·循证神经系统疾病·

重组组织型纤溶酶原激活物治疗合并大脑中动脉高密度征的急性缺血性卒中有效性和安全性的系统评价

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【摘要】 **目的**　系统评价合并大脑中动脉高密度征(HMCAS)的急性缺血性卒中患者重组组织型纤溶酶原激活物(rt-PA)静脉溶栓治疗的有效性和安全性。**方法**　以hyperdense middle cerebral artery sign/HMCAS/hyperdense artery sign/hyperdense cerebral artery sign、ischemic stroke/cerebral infarction/brain infraction/cerebral embolism、thrombolysis/thrombolytic therapy/rt-PA/recombinant tissue plasminogen activator,以及大脑中动脉高密度征/致密动脉征/大脑中动脉致密征/脑动脉高密度征、缺血性脑卒中/缺血性卒中/脑梗死/脑梗塞/脑栓塞、溶栓治疗/rt-PA/重组组织型纤溶酶原激活剂等中英文词组为检索词,计算机检索1994年1月–2014年12月美国国立医学图书馆生物医学信息检索系统、荷兰医学文摘、Cochrane临床对照试验中心注册库,以及中国生物医学文献数据库等收录的关于rt-PA静脉溶栓治疗合并HMCAS的急性缺血性卒中随机或非随机对照临床试验;分别采用Newcastle-Ottawa量表和RevMan 5.2统计软件行文献质量评价和Meta分析。**结果**　经剔除重复和不符合纳入标准者,166篇英文文献中最终纳入8项非随机对照临床试验共11 373例患者[2455例合并HMCAS(rt-PA静脉溶栓治疗2316例、安慰剂治疗139例)、8918例未合并HMCAS]。Meta分析显示:rt-PA静脉溶栓组患者不良预后风险低于安慰剂组(OR = 0.360,95%CI:0.150 ~ 0.850;P = 0.020),但症状性颅内出血发生率组间差异无统计学意义(OR = 1.640,95%CI:0.380 ~ 7.040;P = 0.500);合并HMCAS患者rt-PA静脉溶栓治疗不良预后风险高于未合并者(OR = 2.830,95%CI:2.550 ~ 3.150;P = 0.000),但症状性颅内出血发生率组间差异无统计学意义(OR = 1.090,95%CI:0.500 ~ 2.410;P = 0.820)。**结论**　尽管rt-PA静脉溶栓治疗合并HMCAS的急性缺血性卒中患者安全、有效,但发病3个月时易出现不良预后,而发生症状性颅内出血风险较低。

【关键词】 脑缺血;　组织型纤溶酶原激活物;　大脑中动脉;　Meta分析

Efficacy and safety of rt-PA intravenous thrombolysis in the treatment of acute ischemic stroke with hyperdense middle cerebral artery sign: a systematic review

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【**Abstract**】 **Objective**　To systematically review the efficacy and safety of recombinant tissue-type plasminogen activator (rt-PA) intravenous thrombolysis in the treatment of acute ischemic stroke with hyperdense middle cerebral artery sign (HMCAS) on CT images. **Methods**　Search online databases such as PubMed, EMBASE/SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL) and China Biology Medicine (CBM) from January 1994 to December 2014 with key words: hyperdense middle cerebral artery sign/HMCAS/hyperdense artery sign/hyperdense cerebral artery sign, ischemic stroke/cerebral infarction/brain infarction/cerebral embolism, thrombolysis/thrombolytic therapy/rt-PA/recombinant tissue plasminogen activator both in Chinese and English, to collect randomized controlled trials (RCTs) or non-RCTs about rt-PA treating patients with acute ischemic stroke and HMCAS. Two reviewers independently

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screened literatures according to the inclusion and exclusion criteria, extracted data, and assessed the risk of bias of included studies. Newcastle-Ottawa Scale (NOS) was used for quality assessment, and Meta-analysis was performed using RevMan 5.2 software. **Results** A total of 8 studies were included after excluding duplicate ones and those which did not meet the inclusion criteria from 166 articles. There were 11 373 patients, including 2455 cases complicated with HMCAS (2316 treated by rt-PA and 139 treated by placebo) and 8918 cases without HMCAS. Meta-analysis showed the occurrence of unfavorable outcome in rt-PA treatment was significantly decreased compared to placebo in HMCAS-positive patients (OR = 0.360, 95%CI: 0.150–0.850; P = 0.020), while there was no statistical difference in the occurrence of symptomatic intracerebral hemorrhage (sICH) between rt-PA and placebo treatment in HMCAS-positive patients (OR = 1.640, 95%CI: 0.380–7.040; P = 0.500). Meta-analysis also showed unfavorable outcome of rt-PA treatment was significantly higher in HMCAS-positive than in HMCAS-negative patients (OR = 2.830, 95% CI: 2.550–3.150; P = 0.000), while there was no statistical difference in the occurrence of sICH after rt-PA treatment (OR = 1.090, 95% CI: 0.500–2.410; P = 0.820). **Conclusions** Although rt-PA intravenous thrombolysis is safe and effective in the treatment for HMCAS-positive patients with acute ischemic stroke, unfavorable outcome is easy to occur after 3 months of onset, however, the risk of symptomatic intracerebral hemorrhage is low.

