际专家的不同调查显示，MMA 也可能表现为脑出血，这是开抗血小板药物的主要担忧之一。[107–109]

很少有研究评估接受抗血小板治疗的患者中风的风险。由于所提供的人群数据存在异质性，因此不可能对该结果进行 meta 分析(Pang 等人评估了个体大脑半球)。[110] Ye 等人对患者进行评估。[111])。The first study found no significant differences in the risk of cerebral infarction (2.3% in the antiplatelet group vs 2.3% in the conservative group) or haemorrhage (5.9% in the antiplatelet groups vs 7.8% in the conservative group) after a mean follow-up of 62 months.[110] On the other hand, Ye et al.[111] reported significantly fewer ischaemic strokes in the group of patients treated with anti- platelets (5.6%) as compared to conservative or surgical treatment (8.4%) after propensity score matching and an average follow-up period of 33 months.[111] Additional cohort studies have addressed the influence of antiplatelet agents on the risk of recurrent stroke.日本烟雾病研究委员会(Research Committee on Moyamoya Disease)的注册研究发现抗血小板对入选前 10 年内首次出现 TIA 或脑梗死的 344 名 MMD 患者的卒中复发率没有影响(2.9%/5 年 vs 1.6%/5 年)。[112] Interestingly, there were significantly more haemorrhagic stroke recurrences in the group of non-antiplatelet therapy (4.2%/5 years vs 0%/5 years).[112] On the other hand, the International Paediatric Stroke Study, in a retrospective analysis of an international multicentre registry which included a total of 174 children >28-days old with MMD (90% of them initially presented with ischaemic strokes), reported 20% of stroke recurrence over a median follow-up of 13 months, without any difference in antiplatelet therapy among those with or without a stroke recurrence.[113]

With regard to disability (defined by mRS > 2–5), Ye et al. found no significant differences in the group of patients treated with antiplatelet therapy as compared to conservative/ surgical groups (22.6% vs 26.4%) after a mean follow-up of 33 months.[111] The J-ASPECT study, in a propensity-matched analysis from a nationwide registry in Japan, concluded that pre-hospital antiplatelet use was significantly associated with good functional status (defined by mRS 0–1) on hospital admission of non-haemorrhagic MMA patients (OR adjusted for covariates 3.82;95%可信区间 1.22-11.99)。[114]

Finally, only two studies provided data related to the mortality outcomes in MMA patients treated with antiplatelet therapy compared to no antiplatelet therapy.[111,115] Ye et al. found a trend of higher frequency of deaths in the group treated with antiplatelets (3.77%) as compared to a group of conservative or surgically treated patients (0.94%) without antiplatelet after a mean follow-up period of 33 months.[111] Seo et al. in a larger and longer study, concluded that antiplatelet therapy was associated with a

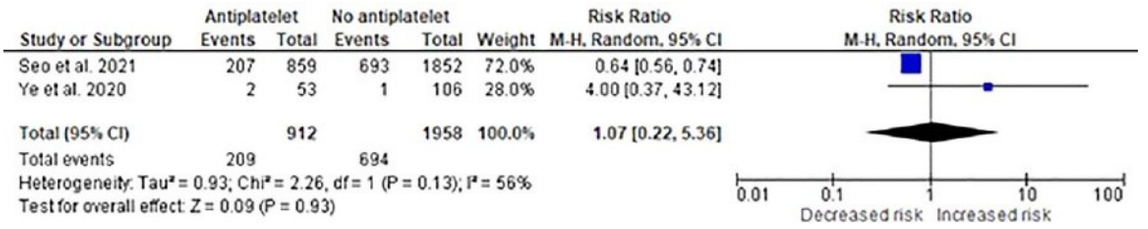

图 1。Meta-analysis (for PICO 4) showing the risk of mortality among antiplatelet users compared to non-users.

表 2。GRADE evidence profile for PICO 4, In patients with moyamoya angiopathy, does antiplatelet therapy (any possible regimen) compared with no antiplatelet therapy reduce the risk of an unfavourable clinical outcome?

确定性评估						没有。病人的情况		效果		重要性
没有。有研究	研究设计	风险偏压	不一致	间接	不精确	其他行程考虑	专业	安慰剂	相对的(95% ci)	绝对(95% ci)	
随访期间死亡											
2	观察研究	严重[a]	不严重	严重[b]	严肃[c]	没有	209/912 (22.9%)	694/1958 (35.4%)	rr 1.07 (0.22-5.36)	1000(从 276 少于 1000 人更多)	很低⨁◯◯◯ 每人多 25	重要

CI:置信区间;RR:相对风险。
[a]纳入的研究本质上是观察性的，有中度偏倚风险。[b]Variation in follow-up period.
[c]宽置信区间。
GRADE Working Group grades of evidence:
低确定性:真实的效果可能与估计的效果显著不同。

reduced risk of death in a multivariate model after a total follow-up of 163,347 person-years (HR 0.77;95% 可信区间 0.70- 0.84)。[115] However, our meta-analysis (Figure 1), including 2870 MMD patients, found no significant effect of antiplatelet therapy on the risk of mortality with a pooled relative risk of 1.07 (95% CI: 0.22–5.36).[111,115] 由于考虑到效应估计的偏倚风险、异质性和不精确性，本次评估中 GRADE 评估的确定性非常低(表 2;Figure 1 and Supplemental Materials-Table 4).

附加信息。在 MMA 的治疗策略中，必须平衡三种主要风险:血流动力学缺血事件、易碎烟雾血管出血风险和栓塞性中风。对于后者，有一些研究描述了使用经颅多普勒在 MMA 患者中发现微栓塞信号(MES)或高强度瞬态信号(HITS)，[116–118] 这可能代表了栓塞的风险。[119] One retrospective study in a small population of MMA observed a reduction of MES after antiplatelet administration or regimen change.[120] 直接栓塞甚至在 MMA 病人的手术过程中也被观察到。[121] Evaluating the type of antiplatelet drugs, the most commonly used agents in the studies included in this analysis were aspirin, clopidogrel or cilostazol as monotherapy, with only a minority of patients receiving dual antiplatelet therapy.[93,110,115] Since the literature search for this PICO question was focused on the comparison between antiplatelet versus no antiplatelet therapy, we did not retrieve any randomised clinical trial 以比较疗效为重点。一些观察性研究根据使用的抗血小板药物进行亚组分析，一些研究报告与药物效力相关的结果没有差异[110]而其他人则认为西洛他唑比其他抗血小板药物更能复位术死亡率。[115]

Only one of the studies included in this analysis specifically analysed the effect of antiplatelet therapy in a cohort of 5308 MMD patients initially presenting with cerebral haemorrhage, 4008 of them were treated with antiplatelet drugs.[115] Interestingly, the Cox regression analysis showed a reduced odds of long-term mortality in the cohort of patient with prior haemorrhagic stroke with the use of aspirin (0.49;95% CI 0.32-0.75)，西洛他唑(0.40;95% CI 0.30-0.53)或氯吡格雷(0.57;95% CI 0.46–0.71) as compared to no antiplatelet therapy.[115]

循证推荐

In patients with MMA there is continuing uncertainty over the benefits and risks of long-term antiplatelet therapy.证据质量:低可信度
推荐强度:-

专家共识声明

在非出血性 MMA 患者中，我们建议使用长期抗血小板疗法，以减少栓塞性中风的风险，但不增加出血性中风的风险。投 9/9 票。

PICO5: In patients with MMA, does revascularization surgery compared with no surgery reduce the risk of an unfavourable clinical outcome?

