Mitral Regurgitation and the Risk of Stroke among Patients with Atrial Fibrillation and Heart Failure

Anat Berkovitch MD[1,2]*, Michael Arad MD[1,2]*, Israel Mazin MD[1,2], Yishay Wasserstrum MD[1,2], Ori Vatury MD[1,2], Rafael Kuperstein MD[1,2], Dov Freimark MD[1,2], Eyal Nof MD[1,2], Roy Beinart MD[1,2], Ilan Goldenberg MD[3], and Avi Sabbag MD[1,2]

[1]Department of Cardiology, Leviev Heart Center, Sheba Medical Center, Tel Hashomer, Israel
[2]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel
[3]Clinical Cardiovascular Research Center, University of Rochester Medical Center, New York, NY, USA

ABSTRACT **Background:** Significant mitral regurgitation (MR) is associated with less spontaneous echo contrast but its effect on the occurrence of ischemic stroke in patients with atrial fibrillation (AF) is unknown.

Objectives: To examine the association of MR grade and the risk of ischemic stroke (IS) in AF patients with heart failure (HF).

Methods: We investigated 2748 patients with known AF who were hospitalized due to acute decompensated HF. All patients underwent echocardiography during hospitalization. Patients were divided into groups based on the degree of MR (high-grade MR [3–4] vs. no/low-grade MR [0–2]). The primary endpoint was IS during long term follow-up.

Results: Mean age was 79 ± 11 years, 48% were women. After 2 years of follow-up, the cumulative incidence of IS among patients with high-grade MR was significantly lower compared to patients with no/low-grade MR (6% vs. 12%, respectively; *P*-value = 0.0064). Multivariate Fine and Gray analysis, adjusting for CHA_2DS_2-VASc, and accounting for the competing risk of death and valve intervention, showed the presence of high-grade MR was associated with a significant 50% (*P* = 0.013) reduction in the risk of IS compared with no/low-grade MR. When added to the CHA_2DS_2-VASc score, MR grade allowed more accurate prediction of IS with an overall improvement of 12% (95% confidence interval 5–17%) using net reclassification index analysis.

Conclusions: Our findings suggest an inverse correlation between MR grade and the risk of stroke among AF patients with HF. These findings may be used for improved risk assessment in this population.

IMAJ 2025; 27: 719–724

KEY WORDS: atrial fibrillation, cerebrovascular attack, heart failure, ischemic stroke, mitral regurgitation

*These authors contributed equally to this study

Mitral regurgitation (MR) affects the flow parameters in the left atrium through a swirling-like activity and by increasing the blood volume traversing the chamber. Elimination of blood stasis manifests by decreasing the density of spontaneous echo contrast (SEC) seen in patients with atrial fibrillation [1]. The notion that the presence of MR may be associated with a reduction in the risk of thromboembolic events has been previously suggested in several studies, predating the widespread use of oral anticoagulation [2-4].

The presence of SEC is an independent risk factor for thrombus formation and subsequent ischemic stroke (IS) events [5]. Mitral regurgitation severity and SEC formation are inversely related, and significant MR has been shown to reduce SEC [3]. Disruption of blood stasis in the left atrium by the regurgitant jet is thought to account for its protective effect [5].

The CHA_2DS_2-VASc score is widely used to assess the annual risk of stroke among patients with nonrheumatic atrial fibrillation (AF). It is endorsed by both the European Society of Cardiology [6] and the American Heart Association [7] as a main tool to guide anticoagulation in AF. While risk of bleeding is routinely considered, protective factors that might modify the risk of thromboembolism are only seldom considered.

In this study, we evaluated the long-term risk of IS by the presence and severity of MR among AF patients with heart failure in the era of direct oral anticoagulation. We hypothesized that the presence of MR may have a protective effect against the risk of IS in AF patients due to reduced SEC and therefore may provide incremental prognostic implications to conventional CHA_2DS_2-VASc score risk-assessment in this population.