【Key words】 Brain ischemia; Tissue plasminogen activator; Middle cerebral artery; Meta-analysis

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缺血性卒中是导致永久性残疾的主要原因之一，亦是引起死亡的三大原因之一。据世界卫生组织（WHO）的数据，全球每年新发脑卒中病例约15×10^6例[1]，我国每年约2.50×10^6例[2]。缺血性卒中发病早期CT表现为大脑中动脉高密度征（HMCAS）、岛带征、豆状核轮廓模糊和灰白质界限消失等征象[3]，其中以HMCAS最具特征性，对诊断大脑中动脉近段闭塞有较高的阳性预测值[4]。HMCAS系急性缺血性卒中大脑中动脉血栓形成和大脑中动脉M1段闭塞所特有的征象，可见于26%～35%急性缺血性卒中患者的早期CT表现[5]。静脉溶栓是急性缺血性卒中的标准治疗方案，常用药物包括链激酶、尿激酶和重组组织型纤溶酶原激活物（rt-PA），但目前仅rt-PA是美国食品与药品管理局（FDA）批准上市的唯一溶栓药物[6]，并已经多项高质量随机对照试验（RCT）和系统评价证实具有改善急性缺血性卒中患者神经功能预后之功效[7-10]。目前对静脉溶栓治疗合并HMCAS的急性缺血性卒中患者预后尚存争议[11-13]，2013年美国心脏协会（AHA）和美国卒中协会（ASA）制定的急性缺血性卒中早期管理指南（以下简称AHA/ASA指南）仅推荐以合并大脑中动脉点征作为静脉溶栓治疗之适应证[14]，而合并HMCAS者不在其列。鉴于此，我们拟对合并HMCAS的急性缺血性卒中患者rt-PA静脉溶栓治疗的有效性和安全性进行系统评价，以期指导临床用药。

资料与方法

一、文献筛选

1. 研究类型　rt-PA静脉溶栓治疗合并HMCAS的急性缺血性卒中随机和非随机对照临床试验。

2. 研究对象　（1）纳入标准：符合1989年世界卫生组织[15]或1995年第四届全国脑血管病学术会议制定的脑卒中诊断标准，并经头部CT和（或）MRI检查证实；发病＜4.50 h接受rt-PA静脉溶栓治疗；HMCAS定义为CT显示大脑中动脉（M1段或合并M2/M3段）高密度影，且密度高于周围脑组织和对侧大脑中动脉。（2）排除标准：发病≥4.50 h方行静脉溶栓治疗的患者；溶栓药物为尿激酶或其他药物；CT仅显示大脑中动脉点征（即M2或M3段高密度影）[16]。

3. 干预措施　试验组为rt-PA静脉溶栓治疗合并HMCAS的急性缺血性卒中病例，对照组为安慰剂治疗合并HMCAS或rt-PA静脉溶栓治疗未合并HMCAS的急性缺血性卒中病例。

4. 结局指标　（1）主要结局指标：采用改良Rankin量表（mRS）和Barthel指数（BI）评价患者发病3个月时预后（包括神经功能和日常生活活动能力），以mRS评分≥2分或BI评分≤95分为预后不良［定义为死亡或依赖（即日常生活需要他人帮助）］。（2）次要结局指标：rt-PA静脉溶栓治疗后出现症状性颅内出血。症状性颅内出血定义参考一项

多中心临床研究[17]和一项已发表的系统评价[18]：溶栓治疗后22～36 h CT显示2型脑实质出血且美国国立卫生研究院卒中量表（NIHSS）评分较治疗前减少≥4分，或溶栓治疗后24 h内死亡[脑卒中溶栓安全性监测研究（SITS-MOST）定义]。若研究仅报道出血性转化的影像学改变，但未报道临床定义的症状性颅内出血，则定义为2型脑实质出血[19]；若研究报道为脑实质出血，但未进一步分型（1型或2型脑实质出血），则认为是症状性颅内出血。