成人患者

*对现有证据的分析。*We identified one completed RCT, the JAM trial, addressing PICO 5 which compared direct revascularization with best medical treatment in adult MMD with haemorrhagic presentation.[122] It was a multicentre, randomised control, open label study (Table 3, GRADE profile and Table 4, risk of bias assessment).入选前 12 个月内有脑内、脑室内或蛛网膜下腔出血病史、年龄 16 - 65 岁、功能独立的成年患者。Patients with diastolic blood pressure >110 mm Hg or treated with extracranial-intracranial bypass surgery before enrolment were excluded.The JAM trial included 80 patients and randomly allocated participants to either conservative medical care or extracranial-intracranial direct bypass on both sides (each side to be performed within 3 months of inclusion).有意向治疗的人群包括手术组 42 例，保守组 38 例。There was one protocol violation in the surgical group with one patient receiving direct bypass on one side and indirect bypass on the other side.To increase the number of events and power, the primary outcome was a composite endpoint defined by recurrent bleeding, completed stroke causing significant morbidity, mortality or significant morbidity from other medical causes or requirement for extracranial- intracranial bypass for a nonsurgical patient.The primary composite endpoint occurred in 6 (14.3%) patients in the surgical group and 13 (34.2%) patients in the nonsurgical group during a mean follow-up period of 4.32 years (HR: 0.39 [95% CI, 0.15–1.03], p = 0.057).The log-rank test revealed that the surgical group was at significantly lower risk than the nonsurgical group for the primary end-point (3.2%/y vs 8.2%/y;*P = 0.048)*。这些结果的差异可能与本研究纳入的样本量较小有关。初始计算样本量(n = 160)，假设非手术组不良神经事件发病率为 8%/y，手术组为 4%/y(检测两组间的差异，显著性水平为 0.05)。由于符合条件的患者数量低于预期，最终将样本量设定为 80(基于手术组事件率<2.8%)。Perioperative complications were observed in eight patients (9.5%) and included hyperperfusion syndrome, TIA, seizure, scalp bedsore and tear of subcutaneous drainage tube.这些并发症除 1 例外均为暂时性的。This low rate of perioperative complications, including mainly transient events, may be related in part to the experience in extracranial- intracranial bypass in MMD of all centres participating in 这次试验并提出了在实地进行充分培训的重要性。

在缺血性先露患者中，我们的系统回顾没有发现关于血运重建手术的疗效和安全性的随机数据。在这一亚组患者中，只发现了五项具有可用于荟萃分析数据的比较观察性研究。[60,111,123–125] A reduction in any stroke was found in MMD adult patients with ischaemic onset who underwent revascularization surgery compared to conservative treatment with a pooled relative risk of 0.54 (95% CI: 0.28–1.01), p = 0.06) (Figure 2). However, it is important to consider that most of these studies were retrospective, conducted at a single centre, and lacked matched control groups.The indication for surgery was at the discretion of each surgeon and based on variable clinical or imaging parameters, explaining why demographic and clinical characteristics differed in all studies between surgical and conservative groups.此外，血运重建程序和保守治疗以及随访也不规范。这些事实强调了解释数据时需要考虑的证据水平(表 3，年级概况，补充材料-表 5)。

对于没有 TIA 或中风病史的烟雾病患者，我们对文献进行系统回顾，发现只有一项观察性比较研究，具有不同的成人数据集。其中保守治疗 36 例，间接血运重建 4 例。During a median follow-up of 32 months, no patient had a stroke and 3 conservatively treated patients had a TIA which was associated with decreased CVR on SPECT imaging.[66] 对于无症状的 MMD 患者，其自然史、临床和影像学上关于手术血运重建恶化和潜在益处的预测因素仍有待阐明。正在进行的日本爱的登记可能阐明长期预后的这一亚组患者 [126]

*附加信息。*Few predictive studies have been conducted prospectively on non-operated patients to identify subgroups of patients at higher risk of cerebrovascular complications to help decision making for surgical revascularization.Regarding patients with haemorrhagic presentation, an ancillary prospective cohort study of the JAM trial using 5-year follow-up data on 37 patients included in the non-surgical arm has suggested that choroidal anastomosis could be an independent predictor of rebleeding in haemorrhagic MMD[127] In this study, the incidence of rebleeding was significantly higher in the choroidal anastomosis-posi- tive group (13.1% /year) than in the negative group (0.3%/ year, p = 0.008).Moreover, in the positive group, the haematoma was located in the choroidal artery territory in 7 of 10 patients suggesting a causal association between the presence of choroidal anastomosis and the occurrence of rebleeding.Another supplementary analysis in the same

表3 。GRADE evidence profile for PICO 5, In adult patients with moyamoya angiopathy, does revascularization surgery compared with no surgery reduce the risk of an 不良的临床结果？

确定性评估影响确定重要性No	。研究设计偏倚风险不一	致性间接不精确性其他干预比较者相对(95%	绝对(95%
研究考虑因素			
复发性出血（出血性烟雾病人群）- HR	未调整分析		
5/42 (11.9%) 12/38 (31.6%) HR 0.36	每 CRITICAL(0.12-1.01) 1000	减少188（自271 Low	不严重
少到3个以上)⊕⊕◯◯			严肃的
任何中风（缺血性烟雾病人群）			
5 观察严重严重 64/611 (10.5%)47/344 (13.7%)RR 0.54	每减少63个		
研究(0.28-1.01)1000（从98⊕◯◯◯ 临界非常低			
由少到多）			
残疾（缺血性烟雾病人群）			
1 观察严重不严重不严重非常严重无7/53 (13.2%)19/106 (17.9%)RR 0.74	每		
研究(0.33-1.64)1000（来自120⊕◯◯◯ 临界非常低			
少于115			
更多）			

CI:置信区间;HR:风险比;烟雾病:烟雾病疾病;RR:相对风险。

a 由于评估人对分配不知情，所以存在很大的偏差风险。

b 未满足最低信息量(事件少，样本量低)，置信区间接触无影响线。

c 纳入的研究是观察性的，有中等至高的偏倚风险。

d 显著的异质性(I2 = 63%)。

e Variation in surgical methods (intervention) and in follow-up periods.

f 中度偏倚风险。

g 置信区间越过临床决策阈值，患者数量较少。

GRADE Working Group grades of evidence:

非常低的确定性:真实的效果可能与估计的效果明显不同。

低确定性:真实的效果可能与估计的效果显著不同。

表 4。PICO 5 随机对照试验的偏倚风险。

研究作者，结果年份	随机化过程产生的偏差	因偏离预期干预措施而产生的偏差	由于缺少结果数据而产生的偏差	偏倚中偏倚选择对所报道的结果结果进行总体偏倚测量	
宫本茂等人。复发 2014122 出血	+	+	+	X	!	X

+ 低风险 ! 一些担忧 X 高风险。

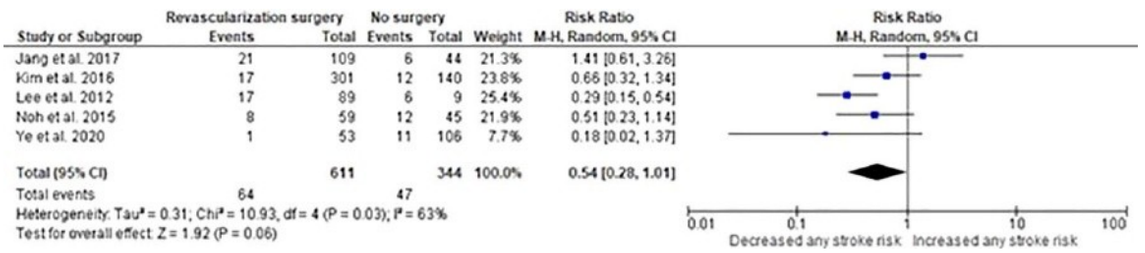

图 2。Meta-analysis (for PICO 5) showing the risk of any stroke in adult MMD patients with ischaemic presentation who underwent revascularization surgery compared to standard of care.