PATIENTS AND METHODS

STUDY POPULATION

The study population has been described previously [8]. All patients hospitalized at the Sheba Medical Center between January 2008 and March 2017 who had been diagnosed with acute heart failure exacerbation, acute on chronic heart failure, or decompensated heart failure were included in the current study. Hospitalized patients with a primary diagnosis of heart failure often exhibit a complex interplay of structural and rhythm-related cardiac abnormalities, making them a meaningful cohort for investigating the association between mitral regurgitation, atrial fibrillation, and stroke risk. The complete database includes 10,232 patients. Patients without AF at baseline were excluded (n=6435) as were those without documentation of MR grade (n=1049). Missing information regarding MR grade was due to technical issues, inability of the operator to determine grade, and request of further tests or a test preformed outside Sheba Medical Center. Thus, the final study sample comprised 2748 patients.

DATA COLLECTION

A complete physical examination by a physician followed by blood tests, which were analyzed at the center's laboratory, were performed in all patients. Medical history and current medications were documented in the patient's chart. All patients underwent transthoracic echocardiography within 48 hours of admission, according to the Sheba Medical Center standardized protocol and were read by an echocardiography specialist as part of the routine clinical practice. All information was recorded on a computerized database, which serves as the data source for this study.

DEFINITIONS AND OUTCOME MEASURES

The diagnosis of MR as well as quantification and assessment of its severity were conducted according to American society of Echocardiography guidelines [9]. For the primary analysis, patients were divided into two groups: no/low-grade MR (n=2494; none-moderate) and high-grade MR (n=254; moderate-severe to severe).

Data on the burden of co-morbidities was extracted for the medical record and was based on a comprehensive analysis of the list of diagnosis, medication history (e.g., oral anticoagulation or antihypertensive drugs), electrocardiograms documenting AF, lab results including hemoglobin A1C, imaging data indicating stroke or transient ischemic attack and history of percutaneous coronary intervention.

All patients had undergone a comprehensive echocardiography exam during or contiguous to acute hospitalization at the Sheba Medical Center echocardiography unit. The degree of MR and left ventricular function were evaluated in all cases.

The primary outcome of the current study was the first occurrence of IS during long-term follow-up. A new diagnosis of IS was based on any new neurologic deficit found on clinical evaluation followed by brain computed tomography or brain magnetic resonance imaging demonstrating new infarct. All hospitalization data were extracted from the computerized medical data at the Sheba Medical Center. Mortality data were ascertained using the Israeli National Population Registry.

STATISTICAL ANALYSIS

Categorical data were compared by MR severity using Student's *t*-test and one-way ANOVA. Categorical data were compared with the use of chi-square test or Fisher's exact test. The cumulative incidence of IS over 2 years of follow-up was assessed by MR grade, with comparisons using Gray's test in a competing risk setting. Multivariable regression analysis was used to evaluate hazard ratios for an IS event. We used Fine and Gray modeling that considered the competing risk of death and valve intervention. The risk associated with MR grade was evaluated in two separate models adjusted for different covariates. The first adjusted for the CHA_2DS_2-VASc score as a single additional covariate; and the second replaced the CHA_2DS_2-VASc score with the individual components of the score including age, sex, and cardiovascular risk factors (e.g., hypertension, diabetes mellitus, prior stroke, peripheral artery disease). The association between MR grade and the risk of IS was assessed with MR grade dichotomized in the primary analysis. Net reclassification index (NRI) was used to determine whether incorporation of MR grade to the CHA_2DS_2-VASc score can improve prediction of IS. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA) and Statistical analyses were performed using R Statistical Software, 2024.09.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among the 2748 study patients, mean age was 79 ± 11 years and 48% were female. The baseline clinical and echocardiography characteristics by the pre-specified MR groups are presented in Table 1. Patients with low grade

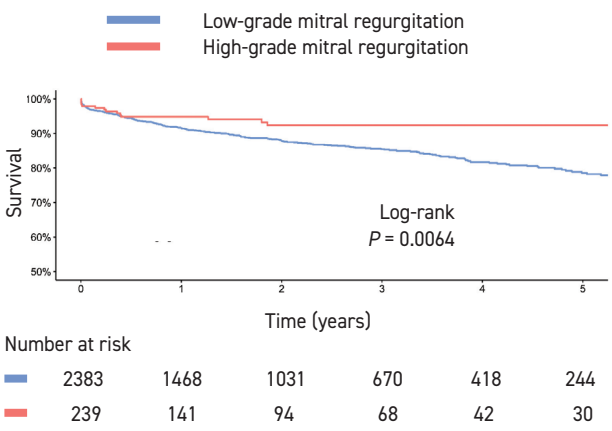
Table 1. Baseline characteristics of the atrial fibrillation population according to pre-specified mitral regurgitation groups