二、文献检索

计算机检索1994年1月–2014年12月美国国立医学图书馆生物医学信息检索系统（PubMed）、荷兰医学文摘（EMBASE/SCOPUS）、Cochrane临床对照试验中心注册库（CENTRAL），以及中国生物医学文献数据库（CBM）等数据库收录的关于rt-PA静脉溶栓治疗合并HMCAS的急性缺血性卒中随机和非随机对照临床试验。语言限制为英文和中文，英文检索词选择：hyperdense middle cerebral artery sign/HMCAS/hyperdense artery sign/hyperdense cerebral artery sign，ischemic stroke/cerebral infarction/brain infarction/cerebral embolism，thrombolysis/thrombolytic therapy/rt - PA/recombinant tissue plasminogen activator；中文检索词为：大脑中动脉高密度征/致密动脉征/大脑中动脉致密征/脑动脉高密度征，缺血性脑卒中/缺血性卒中/脑梗死/脑梗塞/脑栓塞，溶栓治疗/rt-PA/重组组织型纤溶酶原激活剂。

三、文献筛选和数据提取

根据纳入与排除标准，首先由两位评价者独立阅读文题和摘要，排除明显不符合纳入标准者；第二步对可能符合纳入标准的文献进行全文阅读，以确定是否符合纳入标准；第三步由两位评价者交叉核对结果，如有分歧与第三位评价者讨论后决定取舍。对资料存疑或资料缺失的文献，尽可能与作者或通讯作者取得联系以确认或补充。对符合纳入标准的文献提取以下资料：（1）一般资料，包括文题、作者、来自国家或地区、发表日期等。（2）研究特征，包括研究对象一般资料、各组基线可比性、干预措施、观察时间等。（3）结局指标，包括mRS和BI评分，以及症状性颅内出血发生率。

四、文献质量评价

由两位评价者独立对所纳入的文献质量进行评价并交叉核对，如有分歧与第三位评价者讨论后决定取舍。随机对照临床试验的质量评价采用Cochrane系统评价手册5.1.0[20]，分别对随机分配方法，分配方案隐藏，对研究对象、治疗方案实施者、结果测量者采用盲法，研究数据完整性，选择性报告研究成果，以及其他偏倚来源等进行评价。非随机对照临床试验的质量评价采用Newcastle-Ottawa量表（NOS）[21]，分别对研究对象选择、组间可比性和暴露因素测量进行评价：（1）研究对象选择，共计4分，分为4项条目，即病例确定是否恰当、病例代表性、对照者的选择、对照者的确定。（2）组间可比性，共2分，仅1项条目，即研究设计和统计分析中病例与对照者的可比性。（3）暴露因素测量，共3分，分为3项条目，即暴露因素的确定、是否采用相同方法确定病例和对照者的暴露因素、有无应答率。总评分为9分，评分≥5分者为高质量文献、评分＜5分者为低质量文献。

五、统计分析方法

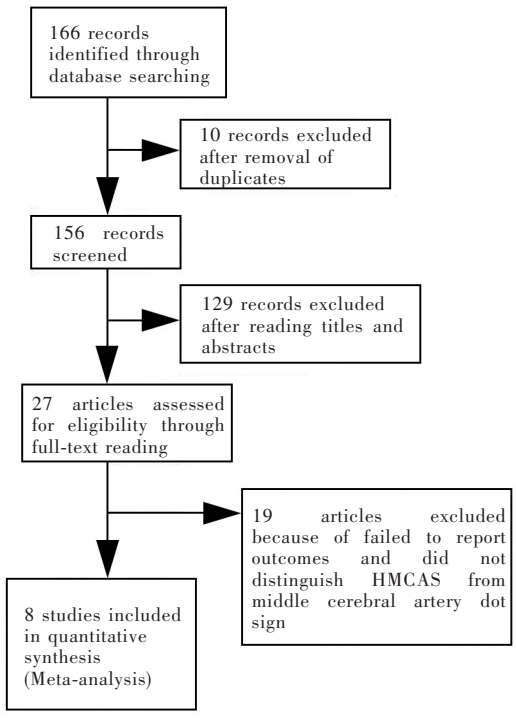
采用Cochrane协作网提供的RevMan 5.2统计软件行Meta分析。计数资料以比值比（*OR*）表示，计量资料以均数差（*MD*）表示，区间估计以95%CI表示，效应量的检验水准为$\alpha = 0.05$。各项研究之间的异质性检验采用χ^2检验，当$P > 0.010$和$I^2 < 50.000\%$时，无异质性，采用固定效应模型进行合并效应分析；当$P \leq 0.010$和$I^2 \geq 50.000\%$时，存在异质性，分析其异质性来源，采用随机效应模型进行合并效应分析。通过敏感性分析对Meta分析结果之稳定性进行评价，将固定效应模型与随机效应模型相互转换并重新计算合并效应量，经上述转换后所得研究结论一致则表明Meta分析结果稳定，反之则不稳定。