cohort, used SPECT imaging before (resting state) and after ACZ challenge to evaluate the impact of cortical haemodynamic failure on rebleeding.[61] 对包括脉络膜络的存在在内的几个潜在的混杂因素进行了多因素分析。Among 72 non-surgical hemispheres, 34 (47.2%) had no haemodynamic impairment and 38 (52.8) had a CVR decrease associated or not with a decrease of baseline blood flow.The presence of haemodynamic failure was found to be an independent predictor of rebleeding (HR 5.37, 95% CI 1.07–27.02). 脑血流动力学损伤的患者不仅可能有更大的再出血风险，而且对那些手术更有效的患者也是如此。Indeed, in the same study, whereas the occurrence of rebleeding was significantly reduced in the presence of CVR decrease in the surgical arm compared with the conservative arm (HR 0.15, 95% CI 0.04–0.57), there was no significant difference between the two arms in the absence of cerebral haemodynamic impairment (HR1.56, 95% CI 0.22–11.10).Regarding patients with ischaemic presentation, cerebral haemodynamic impairment seems also to be one of the major predictors of poor prognosis.A first prospective study failed to establish a significant association between the occurrence of stroke during follow-up and cerebral regional oxygen extraction fraction which presumably increases at the cerebral tissue level when autoregulation is exceeded.[55] However, the limited number of patients included in these studies, low event rate and large number of censored cases due to the decision to pursue revascularization surgery might explain these negative results. 最近的一项预测研究使用了一种全局方法，其中几个参数被测试为 potential predictors of clinical or cerebral tissue changes in 90 adult patients with MMD or MMS, including more than 60% of ischaemic presentation.[43] In this cohort, the detection of regional alterations in CVR (HR: 4.4, 95% CI 1.2– 16.1), a history of TIAs (HR: 4.18, 95% CI 1.37–12.75) and East Asian origin (HR: 2.63, CI 1–6.94) were independently associated with an increased risk of stroke or incidence of ischaemic or haemorrhagic lesions on MRI.The predictive value of cerebral haemodynamic status in ischae- mic MMD is reinforced by the low risk of stroke occurrence observed in a prospective cohort of ischaemic MMD adult patients without misery cerebral perfusion on PET imaging.[128,129] The incidence of further ischaemic events was only 6% per 5 years of follow-up in this population of patients having no cerebral area with abnormally elevated oxygen extraction fraction (OEF).

有关手术并发症预测因素的资料较少。A grading system has been proposed to stratify the individual risk of perioperative complications in adult MMD.[130] 该量表基于以下三个成像关键参数:1/ the degree of steno-occlusive lesions and the development of intracranial and extracranial collaterals on conventional angiography (1–3 points), 2/ the absence or presence of ischaemic or haemorrhagic lesion on MRI (0 or 1 point) and 3/ the CVR capacity (>−5% = 0 point, <−5% = 2 points).MMD，一级为 1-2 分，二级为 3-4 分，三级为 5-6 分。This grading system was first evaluated in 37 MMD patients treated by a bilateral and one-staged revascularization approach.[74] 根据该分级系统对烟雾病的分化与烟雾病的发生有关

术后脑缺血事件(I 级:0%，II 级:9%，III 级:16%，$p < 0.05$)。The predictive value of this grading system has been replicated in an independent Japanese dataset of 89 adult patients treated by unilateral combined revascularization strategy.[131] 14.6%的手术半球发生了围手术期缺血性和出血并发症，分级与它们的发生相关($p < 0.001$)。

循证推荐

In adult MMA patients with haemorrhagic presentation, we recommend revascularization surgery (evidence only for direct STA-MCA bypass) in case of cerebral haemodynamic impairment and presence of choroidal collaterals.证据质量:低⊕⊕
推荐力度:弱为干预↑?在成人 MMA 患者的缺血性先露中，对于大脑血运重建的风险和益处仍存在不确定性。
证据质量:低可信度
推荐强度:-
在成人无症状 MMA 患者中，对于脑血运重建的风险和益处仍存在不确定性。
证据质量:低可信度
推荐强度:-

专家共识声明

对于成人 MMA 患者的缺血性先露，我们建议在出现临床症状和/或血流动力学障碍的影像学标记时，应考虑血运重建手术。投 9/9 票。
在成人无症状 MMA 患者中，我们建议考虑保守治疗，但在同一大脑部同时存在脑血流动力学损害和静止性缺血损伤的患者除外。投 9/9 票。
对于有症状和无症状的成人 MMA 患者，我们建议在转诊中心由具有丰富外科血运重建技术经验的神经外科医生进行外科血运重建。投 9/9 票。

儿科病人

*对现有证据的分析。*我们对 MMA 患儿进行了系统回顾，没有发现 RCT，只有一项观察性研究，对这些指南中选择的结果进行了手术治疗和保守治疗的比较。在这项回顾性多中心研究中，282 名儿科患者被回顾性分析。[132] Among them, 214 patients underwent surgical revascularization (direct bypass, combined bypass or indirect bypass) and 68 were treated conservatively.During a mean follow-up period of 41 (9–145) months, a significant reduction in any stroke was found in MMD paediatric patients who underwent r -血管化手术(2.8%)与保守治疗(13.2%)相比，相对风险为 0.21 (95% CI:0.08–0.57) (Table 5, GRADE profile, Supplemental Materials-Table 5). In addition, at the end of the follow-up period, a significant reduction in disability was found in patients who underwent revascularization surgery (2.8%) compared to conservative treatment (20.6%), with a relative risk of 0.14 (95% CI: 0.05–0.34).

*附加信息。*One historical comparative study of children with MMD compared outcomes in terms of activities of daily living (ADL) (1–5 grades) of a total of 88 MMA patients (48 paediatric) with and without surgery at a follow-up period of 6–86.4 months.In the 33 patients with surgery, ADL improved in 61% versus only 26% in the non-surgical group.This improvement was more prominent in the paediatric group.[133] These results reflect the particularly severe natural course of the disease in children compared with adults resulting in an increased burden of stroke and long-term disability.Recent single centre studies with 100 and 73 paediatric MMA patients respectively and a multicentre study of 63 MMA patients, all of mainly European ethnicity, confirmed the high risk of progression with recurrent strokes in MMA children and more so in the younger age groups as well as in those showing PCA involvement.[88,134,135] 在一份关于东亚儿科烟雾病患者的较早的出版物中，Kim 等人重申了这种侵略性的临床病程[136] In a recent follow-up study of 415 paediatric MMD patients, the same authors showed a favourable clinical outcome in 81% of the patients about 3 years after revascularization surgery.Good results of surgical revascularization in paediatric MMA on short- and long-term prognosis has been shown in several other studies to date.[137,138]

循证推荐

在儿科 MMA 患者中，对于大脑血运重建的风险和益处仍存在不确定性。证据质量:低可信度
推荐强度:-

专家共识声明

在儿科 MMA 患者中，我们建议在有持续缺血症状或脑血流动力学障碍的证据的情况下进行血运重建手术。投 9/9 票。对于患有反复发作 TIA 或反复发作缺血性中风的儿科 MMA 患者，我们建议尽早进行血运重建手术，除非出现大面积的区域性缺血性损伤。投 9/9 票。在儿科 MMA 患者中，我们建议外科血运重建在转诊中心进行，并由在外科血运重建技术方面具有丰富经验的神经外科医生进行。投 9/9 票。

表 5。PICO 5 在患有烟雾病血管病的儿科患者中的分级证据分析，血运重建手术与不手术相比是否降低了不良临床结果的风险?
确定性评估影响确定重要性 No。研究设计偏倚风险不一致性间接不精确性其他干预比较者相对绝对

研究考虑事项									
任何中风(儿科烟雾病患者)									
1 观察严重不严重不严重非常严重 b 无 6/214 (2.8%)9/68 (13.2%)RR 0.21(0.08-0.57)每关键研究减少 105 项 1000 非常低									(从 122 个减少?○○○ 减少到 57 人)
残疾(儿童烟雾病患者)									
1 观察严重不严重不严重非常严重 b 无 6/214 (2.8%)14/68 (20.6%)RR 0.14(0.05-0.34)每关键研究减少 117(0.05-0.34)1000 非常低									(少于 196 个?○○○ 少 136 人)

CI:置信区间;烟雾病:烟雾病疾病;RR:相对风险。

a Risk of bias was judged at high risk because of missing outcome data during follow-up.

b Less number of patients and follow-up variation.

n in the intervention and control arm.