	No/Low-grade mitral regurgitation, n=2492	High-grade mitral regurgitation, n=254	*P*-value
Age*	79 ± 10	77 ± 12	0.008
Female sex**	1228 (49)	103 (41)	0.008
Diabetes mellitus **	765 (31)	64 (25)	0.07
Prior cerebrovascular attack**	469 (19)	28 (11)	0.002
Peripheral artery disease**	1151 (46)	112 (44)	0.53
Hypertension**	1527 (61)	134 (53)	0.009
Ischemic heart disease**	1285 (51)	131 (51)	0.99
Prior percutaneous coronary intervention*	23 (9.1)	361 (14.5)	0.059
Dyslipidemia**	1252 (50)	101 (40)	0.003
Chronic kidney disease**	698 (28)	80 (31)	0.24
Left ventricular ejection fraction*	49.2 ± 14	42.2 ± 17	< 0.001
Reduced ejection fraction	706 (30)	117 (49)	< 0.001
Left atrial area*	26.7 ± 6.5	31.7 ± 8.2	< 0.001
Anticoagulation use**	2235 (90)	232 (91)	0.388
Warfarin (among patients on anticoagulation)	1624 (73)	184 (79)	0.029
CHA_2DS_2-VASc*	4.8 (1.66)	4.3 (1.6)	< 0.001

*Values are represented as mean ± standard deviation

**Values are represented as n (%)

Figure 1. Cumulative incidence function curves according to mitral regurgitation grade



MR were older. They were more likely to be women, and they had a higher frequency of cardiovascular risk factors including hypertension, diabetes mellitus, dyslipidemia, and prior stroke. They had a significantly higher ejection fraction and smaller left atrial area. More than 90% of the study population were treated with anticoagulation with a similar rate in both groups. Most patients were discharged with warfarin (64%) while the minority were discharged with NOAC (36%). Patients in the high-grade MR group were more likely to be treated with warfarin compared to the no/low grade MR group (79% vs. 72%, $P = 0.029$). Mean INR value at admission was 2.0 ± 1.3 for the entire cohort, without significant difference between the two groups (2.0 for low grade MR and 1.96 for high grade MR, P = NS). According to common practice and the ESC guidelines of valvular heart disease, among patients with severe MR, 25 patients (10%) had mitral valve repair and 33 patients (13%) had mitral valve replacement. A total of 1247 patients were in sinus rhythm during the echocardiography test: 46% among the no/low MR group and 38% of the high grade MR group.

During a mean follow-up of 710 days (interquartile range 110–1105), 317 events of IS (11.2%) occurred. Crude incidence of IS according to MR grade after 2 years of follow-up found that the rate of IS was significantly higher among patients with trivial/none, mild, mild-moderate, and moderate-MR (19%, 17%, 17%, 18%, respectively) as compared with moderate-severe and severe MR (7% and 9%, respectively; $P = 0.003$ for the overall difference during follow-up).

Cumulative incidence function curves for the risk of stroke by the prespecified MR grade groups are shown in Figure 1. This analysis showed that at 2 years the cumulative incidence of IS was significantly lower among patients with high grade MR (6%) as compared with no/low grade MR (12%) ($P = 0.0064$) [Figure 1]. Univariate Fine and Gray analyses found that high-grade MR was associated with a 54% (hazard ratio 0.46, 95% confidence interval [95%CI] 0.27–0.79, $P = 0.0047$). reduced risk of IS compared to patients with no/low grade MR.