结　果

一、文献检索结果

1. 文献筛选　经初步检索共获得166篇相关英文文献，阅读文题和摘要并剔除重复文献139篇；进一步仔细阅读全文，排除未报道脑卒中发病3个月时预后或症状性颅内出血、未严格区分HMCAS和大脑中动脉点征的文献19篇，最终获得8项非随机对照临床试验[1,4-5,11-12,22-24]共11 373例急性缺血性卒中患者，其中2455例合并HMCAS（rt-PA静脉溶栓治疗2316例、安慰剂治疗139例）、8918例未合并HMCAS。文献筛选流程参见图1，所纳入8项临床研究的基线资料参见表1。

2. 方法学质量评价　根据NOS量表的质量评



HMCAS, hyperdense middle cerebral artery sign, 大脑中动脉高密度征

图1 文献检索流程图

Figure 1 Flow diagram of screening articles.

价标准，8项临床研究中仅1项[12]NOS评分为4分，其余7项均为6分；所纳入临床研究均采用盲法判断是否合并HMCAS，仅1项研究[1]采用盲法进行mRS评分。8项临床研究中1项[4]为前瞻性研究，其余7项均为回顾性研究。本研究方法学质量评价参见表1。

二、Meta分析结果

1. 疗效评价 （1）合并HMCAS的急性缺血性卒中患者rt-PA静脉溶栓与安慰剂疗效的比较：有2项临床试验[5,22]对rt-PA静脉溶栓与安慰剂的疗效进行比较，二者无异质性（$P=0.170$，$I^2=48.000\%$），故采用固定效应模型进行合并效应分析。结果显示：rt-PA静脉溶栓组患者脑卒中发病3个月时不良预后风险低于安慰剂组（$OR=0.360$，95%CI：0.150～0.850，$P=0.020$；图2）。（2）合并与不合并HMCAS的急性缺血性卒中患者rt-PA静脉溶栓疗效的比较：有6项临床试验[1,4-5,11-12,23]采用mRS量表对脑卒中发病3个月时预后进行评价，其中4项[4-5,11,23]将mRS评分2～6分定义为预后不良、2项[1,12]将3～6分定义为预后不良。各项研究之间不存在异质性（$P=0.670$，$I^2=0.000\%$），故采用固定效应模型进行合并效应分析。结果显示：合并HMCAS的急性缺血性卒中患者不良预后风险高于未合并者（$OR=2.830$，95%CI：2.550～3.150，$P=0.000$；图3）。

2. 安全性评价 8项临床试验中5项[1,11-12,22,24]报道rt-PA静脉溶栓后发生症状性颅内出血，余3项未行安全性评价。（1）合并HMCAS的急性缺血性卒中患者rt-PA静脉溶栓与安慰剂治疗的安全性评价：有2项临床试验[22,24]采用SITS-MOST定义的症状性颅内出血对rt-PA静脉溶栓的安全性进行评价，二者之间不存在异质性（$P=0.400$，$I^2=0.000\%$），故采用固定效应模型进行合并效应分析。结果显示：rt-PA静脉溶栓与安慰剂治疗后症状性颅内出血发生率差异无统计学意义（$OR=1.640$，95% CI：0.380～7.040，$P=0.500$；图4）。（2）合并与未合并HMCAS的急性缺血性卒中患者rt-PA静脉溶栓的安全性评价：有3项临床试验[1,11-12]对rt-PA静脉溶栓的安全性进行评价，其中1项[1]将脑实质出血定义为症状性颅内出血、2项[11-12]以SITS-MOST标准定义症状性颅内出血，各项研究间之间存在异质性（可能与症状性颅内出血定义不同有关；$P=0.100$，$I^2=56.000\%$），故采用随机效应模型进行合并效应分析。结果显示：合并与未合并HMCAS患者症状性颅内出血发生率差异无统计学意义（$OR=1.090$，95% CI：0.500～2.410，$P=0.820$；图5）。