GRADE Working Group grades of evidence:
非常低的确定性:真实的效果可能与估计的效果明显不同。

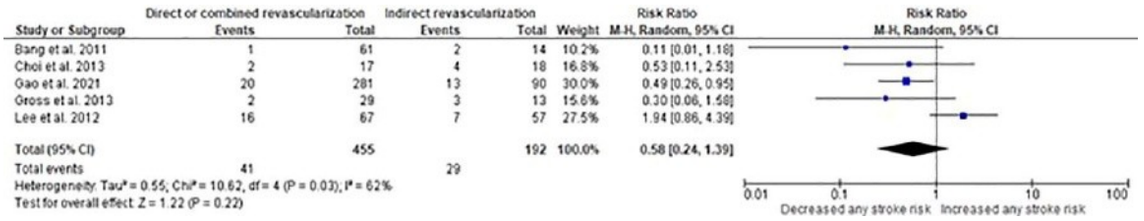

图 3。 Meta-analysis (for PICO 6) showing the risk of any stroke in adult MMD patients who underwent direct or combined revascularization surgery compared to indirect revascularization surgery.

PICO6 In patients with MMA, does direct or combined revascularization techniques compared with indirect revascularization alone reduce the risk of an unfavourable clinical outcome?

In surgical practice, three different revascularization strategies are applied: indirect, direct, and combined revascularization.对于烟雾病患者，间接治疗和联合治疗是最常用的治疗策略。Currently, there is still no consensus about the best type of revascularization surgery.To answer this question, we first analysed the overall data on indirect versus direct revascularization strategies.In a second step, we differentiated the adult population from the paediatric population as the key factor affecting the benefit-risk balance, that is the efficacy of indirect revascularization, differs in these two situations.儿童的特点可能是其脑血管系统具有较高的可塑性和血管生成活性。In contrast, in adults the cerebrovascular system displays a reduced angiogenic activity as a function of age.Thus, indirect techniques may result in better vessel growth rates in the paediatric population, providing better results than in adults.值得注意的是，在我们的分析中，我们没有区分文献中描述的不同间接技术。

成人患者

*对现有证据的分析。*Our analysis identified no RCT and 7 observational study on adults with MMA, comparing combined with indirect revascularization strategies for the outcomes selected in these guidelines.在 7 项研究中，有 5 项 [125,139–142] 有任何中风报告和三项研究 [125,143,144] assessed disability as outcome parameter.

Bang 等人，[139] reported 65 patients with MMA undergoing either indirect or combined revascularization.The authors used combined STA-MCA bypass with a variety of indirect techniques encephalo-myo-synangiosis (EMS), encephalo-duro-arterio-synangiosis (EDAS), enceph- alo-duro-arterio-myo-synangiosis (EDAMS).The mean age was 35.0 ± 12.4 years (range: 16–65 years), thus, only including adult patients.Mean follow-up time was 63.8 ± 29.7 months (range: 18–139 months).This study supported a trend for superiority of the combined technique over the indirect technique in preventing any form of stroke (2% vs 14%, RR 0.11 [95% CI: 0.01-1.18]).Choi 等人报道了一个较小的患者队列。[140] 这里有 17 个病人 18 例患者行间接分流术移植术。Again, only adult patients were studied with a mean age of 43.6 ± 8.5 years.平均随访时间为 54.4±23.8 个月。The stroke incidence for the combined revascularization group was 12%, while 22% suffered stroke following indirect bypass alone (RR 0.53 [95% CI: 0.11-2.53]).Gao 等人最近发表了一项规模最大的研究。[141] Here, 281 patients underwent combined/ direct revascularization strategies and 90 patients received an indirect bypass.Only adult patients were reported with a mean age of 39.0 ± 11.1 years.The mean follow-up time accounted to 41.5 ± 23.0 months, with a wide range of 6.1– 83.4 months.This study demonstrated superiority of the combined/direct approach over indirect revascularization strategies with an OR of 0.49 (stroke events in 7% and 14%, respectively, during the observation period).第四项研究 [142] is characterised by a heterogenous patient cohort and included patients with typical MMD as well as patients with atypical unilateral MMA and MMS.The study focussed on adult patients with a mean age of 39.2 ± 12.2 years.患者的观察时间平均为 2.7 年。两组的样本量均较小，29 例接受联合干预，13 例接受间接分流术。尽管存在这种异质性，但本研究支持联合技术优于间接技术的趋势(7% vs 23%;Rr 0.30[95%可信区间:0.06- 1.58])。与这四项研究相比，第五项研究更倾向于联合使用技术而不是间接使用技术 [125] 发现间接技术有更好的效果。在这里，共有 124 名患者被报道，67 名接受联合血运重建策略，57 名接受间接血运重建策略。与其他研究相似，本研究仅纳入成人患者(平均年龄 43.1±10 岁)，平均观察时间为 55±19.2 个月。联合分流术组包括标准的 STA- mca 分流术和颅内 duro-galeo(骨膜)-synangiosis (EDAGS)，使用 STA-galeal 皮瓣和 STA-galeal 蒂，后者是一种不太常见的间接策略。在间接组中，采用了不同的策略，包括 EDAS、EMS 和 EDAGS，使得两组的间接策略难以比较。联合分流术治疗组卒中发病率为 24%，间接治疗组仅为 12% (RR 1.94[0.86-4.39])。我们对这五项研究的荟萃分析(图 3)显示，在接受 MMD 治疗的患者中，发生任何卒中的风险没有显著复位术

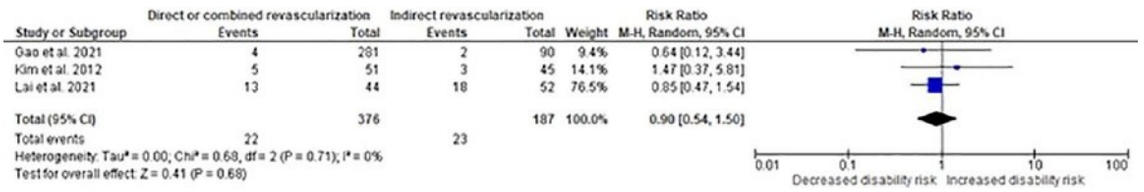

图 4。 Meta-analysis (for PICO 6) showing disability risk in adult MMD patients who underwent direct or combined revascularization surgery compared to indirect revascularization surgery.

direct or combined revascularization surgery compared to indirect revascularization surgery [RR 0.58 (95% CI: 0.24– 1.39)].由于考虑到效应估计的偏倚风险、实质性异质性和有限的精度，本次评估中 GRADE 评估的确定性非常低(表 6,GRADE 剖面图，图 3，补充材料-表 6)。