Multivariate Fine and Gray analyses adjusted for the CHA_2DS_2-VASc score showed that MR grade was independently associated with a significantly lower risk of stroke. High grade vs. no/low grade MR was associated with a significant 50% ($P = 0.013$) reduction in the risk of IS during long-term follow-up [Table 2]. Consistent results were shown when the CHA_2DS_2-VASc score was replaced by prespecified risk covariates [Table 3]. This analysis showed that high grade MR was associated

Table 2. Multivariate Fine and Grey analysis for long term stroke risk adjusted for CHA_2DS_2-VASc score

	Hazard ratio	95% confidence interval	*P*-value
High grade vs. no/low grade mitral regurgitation	0.50	0.29–0.86	0.013
CHA_2DS_2-VASc	1.19	1.10–1.28	< 0.001

Table 3. Multivariate Fine and Gray analysis for long term stroke risk adjusted for individual CHA_2DS_2-VASc score components

	Hazard ratio	95% confidence interval	*P*-value
High grade mitral regurgitation vs. low grade mitral regurgitation	0.49	0.28–0.84	0.009
Age, per year	1.00	0.99–1.01	0.54
Female sex	1.03	0.81–1.31	0.79
Hypertension	0.92	0.72–1.18	0.52
Diabetes mellitus	0.93	0.72–1.19	0.55
Prior cerebrovascular event	1.66	1.47–1.88	< 0.001
Peripheral vascular disease	0.91	0.71–1.16	0.43

with a significant 51% ($P = 0.009$) reduction in the risk of IS compared to patients with no/trivial MR during long-term follow-up [Table 3].

The NRI analysis was used to assess improvement in classification for the risk of IS among the study population. When added to the CHA_2DS_2-VASc score, MR grade allowed more accurate prediction of IS with an overall improvement of 12% (95%CI 5–17%).

DISCUSSION

The current study depicts a large cohort of AF patients with HF treated according to contemporary guidelines. We have shown that MR grade is associated with an inverse correlation with the risk of IS in this population. When assessed as a categorical co-variate, high grade MR was independent associated with a significant 50% reduced risk of IS. The association of MR grade with the risk of IS was sustained during 2 years of follow-up. The incorporation of MR grade in the risk assessment for IS provides incremental predictive value to the traditional CHA_2DS_2-VASc score.

A possible mechanism related to our findings may be related to the reduced SEC associated with MR in patients with AF. Left atrial enlargement and blood stasis in the left atrium are believed to be associated with thrombus formation and higher risk of cardio-embolic events [10-12]. This finding is supported by previous studies that found increased incidence of SEC, left atrium thrombus, and embolic events among patients with left atrium dilatation [13]. It is speculated that backward jet from the MR reduces LA stasis, increases left atrium appendage peak flow velocity and consequently decreases stroke risk [4]. Our findings are consistent with these data and suggest that significant MR may have a protective effect on cardio-embolic risk, regardless of anticoagulation use, possibly due to a corresponding reduction in blood stasis that manifests by reduced SEC. The importance of MR as a determinant of IS is accentuated by the fact that it was tested in a high-risk cohort with a high prevalence established predictors. Importantly the protective effect of MR remained significant even in the presence of stroke strong determinants such as advances age, heart failure, and previous history of stroke or chronic treatment with OAC.

In 1998, Nakagami and colleagues [13] were the first to evaluate whether MR degree is associated with reduced risk of stroke. In a relatively small cohort of patients with nonrheumatic MR, those with severe regurgitation had fewer ischemic stroke events during 8 years of follow-up, regardless of left atrium size. However, probably due to small sample size, the study did not correct for multiple co-variants including established risk factors for thromboembolic events.

While multiple studies have evaluated the risk factors for ischemic strokes among patients with AF [14], little attention is given to protective factors. Modification of the well-known risk factors might reduce the risk of stroke, especially among patients with high CHA_2DS_2-VASc scores [10]. To date, the only well-known, well-established factor that reduces the risk of ischemic stroke among patients with AF is anticoagulation use [11-13,15]. The decision to recommend lifelong anticoagulation therapy is never taken lightly. It is common practice to balance a patient's risk for stroke using the CHA_2DS_2-VASc on the one hand [16] with the bleeding risk using scores such as the HAS-BLED on the other [17]. Our results suggest that the risk of stroke may be reduced by a significant mitral regurgitate flow in heart failure patients with AF, which may facilitate clot dissolution and prevention blood stasis and thrombus formation. These data, if confirmed by additional prospective clinical studies, suggest that MR grade should be incorporated in the risk assessment for

IS in this population, with a possible consideration of MR as a protective factor in AF patients with a lower CHA_2DS_2-VASc score who are at a high risk of bleeding when discussing the need for oral anticoagulant therapy. Importantly, our NRI analysis showed that adding MR grade to the conventional CHA_2DS_2-VASc score improved risk assessment for IS in our study population.

