

## Stroke Risk Period After Acute Myocardial Infarction Revised

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Ischemic stroke is infrequent yet one of the most feared complications of acute myocardial infarction (MI). Ischemic stroke burdens 0.9% of MI patients within 1 month and 3.7% within a year after an acute MI with a doubled 1-year mortality compared with those not complicated with stroke.<sup>1,2</sup> Acute MI has been considered a cause for ischemic stroke only if it occurs within 1 month of the stroke.<sup>3–5</sup> However, the precise duration of this heightened risk period and related clinical factors, such as reperfusion therapy, revascularization procedures, and new-onset atrial fibrillation (AF), have remained unclear.

To study the duration of elevated post-MI stroke risk, Merkler et al in this issue of the *Journal of the American Heart Association (JAHA)* performed a retrospective cohort study that utilized a representative 5% sample of Medicare claims data from 2008 to 2015, providing a cohort of 1 746 476 beneficiaries of which 46 182 were hospitalized for acute MI and 80 466 for ischemic stroke.<sup>6</sup> They focused solely on the end point of stroke caused by ischemia, while prior studies may have accepted all strokes. Importantly, the study was able to control for potential periprocedural strokes resulting from percutaneous coronary interventions (PCI) and coronary artery bypass grafting, performed either during the index hospitalization or after discharge. Further sensitivity analyses addressed other confounders such as strokes because of known or newly diagnosed atrial fibrillation (AF). Moreover, they addressed the potential effect of misclassification among *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* in the claims database.

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After adjustment for demographics and comorbidities, Merkler et al found that, compared with beneficiaries without acute MI, the risk of ischemic stroke was highest—almost 3-fold—during the first 4 weeks after MI (hazard ratio 2.7; 95% confidence interval 2.3–3.2), but remained heightened during weeks 5 to 8 (hazard ratio 2.0; 95% confidence interval 1.6–2.4) and even during weeks 9 to 12 (hazard ratio 1.6; 95% confidence interval 1.3–2.0). Notably, the associations were unaltered after excluding patients with prior or concurrent diagnosis of AF and even strengthened for weeks 0 to 4 when patients were censored at the time of coronary revascularization after discharge for acute MI. If patients were censored at the time of AF detection after discharge, the short-term results were in accordance with the main analysis, but clearly attenuated from weeks 5 to 8 onwards.

The key results of the study were further positioned in the perspective of 1-year mortality, which was about 15% higher for patients with acute MI plus stroke (51.5%) than for those with MI without stroke (37.1%).

The study structure used by Merkler et al cannot give definitive answers regarding the pathogenic mechanisms of the heightened stroke risk after acute MI. Left ventricular (LV) thrombi early after MI in the setting of anterior wall infarction is considered the prevailing cause for MI-associated ischemic stroke, resulting from LV regional wall akinesia and dyskinesia leading to blood stasis as well as inflammatory changes and hypercoagulability during acute MI.<sup>7</sup> The frequency of LV thrombi after acute MI has declined over time, from as high as 46% in the early days<sup>8</sup> to 15% in patients with ST-segment-elevation MI (STEMI) and 25% in anterior STEMI.<sup>9</sup> This decline has probably occurred because of widely available primary PCI, more aggressive antithrombotic treatment, and attenuated adverse LV remodeling.

Interestingly also, the risk of ischemic stroke was similarly elevated for up to 12 weeks for both STEMI and non-STEMI in the analysis by Merkler et al. Apart from LV thrombus, other potential mechanisms may explain the heightened risk of stroke after MI with restricted ischemia and minor wall motion abnormalities. These mechanisms may include delayed new-onset atrial fibrillation<sup>1</sup> (supported by Merkler and colleagues' finding of weaker association between stroke and MI when patients were censored at the detection of AF after discharge) and atrial dysfunction or atrial cardiopathy that carries a

heightened risk of ischemic stroke even in the absence of AF.<sup>10</sup> Furthermore, MI may reflect more generalized and severe atherosclerotic disease with systemic inflammatory changes and alterations in the function of the neurocardiac axis<sup>11</sup> that, in turn, may be associated with ischemic stroke risk also with noncardiac mechanisms, such as thromboembolism from the aortic arch or carotid or intracranial arteries, or small penetrating artery thrombosis.

While there is a growing body of data on how to manage patients with preexisting AF presenting with acute MI,<sup>12</sup> data on stroke prevention after acute MI are more limited for those without AF.<sup>13</sup> A number of randomized controlled trials in acute MI patients with AF have assessed the effect of direct oral anticoagulants as an add-on therapy to dual antiplatelet therapy with aspirin and clopidogrel.<sup>14</sup> However, only 1 phase III trial, ATLAS ACS 2 (Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndromes – Thrombolysis In Myocardial Infarction 51), studied MI patients without AF and found that a favorable effect with low doses of rivaroxaban—specifically, 2.5 mg BID in addition to dual antiplatelet therapy—was associated with a significant reduction of cardiovascular death, MI, or stroke as compared with a standard dual antiplatelet therapy regimen, but with a drawback of a 2-fold increase in the risk of major bleeding.<sup>15</sup>