The three studies focussing on disability as primary outcome (mRS > 2–5) failed to reveal a clear superiority of any of the bypass strategies.这很可能是因为一个不利的，围手术期或术后过程导致残疾是非常罕见的幸运事件。Gao 等人。[141] 也研究了他们的 371 名患者的残疾。因此，在 281 例接受联合血运重建的患者中，仅有 1%的患者有致残的结果，而在 90 例接受间接血运重建的患者中，仅有 2%的患者有致残的结果。Kim 等人的研究。[143] focused only on outcome as measured by the mRS. Fifty-one patients were treated with a combined and 45 patients with an indirect bypass.所有患者均为成年人，平均年龄 38 岁 (18-68 岁) 。 The follow-up period only covered the perioperative period up to 6 weeks following surgery, rather reflecting the risk and complications of the bypass strategies.在术后早期，联合组的 10%和间接组的 7%被归类为残疾(RR 1.47[0.37-5.81])。然而，由于随访时间短以及一些患者在手术前已经因中风而致残的偏见，这些数据必须仔细解释。Lai 等人。[144] 相比之下，上患者至少 6 个月，这仍然是相对较短的时间。其中包括 96 名患者，44 名采用联合治疗，52 名采用间接血运重建治疗。患者均为成年人，平均年龄 42±11 岁(18-69 岁)。在本研究中，两组患者的残疾相当，但令人惊讶的是，两组患者的致残率分别为 30%和 35% (RR 0.85([0.47-1.54])。对这三项研究的共同分析受到了残疾患者随访时间和频率的巨大异质性的阻碍。荟萃分析结果(图 4)显示，直接或联合血运重建手术与间接血运重建手术在降低烟雾病患者残疾风险方面无显著相关性(p = 0.68)。由于汇总评估中存在低至中度的偏倚风险、异质性和不精确性，GRADE 评估的确定性较低(表 6,GRADE 剖面图，补充材料-表 6)。

*附加信息。*Indirect revascularization relies on neovascularization of the cortical surface via angiogenic mechanisms from pedicle-based grafts.用于血管移植的技术和组织的变异性是巨大的。Several variations of indirect revascularization have been developed: EMS, encephalo-arterio-synangiosis (EAS), encephalo-myo-arterio-synangiosis (EMAS), enceph- alo-duro-synangiosis (EDS), EDAS, EDAMS, EDAGS, as well as various combinations of these.间接技术的种类很多，如果有的话，哪一种技术优于其他技术仍然是未知的。一般来说，间接技术较容易实施，因为他们不包括直接吻合。Moreover, cerebral revascularization, along with the haemodynamic protection of the brain, may take months to develop.

All studies agree that the perioperative complication rates do not differ between direct/combined versus indirect revascularization techniques: Kim et al.[143,145] 确认包括直接干预的程序在卒中、不可逆/短暂性神经系统缺血缺陷、出血、皮肤坏死和感染方面没有更大的风险。邓等人。[146] comparing direct versus indirect revascularization among adults, also did not detect any significant increase in perioperative complications by direct revascularization techniques.Furthermore, another meta-analysis that focused on perioperative complications in adults demonstrated that despite a higher incidence of haemorrhagic complications in the direct bypass group, direct and combined revascularization techniques were superior in providing long-term favourable outcome.[147] Here, the beneficial effects of combined revascularization techniques (via the direct bypass component) outweighed the higher complication rate.

循证推荐

In adult MMA patients with ischaemic presentation, there is continuing uncertainty over the superiority of direct/ combined over indirect cerebral revascularization strategies.证据质量:低可信度
推荐强度:-

专家共识声明

In adult MMA patients, we suggest direct/combined revascularization instead of indirect strategies for reducing risk of stroke.投 9/9 票。

表 6。 GRADE evidence profile for PICO 6, In adult patients with moyamoya angiopathy, does direct or combined revascularization techniques versus Indirect revascularization alone reduce the risk of an unfavourable clinical outcome?
确定性评估影响确定重要性 No。研究设计偏倚风险不一致性间接不精确性其他干预比较者相对绝对

研究考虑事项
任何中风(成年烟雾病患者)

5 观察性严重 a 严重 b 不严重严重 c 不严重 41/455 (9.0%)29/192 (15.1%)RR 0.58(0.24-1.39)减少 63 / 1000 个关键研究(从减少 115 个到非常低)

59 more⨁●●●

残疾(成年烟雾病患者)
3 观察严重不严重严重无 22/376 (5.9%)23/187 (12.3%)RR 0.90(0.54-1.50)减少 12 / 1000 个关键研究(从 57 个减少到非常低)

61)⨁●●●

CI:置信区间;烟雾病:烟雾病疾病;RR:相对风险。

a 纳入的研究是观察性的，有低至中等偏倚风险。
b 异质性显著(I2 = 62%)。
c 置信区间宽。
d 低至中度偏倚风险。
e Variation in follow-up and in intervention types.
GRADE Working Group grades of evidence:
非常低的确定性:真实的效果可能与估计的效果明显不同。
低确定性:真实的效果可能与估计的效果显著不同。

儿科病人

对现有证据的分析。 Our systematic review identified no RCT and only two observational studies on children with MMA, comparing combined revascularization and indirect revascularization strategies for the outcomes selected in these guidelines.石川等。[38] 分析了 64 名平均年龄为 7.6±3.6 岁的儿科患者。因此，很大一部分患者年龄在 5 岁以下。In 48 patients, the authors succeeded to realise an STA-MCA anastomosis in combination with an EDAGS.In 16, they failed to do so and ended up with an indirect revascularization strategy only, using EDAGS again.The incidence of stroke during the observation period of 6.6 ± 3.8 years was remarkably low for both groups, that is 0% in both groups, which is markedly lower than observed for adults.类似地，Sadashiva 等人。[148] reported their series of 108 paediatric MMA patients undergoing combined (58 patients) or indirect (50 patients) revascularization strategies.值得注意的是，他们的患者队列年龄较大，平均年龄为 13.8 岁。During the mean follow-up period of 15.9 months (3–62 months), again only a limited number of patients experienced stroke after revascularization.Following combined revascularization, the stroke incidence was 5% and following indirect revascularization, only 2%.Taken together, these results suggest that the superiority of combined revascularization strategies over indirect techniques is not obvious in the paediatric population.

附加信息。 A high level of plasticity and angiogenic potential of the brain tissue and vasculature are required for the success of indirect revascularization techniques.The cerebrovascular plasticity in patients with MMD seems to be age dependent, with indirect revascularization procedures showing a higher success rate in children compared with adults.[130,149] On the other hand, direct revascularization strategies carry relevant advantages over indirect techniques.[145] Thus, they provide an immediate increase of cerebral blood flow and improvement of CVR capacity while indirect techniques depend on an ingrowth of collateral blood vessel into the brain pial surface and provide a delayed increase of cerebral blood flow and improvement of CVR capacity only.Even in children, this delay may last up to 3–6 months leaving especially haemodynamically unstable children unprotected for several weeks or months and exposing them to an increased short-term risk for stroke.In addition, the surgical approach for a direct revascularization strategy is less invasive since indirect techniques depend on a large exposure of the brain surface for covering the cortex with the pedicle graft.

循证推荐

In paediatric MMA patients, there is continuing uncertainty on the superiority of combined cerebral revascularization over indirect revascularization
证据质量:低可信度
推荐强度:-

专家共识声明

In paediatric MMA patients, we suggest combined revascularization instead of indirect strategies whenever technically possible, to decrease short term risk of stroke.投 9/9 票。

PICO 7: In patients with MMA, does discontinuation compared with continuation of antiplatelet therapy during the revascularization procedure increase the risk of an unfavourable clinical outcome?