Our findings suggest that MR grade and echocardiographic findings can be used to refine personalized risk assessment in elderly patients with heart failure, for example in patients with a high bleeding risk showing a borderline CHA_2DS_2-VASc score.

LIMITATIONS

First, this historical prospective, non-randomized, non-blinded observational study is subjected to limitations inherent to this design. Our results, while robust, are merely thought provoking and any change in our clinical approach should be first evaluated in a prospective study. Second, our cohort comprised exclusively patients with HF admitted with acute decompensation. Our specific and very high-risk population limits the generalization of our conclusions. Third, we do not have information regarding the lack of intervention among the patients outside our facility. Since our facility is a tertiary referral center, we assume that such interventions did not take place in other facilities and that surgical risk was too high. Mitral clips were only introduced at later stages and probably had neglecting effects on these patients. Fourth, data regarding the classification of atrial fibrillation as paroxysmal, persistent, or permanent were not collected, limiting our ability to assess potential differences in outcomes based on AF subtype. Another limitation is the lack of detailed information regarding the underlying etiology of valvular disease, including the presence of mechanical mitral valves or rheumatic mitral stenosis, which may have influenced. However, the proportion of patients treated with warfarin dose provides an approximation of the prevalence of these important entities in our cohort. The fact that warfarin use was higher in the high-grade MR group, while the rate of stroke was lower, further strengthened our findings. Data on prior atrial fibrillation ablation and cardioversion were incomplete and therefore could not be included in the analysis, potentially limiting the assessment of prior rhythm control strategies in the study population. Last, the high proportion of patients treated with anticoagulation in our cohort further limits our ability to assess the effect of MR on SI.

CONCLUSIONS

Our findings from a large cohort of heart failure patients with AF suggest that MR grade is inversely related to the risk of IS. Further prospective studies are needed to confirm our findings regarding the incremental predictive value of MR in the risk assessment of ischemic stroke in this population.

Correspondence

Dr. A. Berkovitch
Dept. of Cardiology, Leviev Heart Center, Sheba Medical Center, Tel Hashomer 52621, Israel
Email: anatberko@gmail.com

References

1. Chimowitz MI, DeGeorgia MA, Poole RM, Hepner A, Armstrong WM. Left atrial spontaneous echo contrast is highly associated with previous stroke in patients with atrial fibrillation or mitral stenosis. *Stroke* 1993; 24 (7): 1015-9.
2. Movsowitz C, Movsowitz HD, Jacobs LE, Meyerowitz CB, Podolsky LA, Kotler MN. Significant mitral regurgitation is protective against left atrial spontaneous echo contrast and thrombus as assessed by transesophageal echocardiography. *J Am Soc Echocardiogr* 1993; 6 (2): 107-14.
3. Blackshear JL, Pearce LA, Asinger RW, et al. Mitral regurgitation associated with reduced thromboembolic events in high-risk patients with nonrheumatic atrial fibrillation. Stroke Prevention in Atrial Fibrillation Investigators. *Am J Cardiol* 1993; 72 (11): 840-3.
4. Karatasakis GT, Gotsis AC, Cokkinos D V. Influence of mitral regurgitation on left atrial thrombus and spontaneous echocardiographic contrast in patients with rheumatic mitral valve disease. *Am J Cardiol* 1995; 76 (4): 279-81.
5. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol* 1994; 23 (4): 961-9.
6. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) [Available from: https://www.escardio.org/static-file/Escardio/Guidelines/Documents/ehaa612.pdf]. [Accessed 7 October 2021].
7. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration with the Society of Thoracic Surgeons. *Circulation* 2019; 140 (2): e125-e151.
8. Berkovitch A, Mazin I, Younis A, et al. CHA_2DS_2-VASc score performance to predict stroke after acute decompensated heart failure with and without reduced ejection fraction. *Europace* 2019; 21 (11): 1639-45.
9. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021; 143 (5): e35-e71.