Randomized trials to study the value of contemporary antithrombotic therapy regimens specifically aiming to prevent LV thrombus formation in acute MI have not been conducted. Yet, based on observational data, American College of Cardiology Foundation/American Heart Association prevention guidelines suggest considering treatment with anticoagulation for 3 months in the setting of STEMI with anterior apical akinesia or dyskinesia.<sup>16</sup> American Heart Association/American Stroke Association guidelines suggest the same regimen after acute anterior STEMI complicated with ischemic stroke or transient ischemic attack.<sup>17</sup> In the setting of LV thrombus, prospective data on the best anticoagulation regimen, duration, and combination with antiplatelets are lacking. Once diagnosed, oral anticoagulation is considered for 3 to 6 months, with limited experience for direct oral anticoagulants.<sup>13,16,17</sup>

There are many clinical and scientific implications of the results provided by Merkler and colleagues as they correctly point out. First, the results allow more accurate counseling of patients of their prognosis and stroke pathogenesis. Second, stroke pathogenetic classification systems may be revised according to longer risk period after acute MI. Third, the results are useful for designing clinical trials. Studies aiming to precisely identify the mechanisms and high-risk patients with respect to ischemic stroke after an acute MI are needed. For example, there

are still major uncertainties and gaps in the knowledge regarding the screening strategies, follow-up imaging, and treatment of LV thrombus after acute MI.<sup>9</sup> Moreover, the high mortality rate associated with ischemic stroke following an acute MI justifies randomized studies to find the optimal prevention for post-acute MI patients.

## Disclosures

Dr Putaala has served in Advisory Boards for Bayer, BMS-Pfizer, Boehringer-Ingelheim, and MSD, and received speaker's honoraria from Bayer, BMS-Pfizer, and Boehringer-Ingelheim. Dr Nieminen has served in Advisory Boards for AstraZeneca, Bayer, Boehringer-Ingelheim, and Servier and received speaker's honoraria from BMS-Pfizer, and Boehringer-Ingelheim, Orion, and Servier.

## References

1. Luo J, Li H, Qin X, Liu B, Zhao J, Maihe G, Li Z, Wei Y. Increased risk of ischemic stroke associated with new-onset atrial fibrillation complicating acute coronary syndrome: a systematic review and meta-analysis. *Int J Cardiol*. 2018;265:125–131.
2. Brammas A, Jakobsson S, Ulvenstam A, Mooe T. Mortality after ischemic stroke in patients with acute myocardial infarction: predictors and trends over time in Sweden. *Stroke*. 2013;44:3050–3055.
3. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35–41.
4. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol*. 2005;58:688–697.
5. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New approach to stroke subtyping: the A-S-C-O (phenotypic) classification of stroke. *Cerebrovasc Dis*. 2009;27:502–508.
6. Merkler AE, Diaz I, Wu X, Murthy SB, Gialdini G, Navi BB, Yaghi S, Weinsaft JW, Okin PM, Safford MM, Iadecola C, Kamel H. Duration of heightened ischemic stroke risk after acute myocardial infarction. *J Am Heart Assoc*. 2018;7:e010782. DOI: 10.1161/JAHA.118.010782.
7. Delewi R, Zijlstra F, Piek JJ. Left ventricular thrombus formation after acute myocardial infarction. *Heart*. 2012;98:1743–1749.
8. Asinger RW, Mikell FL, Elsparger J, Hodges M. Incidence of left-ventricular thrombosis after acute transmural myocardial infarction. Serial evaluation by two-dimensional echocardiography. *N Engl J Med*. 1981;305:297–302.
9. McCarthy CP, Vaduganathan M, McCarthy KJ, Januzzi JL Jr, Bhatt DL, McEvoy JW. Left ventricular thrombus after acute myocardial infarction: screening, prevention, and treatment. *JAMA Cardiol*. 2018;3:642–649.
10. Kamel H, Bartz TM, Elkind MSV, Okin PM, Thacker EL, Patton KK, Stein PK, deFilippi CR, Gottesman RF, Heckbert SR, Kronmal RA, Soliman EZ, Longstreth WT Jr. Atrial cardiopathy and the risk of ischemic stroke in the CHS (Cardiovascular Health Study). *Stroke*. 2018;49:980–986.
11. Fioranelli M, Bottaccioli AG, Bottaccioli F, Bianchi M, Rovesti M, Rocchia MG. Stress and inflammation in coronary artery disease: a review psychoneuroendocrine-immunology-based. *Front Immunol*. 2018;9:2031.
12. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, Haeusler KG, Boriani G, Capodanno D, Gilard M, Zeymer U, Lane D; Document Reviewers, Storey RF, Bueno H, Collet JP, Fauchier L, Halvorsen S, Lettino M, Morais J, Mueller C, Potpara TS, Rasmussen LH, Rubboli A, Tamargo J, Valgimigli M, Zamorano JL. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J*. 2014;35:3155–3179.

13. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177.
14. Chiarito M, Cao D, Cannata F, Godino C, Lodigiani C, Ferrante G, Lopes RD, Alexander JH, Reimers B, Condorelli G, Stefanini GG. Direct oral anticoagulants in addition to antiplatelet therapy for secondary prevention after acute coronary syndromes: a systematic review and meta-analysis. *JAMA Cardiol*. 2018;3:234–241.
15. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM; ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366:9–19.
16. O’Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362–e425.
17. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236.

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