三、敏感性分析

将rt-PA静脉溶栓治疗合并HMCAS的急性缺血性卒中疗效和安全性评价结果中的固定效应模型与随机效应模型相互转换，仅1项结论（合并HMCAS的急性缺血性卒中患者rt-PA静脉溶栓与安慰剂疗效比较）与Meta分析结论不尽一致（$OR=0.340$，95%CI：0.080～1.540；$P=0.160$），考虑可能与纳入的文献量较少有关；其余3项研究结论一致，表明Meta分析结果较为稳定（表2）。

讨 论

本研究结果显示，rt-PA静脉溶栓治疗合并HMCAS的急性缺血性卒中患者不良预后风险低于安慰剂组，而二者症状性颅内出血发生率差异无统计学意义，与Manelfe等[25]采用斯堪的纳维亚卒中量表（SSS）评价脑卒中发病3个月时结局的结论相一致。Nichols等[24]的研究显示，rt-PA静脉溶栓治疗后HMCAS消失、大脑中动脉再通、发病24小时后

表1 所纳入8项临床试验的基线资料和质量评价

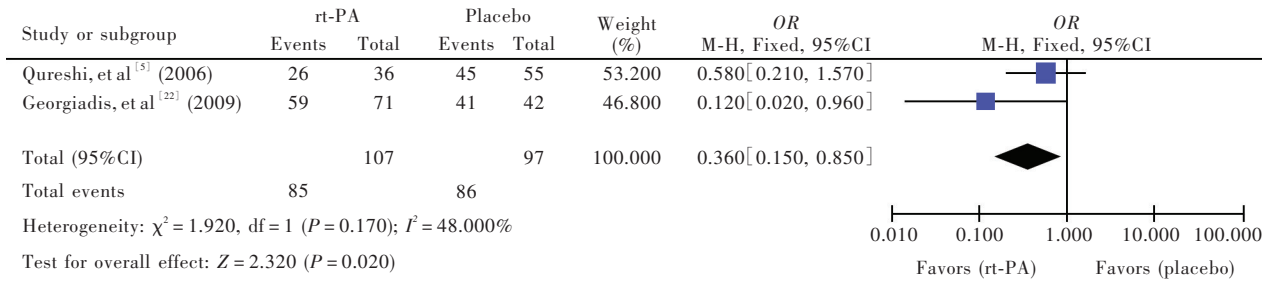
Table 1. General data and quality evaluation of 8 studies included in the systematic review

Study	Group	N	Sex [case (%)]		Age (year)	Intervention	Definition of unfavorable outcome	Definition of sICH	NOS (score)
			Male	Female					
Agarwal, et al [4] (2004)	HMCAS (+)	15	Not available		Not available	rt-PA 0.90 mg/kg	mRS 2–6	Not available	6
	HMCAS (–)	51	Not available		Not available	rt-PA 0.90 mg/kg			
Qureshi, et al [5] (2006)	HMCAS (+)						mRS 2–6	Not available	6
	rt-PA	36	Not available		Not available	rt-PA 0.90 mg/kg			
	Placebo	55	Not available		Not available	Placebo			
	HMCAS (–)	271	Not available		Not available	rt-PA 0.90 mg/kg			
Nichols, et al [24] (2008)	rt-PA	37	15 (40.54)	22 (59.46)	69.60 ± 10.90	rt-PA 0.90 mg/kg	Not available	SITS-MOST	6
	Placebo	42	11 (26.19)	31 (73.81)	63.70 ± 11.70	Placebo			
Georgiadis, et al [22] (2009)	rt-PA	71	41 (57.75)	30 (42.25)	63.00	rt-PA 0.90 mg/kg	mRS 2–6	SITS-MOST	6
	Placebo	42	21 (50.00)	21 (50.00)	58.00	Placebo			
Aries, et al [11] (2009)	HMCAS (+)	104	60 (57.69)	44 (42.31)	67.00 ± 14.00	rt-PA 0.90 mg/kg	mRS 2–6	SITS-MOST	6
	HMCAS (–)	280	140 (50.00)	140 (50.00)	68.00 ± 14.00	rt-PA 0.90 mg/kg			
Kharitonova, et al [12] (2009)*	HMCAS (+)	1905	1107 (58.11)	798 (41.89)	70.00	rt-PA 0.90 mg/kg	mRS 3–6	SITS-MOST	4
	HMCAS (–)	8118	4757 (58.60)	3361 (41.40)	68.00	rt-PA 0.90 mg/kg			
Abul-Kasim, et al [1] (2010)	HMCAS (+)	39	Not available		68.00 ± 13.00	rt-PA with unknown dose	mRS 3–6	Parenchymal hemorrhage	6
	HMCAS (–)	81	Not available		71.00 ± 11.00	rt-PA with unknown dose			
Paliwal, et al [23] (2012)	HMCAS (+)	109	69 (63.30)	40 (36.70)	63.00	rt-PA 0.90 mg/kg	mRS 2–6	Not available	6
	HMCAS (–)	117	72 (61.54)	45 (38.46)	65.00	rt-PA 0.90 mg/kg			