10. Markl M, Lee DC, Carr ML, et al. Assessment of left atrial and left atrial appendage flow and stasis in atrial fibrillation. *J Cardiovasc Magn Reson* 2015; 17 (Suppl 1): M3.

11. Goldman ME, Pearce LA, Hart RG, et al. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: I. Reduced flow velocity in the left atrial appendage (The Stroke Prevention in Atrial Fibrillation [SPAF-III] study). *J Am Soc Echocardiogr* 1999; 12 (12): 1080-7.

12. Fukuda N, Hirai T, Ohara K, Nakagawa K, Nozawa T, Inoue H. Relation of the severity of mitral regurgitation to thromboembolic risk in patients with atrial fibrillation. *Int J Cardiol* 2011; 146 (2): 197-201.

13. Nakagami H, Yamamoto K, Ikeda U, Mitsuhashi T, Goto T, Shimaria K. Mitral regurgitation reduces the risk of stroke in patients with nonrheumatic atrial fibrillation. *Am Heart J* 1998; 136 (3): 528-32.

14. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017; 30 (4): 303-71.

15. Olshansky B, Heller EN, Mitchell LB, et al. Are transthoracic echocardiographic parameters associated with atrial fibrillation recurrence or stroke? Results from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. *J Am Coll Cardiol* 2005; 45 (12): 2026-33.

16. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021; 42 (5): 373-498.

17. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; 138 (5): 1093-100.

Capsule

Parvalbumin interneurons regulate rehabilitation-induced functional recovery after stroke and identify a rehabilitation drug

Okave and colleagues, using a photothrombotic stroke model in male mice, demonstrated that rehabilitation after stroke selectively enhances synapse formation in presynaptic parvalbumin interneurons and postsynaptic neurons in the rostral forelimb motor area with axonal projections to the caudal forelimb motor area where stroke was induced (stroke-projecting neuron). Rehabilitation improves motor performance and neuronal functional connectivity, while inhibition of stroke-projecting neurons diminishes motor recovery. Stroke-projecting neurons show decreased dendritic spine density, reduced external synaptic inputs, and a lower proportion of parvalbumin synapse in the total GABAergic input. Parvalbumin interneurons regulate neuronal functional connectivity, and their activation during training is necessary for recovery. Furthermore, gamma oscillation, a parvalbumin-regulated rhythm, is increased with rehabilitation-induced recovery in animals after stroke and stroke patients. Pharmacological enhancement of parvalbumin interneuron function improves motor recovery after stroke, reproducing rehabilitation recovery. These findings identify brain circuits that mediate rehabilitation-recovery and the possibility for rational selection of pharmacological agents to deliver the first molecular-rehabilitation therapeutic.

Nat Commun 2025; 16, 2556

Eitan Israeli

Capsule

Safety, efficacy, and immunogenicity of a Salmonella paratyphi A vaccine

In a double-blind, randomized, placebo-controlled trial, **McCann** and colleagues evaluated an orally administered live, attenuated *S. Paratyphi* A vaccine (CVD 1902) using a controlled human infection model. A total of 72 participants underwent randomization, of whom 34 in the CVD 1902 group and 36 in the placebo group were challenged with *S. Paratyphi* A. The number of adverse events was generally similar in the two groups, and no vaccine-related serious adverse events were identified. CVD 1902 induced s erum IgG and IgA responses to the O antigen of *S. Paratyphi* A. No increases in serum IgG or IgA titers occurred in the placebo group. In the intention-to-treat population, an *S. Paratyphi* A infection was diagnosed within 14 days after challenge in 21% of the participants in the CVD 1902 group and in 75% of those in the placebo group ($P < 0.001$), resulting in a vaccine efficacy of 73% (95% confidence interval 46–86). The vaccine efficacy was 69% (95% confidence interval 42–84) in the per-protocol analysis.

N Engl J Med 2025; 393: 1704

Eitan Israeli