对现有证据的分析。 The literature search did not identify any RCT or prospective comparative studies specifically analysing the effects of continuation versus no continuation of antiplatelet therapy during the revascularization procedure.

附加信息。 It has been reported that MMA patients are more prone to develop acute thrombogenesis at the anastomotic site just after extracranial-to-intracranial bypass surgery, as compared to similar neurosurgical procedures in non-MMA patients.[150] Symptomatic or asymptomatic cerebral infarction may occur in up to 14% of MMA patients treated with indirect revascularization surgery, half of them within the first day after surgery.[151] 尽管有这些发现，抗血小板在围手术期的作用以及术前是否保留或继续使用仍有待阐明。[107,109]

In a large retrospective analysis of the factors associated with perioperative complications, Schubert et al. reported that preoperative single antiplatelet therapy was not associated with increased haemorrhagic complications, 术后单次抗血小板治疗与出院时预后改善相关(定义为无任何新的神经功能缺损)。[152] 然而，作者并没有特别分析手术时停用抗血小板的患者的结果。Kanamori 等人对接受或不接受阿司匹林的 74 例手术进行了评估，其中 52 例患者曾接受过阿司匹林治疗。[153] They found a significantly lower rate of white thrombus at the anastomosis site and a higher initial bypass patency in patients treated with aspirin, without differences in the rate of ischaemic or haemorrhagic complications.然而，作者们并没有这样做

分别报告 20 例继续服用阿司匹林，26 例 3 天前停止服用阿司匹林，6 例手术当天停止服用阿司匹林的结果。[153]

Two retrospective studies have specifically addressed the effects and safety of aspirin administered postoperatively but results regarding the effect of aspirin on bypass patency were conflicting.Zhao et al. reported no significant differences in bypass patency (95.5% vs 96.1%) after an unadjusted analysis in patients postoperatively treated with aspirin (59 hemispheres) versus no aspirin (138 hemispheres).[154] Lu et al. reported in a retrospective study on 217 patients with ischae- mic-onset MMA undergoing STA-MCA bypass that the continuation of aspirin within the first month after surgery was associated with a higher bypass patency rate (98.7% vs 89.7%;Hr 1.57;95% 可信区间 1.106 ~ 2.235;*P = 0.012)*。[155] None of these two studies found significant differences in the incidence of ischaemic or haemorrhagic events between aspirin users and non-users.However, other factors potentially influencing thrombus formation and bypass patency such as duration of neurosurgical procedure were not analysed systematically.

In patients who discontinue antiplatelet therapy 7 days before the revascularization surgery, there is uncertainty about the timing for restarting it, with both early (day 1–3) or late (day 4–7) timing possibilities described.[156] In a retrospective study, Kraemer et al. analysed the safety of early (day 1–3) or late (day 4–7) restarts of antiplatelet therapy showing no difference in the incidence of subdural haematoma.[156] Bypass patency was 100% at day 4 as well as after 3 months despite paused antiplatelet therapy in the majority of the cohort.[156] However, small silent ischaemic lesions were found on MRI at 6 days post-surgical follow-up in 10.9% of patients, 86% of whom were older than 40 years old.

For Japanese experts, discontinuation of antiplatelets after bypass surgery ‘for a certain period’ of time is a common behaviour[108] reflecting different opinions between East Asian and non-Asian experts as it was emphasised by a worldwide survey of experts on the use of antiplatelet therapy in MMA.[107]

循证推荐

In patients with MMA treated with revascularization surgery, there is continuing uncertainty over the benefits and risks of perioperative antiplatelet therapy.
证据质量:-
推荐强度:-

专家共识声明

For patients with MMA, we suggest that, during bypass surgery continuation of antiplatelet treatment as monotherapy (aspirin) is safe.However, in case of discontinuation, we suggest restarting antiplatelet therapy 1–7 days after surgery, depending on the post-surgery CT scan.投 9/9 票
In case of dual antiplatelet therapy (aspirin+clopidogrel or other antiplatelets), we suggest stopping clopidogrel, or the other second antiplatelet therapy, for 7days before surgery.投 9/9 票。

PICO8: In patients with MMA, does respecting a 6- or 12-week minimum time interval from an acute cerebrovascular event to revascularization surgery compared to earlier and/or immediate surgery reduce the risk of an unfavourable clinical outcome?

*对现有证据的分析。*The literature search did not find any RCT or prospective comparative study specifically analysing the effects of respecting a 6- or 12-week minimum time interval (from an acute cerebrovascular event to revascularization surgery) in comparison to early surgery.

*附加信息。*MMA 患者在最后一次脑血管事件后手术血运重建的时机仍有争议。虽然早期手术可能对缺血性 MMA 有理想的益处，但卒中后早期手术的患者术后并发症的发生率可能更高，这与以下因素有关:(1)颅内出血或无颅内出血的高灌注综合征，[157–160] (2)与急性缺血性卒中相关的出血转化风险，(3)术后早期更显著的血流动力学不稳定有进一步缺血性事件的风险，[161] (4)系统性并发症风险较高，尤其是在卒中后存在显著神经功能缺损的情况下。[162] 此外，对于什么可以被认为是“早”或“晚”的定义，以及在最后一次脑血管事件和手术时间之间所需的延迟，还缺乏共识。

我们的系统综述仅发现了两篇分别考虑 90 天和 6 周时间间隔的出版物。[163,164] 首先是一项回顾性病例对照，对 57 例接受标准颞浅动脉-大脑中动脉(STA- MCA)分流术联合 EDAMS 治疗的 MMA 患者进行了评估。[163] 将患者分为早期(<90 天，n = 28)和晚期(≥90 天，n = 29)两组。与晚期组相比，早期组的初始缺血表现明显更频繁(43% vs 17%;*p = 0.035), while haemorrhagic presentation was more frequent in the late group (62% vs 36%;P = 0.047)*。尽管病例数较少，但作者的结论是，他们的数据支持后期的血运重建策略，因为早期组的术后并发症发生率明显高于晚期组(39.3% vs 13.8%， p = 0.029)。然而，与早期组相比，晚期组患者出现第二次中风或临床恶化的风险没有显著升高(31% vs 11%， p = 0.06)。这项研究的结果没有根据先露(出血性或缺血性)和年龄进行调整。In the latter study, Kim et al. performed a retrospective analysis of 170 indirect revascularization procedures in 90 children with ischaemic MMD and investigated several potential risk factors for ischaemic complications during the 2 weeks following surgery.[164] 延迟

在最后一次缺血事件和手术之间的 6 周内发现与术后缺血性并发症相关。然而，这种关联在多变量分析中不再出现。

循证推荐

在 MMA 患者中，由于缺乏特效药比较研究和异质人群研究，早期或延迟手术的益处和风险仍然存在不确定性。
证据质量:-
推荐强度:-

专家共识声明

对于 MMA 患者，我们建议 MMA 患者在发生急性脑血管事件 6-12 周后再进行手术，以降低术后并发症的发生率。投 9/9 票。
对于 MMA 患者，我们建议在等待手术时避免触发因素，如脱水、发热、换气过度以及低血压。投 9/9 票。对于 MMA 患者，我们建议在儿童等待手术时，应平衡进一步卒中的风险。投 9/9 票。
在 MMA 患者中，我们建议儿科患者，尤其是反复发作 tia、单次或反复发作缺血性中风且数、完全临床康复的患者，可以考虑早期手术治疗。投 9/9 票。

PICO 9: In patients with MMA, both after surgery and with conservative management, does long-term follow-up neuroimaging assessment compared to no follow up assessment modify the clinical practice in term of medical or surgical treatment?