*230 cases were lost to follow up in HMCAS (+) group and 1178 in HMCAS (–) in the comparison of risk for unfavorable outcome; 76 cases were lost in HMCAS (+) group and 373 in HMCAS (–) in the comparison of occurrence of sICH; 该项研究比较rt-PA静脉溶栓治疗合并或未合并HMCAS患者不良预后风险时，试验组失访230例、对照组失访1178例；比较rt-PA静脉溶栓治疗合并或未合并HMCAS患者症状性颅内出血发生率时，试验组失访76例、对照组失访373例。+, positive, 阳性；–, negative, 阴性。sICH, symptomatic intracerebral hemorrhage, 症状性颅内出血；NOS, Newcastle-Ottawa Scale, Newcastle-Ottawa量表；HMCAS, hyperdense middle cerebral artery sign, 大脑中动脉高密度征；rt-PA, recombinant tissue-type plasminogen activator, 重组组织型纤溶酶原激活物；mRS, modified Rankin Scale, 改良Rankin量表；SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Minitoring Study, 脑卒中溶栓安全性监测研究

梗死灶面积缩小。本系统评价通过纳入更多病例数和不同地域病例进一步支持上述研究结果。

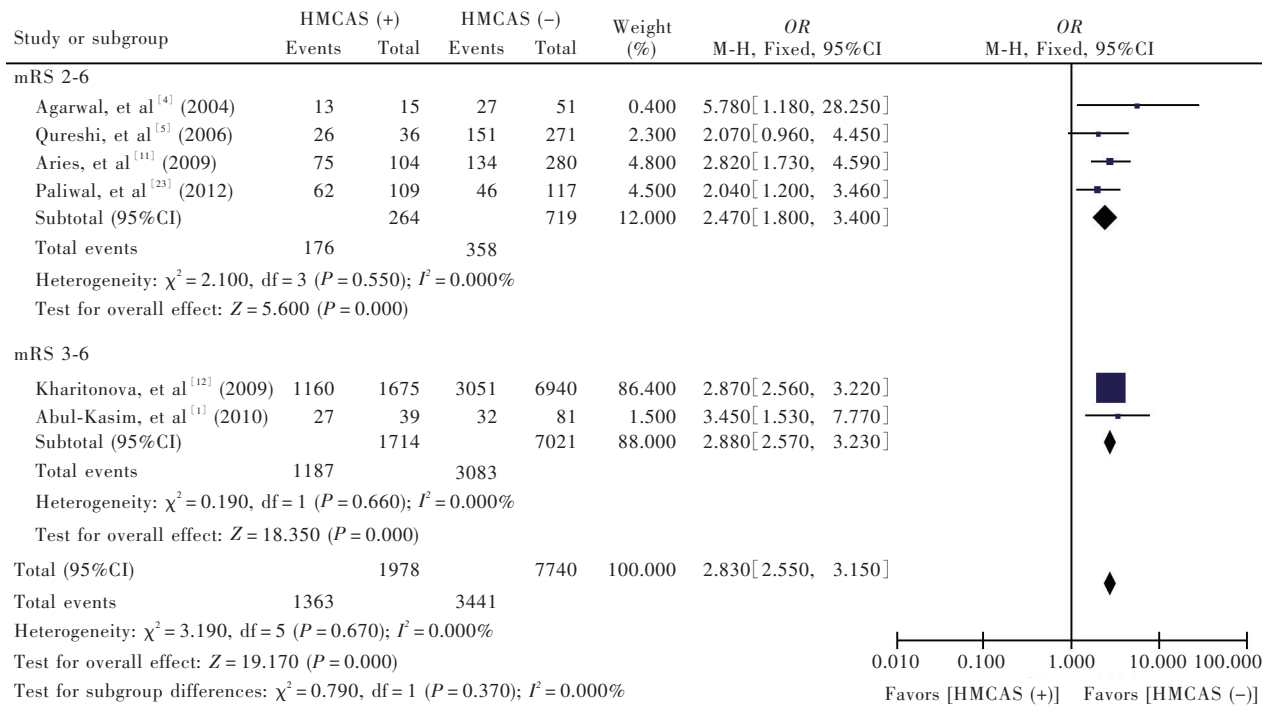
本研究结果还显示，rt-PA静脉溶栓治疗合并HMCAS的急性缺血性卒中患者不良预后风险高于未合并者，而二者症状性颅内出血发生率差异无统计学意义。Abul-Kasim等[1]对合并HMCAS的急性缺血性卒中患者的单因素分析提示，HMCAS是急性缺血性卒中预后不良的危险因素，而进一步行多因素Logistic回归分析（包含神经功能缺损程度评分）则显示急性缺血性卒中合并HMCAS并非预后不良的独立危险因素，推测此类患者预后不良可能与入院时重度神经功能缺损密切相关。Wolpert等[26]认为，与未合并HMCAS者相比，合并HMCAS患者血管再通率低；而rt-PA静脉溶栓治疗后CT显示持续存在的HMCAS方为预后不良的早期预测指标[23]。也有研究显示，合并HMCAS与急性缺血性卒中患者预后不良并无关联性[13]，但本系统评价未纳入该项研究，因其未明确区分HMCAS与大脑中动脉点征。合并HMCAS与预后不良无关联性可能是由于合并大脑中动脉点征的急性缺血性卒中患者rt-PA静脉溶栓疗效与未合并HMCAS者相似[27]，而均优于合并HMCAS者。rt-PA静脉溶栓治疗合并与未合并HMCAS的急性缺血性卒中患者的预后有所不同，如果与合并HMCAS患者血管再通率较低有关，则值得反思：对于此类患者，rt-PA静脉溶栓治疗是否为最佳选择？在某些情况下，动脉溶栓可能疗效更佳。有研究显示，尽管rt-PA动脉溶栓治疗时间晚于静脉溶栓，但动脉溶栓治疗合并HMCAS的急性缺血性卒中的疗效仍优于静脉溶栓[28]。对于大脑中动脉闭塞（MCAO）的急性缺血性卒中患者而言，动脉溶栓联合静脉溶栓疗效较单纯静脉溶栓更佳且更安全[29]。目前，尚缺乏合并HMCAS的急性缺



rt-PA，recombinant tissue-type plasminogen activator，重组组织型纤溶酶原激活物

图2　rt-PA静脉溶栓与安慰剂治疗合并HMCAS的急性缺血性卒中患者不良预后风险比较的森林图

Figure 2　Forest plot for comparison of the occurrence of unfavorable outcome in HMCAS (+) patients after rt-PA therapy or placebo.



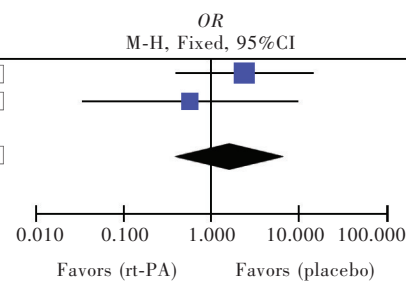
+，positive，阳性；−，negative，阴性。HMCAS，hyperdense middle cerebral artery sign，大脑中动脉高密度征；mRS，modified Rankin Scale，改良Rankin量表

图3　rt-PA静脉溶栓治疗合并或未合并HMCAS的急性缺血性卒中患者不良预后风险比较的森林图

Figure 3　Forest plot for comparison of the occurrence of unfavorable outcome in HMCAS (+) or HMCAS (−) patients after rt-PA therapy.

血性卒中患者动脉溶栓与静脉溶栓疗效比较的随机对照临床试验，上述结论尚待验证。自2013年以来，有多项大型血管内治疗研究结果公布，因此AHA/ASA对其2013年指南进行修订，2015年公布的最新指南共纳入8项新近发表的随机对照临床试验结果，明确推荐支架取栓器用于血管内治疗并可使急性缺血性卒中患者临床获益，尤其是颈内动脉或大脑中动脉M1段闭塞的缺血性卒中患者，而且符合年龄≥18岁、美国国立卫生研究院卒中量表（NIHSS）评分≥6分、脑卒中发病前mRS评分为0或1分、发病4.50小时内予以rt-PA静脉溶栓等项条件者应行支架取栓器血管内治疗（I类推荐，A级证据）[30]。我们推测，合并HMCAS的急性缺血性卒中患者采用rt-PA静脉溶栓治疗后支架取栓器血管内治疗可能较单纯静脉溶栓或动脉溶栓获得更佳效果，但尚待进一步的大样本临床试验加以证实。