*对现有证据的分析。*The literature search identified no RCT or prospective comparative studies specifically examining whether long-term follow-up with neuroimaging assessment modifies medical or surgical treatment.

*附加信息。*我们的系统回顾确定了几个研究，这些研究跟踪了患有偏血管病的 MMA 患者，[165–167] 无症状的最初先露，[67] 或无脑缺血灌注的初始先露。[168] Patients undergoing cerebral revascularization are usually followed for evaluation of surgical efficacy, yet few long-term studies were also available for review.93,169

Regarding patients with unilateral disease, while information on the incidence of progression of unilateral MMD varies in literature to date, Park et al. in 2011 showed a 59% rate of bilateral progression (on MRI-MRA or angiography) in an East Asian paediatric MMD cohort (n = 40/259) where a younger age (age <8 years, FU:14.18 months and age >8, FU: 22.38 months) at first diagnosis demonstrated a faster rate of progression.[167] In Smith and Scott, mainly Caucasian cohort, 30% of unilateral paediatric MMA patients also showed angiographic progression over an average time of 2.2 years.[170] In a cohort of mainly adult Caucasians,[165] angiographic progression from unilateral to bilateral disease was seen in 38.9% of patients at a mean follow-up of 12.7 months, 71% of these patients had adult onset MMA with 57% of patients thereafter undergoing surgical intervention.In another study of adult and mainly East Asian operated and non-operated MMD patients, the incidence of disease progression was 20% over a mean follow-up time of 73.6 months.[171] 这种进展可在单侧和双侧烟雾病中看到，也可在前后循环中看到。在这些患者中，50%以上的疾病进展与临床事件相关，即缺血性或出血性卒中。总之，这些观察性的单臂研究显示，对偏血管病患者的神经成像评估对其进展的早期发现和治疗至关重要。虽然这在儿科人群中更为常见和数，但在成人患者中也可观察到。Female sex and presence of angiographic changes on the contralateral side seem to be predictive indicators of progression.几乎总是进行 MRI-MRA 检查，然后通过血管造影术证实病情进展。

A multicentre, nation-wide Japanese prospective survey followed-up asymptomatic MMA patients (age range 13– 59 years) over an average time of 44 months and found cerebrovascular episodes including TIAs in 21% of patients and an annual risk of ischaemic or haemorrhagic stroke of 3.2%.The angiographical stage of disease was also more advanced with age.Onset of ischaemic symptoms and deterioration of CVR also related to angiographic disease progression.[67] Similar findings were observed in a prospectively analysed cohort of East Asian MMA patients where the incidence of angiographic disease progression was 12% for 5 years in medically treated adult MMD patients with initial ischaemic symptoms but without cortical ischaemic lesion on MRI nor cerebral misery perfusion.[168] Patients with further ischaemic events always exhibited angiographic disease progression.Cerebral perfusion was reduced in patients with angiographic disease progression even when further ischaemic events did not occur.Since, in these studies, onset of symptoms with deterioration in cerebral haemodynamic has been shown to be related to angiographic progression over time, even in initially asymptomatic patients and patients with ischaemic symptoms but without hypoperfusion, follow-up assessment in these subsets of patients also seems to be warranted.

Regarding the course of the disease after revascularization surgery, 93 patients (paediatric and adults) were followed up in a prospective study to 10.5 ± 4.4 years after combined revascularization surgery for the MCA

领土 [93] While late morbidity, that is haemorrhage was seen only in one adult patient 9.5 years after surgery (0.10% per patient-year), progression of angiopathy in the contralateral carotid or the PCA occurred on MRA in 1.5% per patient-year within an interval of 0.5–15 years from first surgery.The authors concluded that longer follow-ups, that is 10 years post-surgery are essential to detect disease progression and prevent late cerebrovascular events.[93]

The question of 'progression' of MMA is an important one, whether this is observed on MRA or conventional angiography or on haemodynamic testing, whether in symptomatic and medically treated or asymptomatic patients, whether in initial unilateral presentation or even surgically treated patients.MWG 同意与疾病进展评估相关的治疗结果。Most of the papers reviewed were not comparative studies (i.e. those specifically referring to follow-up assessment vs no assessment groups), but they do present important observations and highlight the value of serial testing leading to clinically relevant therapeutic decision making.In addition to MRA, non-invasive transcranial duplex ultrasound can be used to follow up bypass patency and progression of vasculopathy in experienced hands.75,172,173

循证推荐

In patients with MMA, there is continuing uncertainty over the advantages and disadvantages of providing systematic long-term neuroimaging follow up assessment.证据质量:-
推荐强度:-

专家共识声明

In patients with MMA, we suggest that neuroimaging follow-up should not only be limited to post-operative evaluations of surgical efficacy but should include long-term follow-up to evaluate progression of angiopathy.投 9/9 票。对于最初诊断为偏 MMA 的患者，应进行神经成像评估，以早期发现进展。投 9/9 票。
在保守治疗的 MMA 患者(无症状和有症状的患者，无论有无血流动力学障碍)中，应进行神经成像评估。投 9/9 票。
In patients with MMA, the neuroimaging follow-up should include at least MRI-MRA and haemodynamic evaluation (MR perfusion, PET, SPECT).
在有经验的人看来，经颅双工超声可能是有用的。投 9/9 票。
对于 MMA 患者，当怀疑有血管改变，需要做出治疗决定或非侵入性技术不能确定时，应优先进行 DSA。投 9/9 票。
后续评估的时间不能严格规定，而且应该因人而异。投 9/9 票。

讨论

虽然全球 MMA 的发病率在不断增加，[3] 有关疾病自然史的数据很少，而且支离破碎，特别是在欧洲国家。由于对 MMA 的自然病程认识不完全，以及病理生理学的未知和疾病的异质性，特别是东亚和西方人群之间的异质性，到目前为止，共同管理策略的发育受到了限制。[9,10,19,35–37] 外科血运重建被认为是能够预防缺血性中风和出血性中风的唯一治疗方法。[38,40] 然而，在术前和随访阶段缺乏关于最佳血运重建类型和手术时机以及患者管理的主治。

本文是欧洲第一个使用 GRADE 方法管理 MMA 的综合性指南。[47,174] The aims of our WG was to conduct a methodologically rigorous and extensive analysis of the available evidence and data and to provide evidence based recommendations, or when not possible, Expert Consensus Statements which may be helpful for clinical decision in diagnostic work up, management and care of MMA world-wide.Recommendations and Expert Consensus Statement are based on the work of a group with broad expertise on MMA and on PICO questions, spanning disciplines (neurology with clinical and research areas, neurosurgery, genetic and methodologists) and several European countries (Italy, France, Germany, Spain, Switzerland).This last point was specifically important for this guideline since most of guidelines are provided by Japanese groups.[41]

The literature search performed to answer our PICO questions, found a marked paucity of high-quality papers and most of our data were derived from observational studies since no specific RCTs were available, except the JAM trial, comparing bilateral direct revascularization to the best medical treatment in adult MMD with haemorrhagic presentation.[169] Therefore, in adult MMA patients with haemorrhagic presentation we recommended (PICO5), with 'low quality' of evidence, direct-bypass surgery, after assessing the haemodynamic and choroidal collateral status.The recommendation was 'weak for intervention' since it was supported by only one small sized RCT.5 个比较观察研究数据(图 2 和表 3)[60,93,123–125] led experts to suggest with very low grade of evidence, revascularization surgery in adults and children with ischaemic MMA, when supported by the presence of clinical symptoms or imaging markers of haemodynamic failure, if performed in referral centres with neurosurgical expertise.The quality of evidence was very low since most studies were retrospective, conducted at a single centre level, suffering from bias in control population selection and variable indication to surgery.