本系统评价尚存在一定的局限性：纳入的临床试验可能不尽全面；纳入的文献数量较少，存在发表偏倚；研究结果受方法学质量所限，仅1项临床试验为前瞻性研究；尽管仅1项临床试验异质性检验



Study or subgroup	rt-PA Events	rt-PA Total	Placebo Events	Placebo Total	Weight (%)	OR M-H, Fixed, 95%CI
Nichols, et al[24] (2008)	4	37	2	42	57.400	2.420[0.420, 14.070]
Georgiadis, et al[22] (2009)	1	71	1	42	42.600	0.590[0.040, 9.620]
Total (95%CI)		108		84	100.000	1.640[0.380, 7.040]
Total events	5		3			

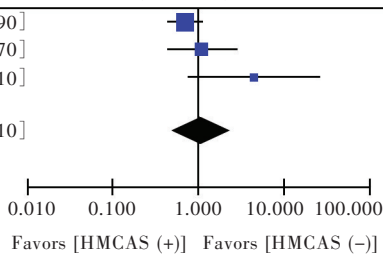
Heterogeneity: $\chi^2 = 0.710$, df = 1 ($P = 0.400$); $I^2 = 0.000\%$

Test for overall effect: $Z = 0.670$ ($P = 0.500$)

rt-PA，recombinant tissue-type plasminogen activator，重组组织型纤溶酶原激活物

图4　rt-PA静脉溶栓与安慰剂治疗合并HMCAS的急性缺血性卒中患者症状性颅内出血发生率比较的森林图

Figure 4　Forest plot for comparison of the occurrence of sICH in HMCAS (+) patients after rt-PA therapy or placebo.



Study or subgroup	HMCAS (+) Events	HMCAS (+) Total	HMCAS (−) Events	HMCAS (−) Total	Weight (%)	OR M-H, Random, 95%CI
Kharitonova, et al[12] (2009)	24	1829	143	7745	51.200	0.710[0.460, 1.090]
Aries, et al[11] (2009)	7	104	17	280	33.500	1.120[0.450, 2.770]
Abul-Kasim, et al[1] (2010)	4	39	2	81	15.300	4.510[0.790, 25.810]
Total (95%CI)		1972		8106	100.000	1.090[0.500, 2.410]
Total events	35		162			

Heterogeneity: $Tau^2 = 0.270$; $\chi^2 = 4.550$, df = 2 ($P = 0.100$); $I^2 = 56.000\%$

Test for overall effect: $Z = 0.220$ ($P = 0.820$)

+，positive，阳性；−，negative，阴性。HMCAS，hyperdense middle cerebral artery sign，大脑中动脉高密度征

图5　rt-PA静脉溶栓治疗合并或未合并HMCAS的急性缺血性卒中患者症状性颅内出血发生率比较的森林图

Figure 5　Forest plot for comparison of the occurrence of sICH in HMCAS (+) or HMCAS (−) patients after rt-PA therapy.

表2　固定效应模型与随机效应模型相互转化的敏感性分析

Table 2.　Sensitive analysis of interconversion bewteen fixed effects model and random effects model

Item	Switch model			Item	Switch model		
	OR value	*OR* 95%CI	*P* value		*OR* value	*OR* 95%CI	*P* value
Unfavorable outcome				Symptomatic intracerebral hemorrhage			
Group A	0.340	0.080–1.540	0.160	Group A	1.620	0.370–7.190	0.520
Group B	2.830	2.540–3.150	0.000	Group B	0.830	0.570–1.210	0.330

Group A，HMCAS (+) with rt-PA treatment vs placebo treatment，合并HMCAS的急性缺血性卒中患者rt-PA静脉溶栓与安慰剂比较；Group B，HMCAS (+) vs HMCAS (−) with rt-PA treatment，合并与不合并HMCAS的急性缺血性卒中患者rt-PA静脉溶栓比较

$I^2 > 50.000\%$，然而由于在诊断HMCAS时不同研究所采用的CT扫描仪和扫描参数不同（影响诊断的敏感性和特异性）、神经科或放射科医师经验不同，仍对研究结果存在一定影响。因此，本研究结论尚待更多的前瞻性或随机对照临床试验加以验证。

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