关于手术类型，不同的血运重建策略被应用于当前的实践(直接、直接和联合血运重建)。虽然直接和联合是最常用的技术，特别是在成人中，最好的血运重建手术的类型仍然是未知的。对于这个问题(PICO6)，没有 RCT，数据来自 7 个观察性研究，随访时间相对较长(分别上 84 个月和 64 个月)。The results of these studies supported the Expert Consensus statement that direct/combined is preferable to indirect cerebral revascularization strategies in adult MMA patients and in children, to reduce the risk of stroke.然而，这些结果可能受到纳入研究中应用的不同间接技术(即 EMS、EAS、EMAS、EDS、EDAS、EDAMS、EDAGS)的影响，这些技术没有单独区分或具体评估。这可能是特别重要的，因为间接技术更容易，特别是有关儿童，因为他们的血管可塑性和血管生成活性。因此，进一步更大规模的研究，特别是 rct 可能有助于评估这些技术中的一种(直接或间接)是否可以被推荐，以及如何处理无症状患者。

我们的专家组还指出，急性脑血管事件发生 6-12 周(PICO8)后再进行手术可能是合理的，尽管仅有两项回顾性比较观察性研究的数据，样本量相对较小。Patients operated on in the early period after acute events might suffer from a higher rate of post-operative complications such as cerebral hyperperfusion syndrome with or without haemorrhage, early haemorrhagic transformation of an acute ischaemic stroke or peri- or postoperative ischaemic events.[157–161]

大系列研究的结果，[110,111,115] 还有登记处 [112,114] were also not conclusive on the benefits and risk of long-term antiplatelet therapy in non-haemorrhagic MMA (PICO7).因此，对于这些患者，我们只能制定一份专家共识声明，建议在这些患者中长期安全使用抗血小板，尽管亚洲医生在 MMA 中不常规使用抗血小板。[107] 相反，我们没有足够的数据来表述出出血性 MMA 患者。由于缺乏数据，我们也不能提供任何建议或专家共识声明，在停止抗血小板治疗期间使用肝阿林来桥接。Moreover, since the analyses were based on data from Japanese studies, environmental or specific susceptibility factors (i.e. resistance to antiplatelet) could limit the translation of these findings in Western countries.Due to the lack of specific comparative studies and to the heterogeneity of the study populations (i.e. operated and not operated patients;适用于评估的不同方法;等)，我们无法提供建议，只能提供一份关于血流动力学研究和 PCA 评估在识别卒中风险方面的优势的专家共识声明

(PICO1 and 2). However, we have to take into account that it could be difficult to implement RCTs on this topic, due to ethical problems and common clinical practice.

We had also no evidence to support the clinical utility of performing the genetic screening of p.R.4810K include' variant of RNF213 gene' (PICO3), despite the fact that it could be useful to look for other variants in the RNF213 gene in children with a very early onset and severe disease.[27–29,112] Since it has been observed that MMA steno- occlusive lesions progress over the years conditioning ischaemic and haemorrhagic clinical events and that unilateral MMA may evolve to bilateral conditions, the MWG agreed in suggesting the neuroimaging assessment of disease progression (MRI, MRA, cerebral perfusion imaging and DSA), based on the potential need for a therapeutic decision (PICO9).However, also in this case most of the papers reviewed were not comparative studies (i.e. those specifically referring to follow-up assessment vs no assessment groups), and the analysis was limited by the different imaging approaches used as well as by the dyshomogeneous time periods studied.[75,172,173] Therefore, given the relevance for therapeutic decision, the implementation of specific studies addressing this question should be encouraged.

我们工作的局限性主要与缺乏随机对照试验(rct)有关，并与大多数被评估的研究的观察性和回顾性性质有关，这使我们能够提供大部分专家共识，而不是建议。此外，大多数研究的小样本量进一步降低了我们发现的确定性。对于某些 PICOs，纳入的人群、结果以及随访时间或采用的方法之间存在显著异质性。Another important limitation may be the fact that we did not specifically separate East Asian patients from American and European series for the analysis.我们意识到，东亚和欧洲的 MMA 患者可能有不同的特点，需要不同的管理。然而，我们没有足够的数据，主要是在欧洲的 MMA 患者，以支持 MMA 可以被认为是一个不同的实体在欧洲的想法。此外，针对不同灌注成像技术的特效药分析、不同的手术或抗血小板策略可能是有用的，但这超出了本研究的范围。

总之，MMA 的诊断工作、临床和手术治疗都在不断发展。尽管仍有一些未满足的需求和缺乏证据，我们相信我们的工作，通过提供这一领域现有发现的详细信息，可以帮助指导临床医生选择最有效的 MMA 治疗和管理策略。此外，通过确定 MMA 诊断和疗法方面的研究空白和未解决的问题，这些指南也可能有助于实施进一步的研究，如 rct 或严格进行的观察性研究。

简洁的语言总结

烟雾病(Moyamoya disease, MMD)是一种罕见的将血液输送到脑的血管疾病。随着时间的推移，颅底部的血液变得狭窄，导致供应脑的血液和氧气不足。

这种疾病影响所有人群，但在东亚更为常见。烟雾病疾病主要影响儿童，但也可发生在成人。与 MMD 相关的问题因人而异。在儿童和成人中，疾病通常表现为中风。Strokes occur when an area of the brain is suddenly cut off from blood flow (called an ischaemic stroke) or when a blood vessel bursts and blood spills into the brain (called haemorrhagic stroke).患有烟雾病的儿童还可能出现严重的头痛、头晕和学习困难。

When the first symptoms appear, a brain magnetic resonance imaging (MRI) scan is often performed.This painless examination gives precise images of the brain and can show signs of brain damage (haemorrhage or infarction).However, the examination that confirms the diagnosis of moyamoya is cerebral angiography.This is a radiological examination, which assesses blood vessels with X-rays, after injection an X-ray dye.This allows a better visualisation of the blood vessels than MRI.

烟雾病的确切病因尚不清楚。Our limited understanding of the disease is one of the reasons we have no tablets that can prevent or reverse moyamoya blood vessel changes.外科手术被用来限制烟雾病的损害。However, brain surgery comes with a risk of complications.做手术的决定很困难，要与病人、家属和医疗团队共同做出决定。Decisions on the suitability for surgery usually depend on the patient's age, condition of the blood vessels and symptoms.

在我们的指南中，评估了所有的证据后，我们建议对有出血型中风的 moy- amoya 患者进行手术干预。我们还建议在高度专业化的中心进行任何手术。中风后应推迟手术以避免并发症。We support that specialised brain scans are used to assess whether the moyamoya blood vessel changes are worsening over time.Finally, we suggest that blood thinning medications (antiplatelets) be used for some people on a long-term basis and during the perioperative period.

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担保人

作为工作组主席的 AB 和 DH 是指导方针的保证

分摊

AB and DH drafted the PICO questions, which were refined by all authors (AB,DH, NK, BF, FA, IC, ETL, PV, MLZ, MK, SL).SL and SH conducted the literature search, conducted data extraction and performed meta-analyses.AB, DH coordinated the whole MWG activities, drafted and revised the manuscript.All authors (AB, DH, NK, BF, FA, IC, ETL, PV, MLZ, MK, SL, SH) participated in the writing of the first draft of the manuscript.所有作者都对稿件的重要知识内容进行了评审和编辑，并批准了稿件的最终版本

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