# Pre- and Post-transcatheter Aortic Valve Replacement (TAVR) Serum Mean Platelet Volume Levels and All-Cause Mortality

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**ABSTRACT** **Background:** Among the most frequent complications following transcatheter aortic valve replacement (TAVR) is hemostasis imbalance that presents either as thromboembolic or bleeding. Deviations in platelet count (PC) and mean platelet volume (MPV) are markers of hemostasis imbalance.

**Objectives:** To determine the predictive value of pre- and post-procedural PC and MPV fL 1-year all-cause mortality in patients who underwent TAVR.

**Methods:** In this population-based study, we included 236 TAVR patients treated at the Tzafon Medical Center between 1 June 2015 and 31 August 2018. Routine blood samples for serum PC levels and MPV fL were taken just before the TAVR and 24-hour post-TAVR. We used backward regression models to evaluate the predictive value of PC and MPV in all-cause mortality in TAVR patients.

**Results:** In this study cohort, MPV levels 24-hour post-TAVR that were greater than the cohort median of 9 fL (interquartile range 8.5–9.8) were the strongest predictor of 1-year mortality (hazard ratio 1.343, 95% confidence interval 1.059–1.703, *P*-value 0.015). A statistically significant relationship was seen in the unadjusted regression model as well as after the adjustment for clinical variables.

**Conclusions:** Serum MPV levels fL 24-hour post-procedure were found to be meaningful markers in predicting 1-year all-cause mortality in patients after TAVR.

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**KEY WORDS:** aortic stenosis, mean platelet volume, mortality, platelet count, transcatheter aortic valve replacement (TAVR)

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Transcatheter aortic valve replacement (TAVR) represents a paradigm shift in therapeutic options for severe aortic stenosis (AS). Since being first described in 2002 [1,2], TAVR has rapidly disseminated, with over 350,000 procedures performed in more than 70 countries [1,2]. The growth in TAVR demand has further increased with the number of calcification-related AS patients rising and is likely to double in the next two decades [3], especially with the recent expansion of TAVR into intermediate and lower-risk patients as recommended by clinical practice guidelines in 2017 [2,4].

TAVR has become the standard of care; thus, there have been efforts to define clinical, hemodynamic, and biochemical parameters to improve patient selection and to guide physicians regarding postoperative care and follow-up post-TAVR [5,6]. Over the last decade, risk stratification research has improved greatly. B-type natriuretic peptide (BNP) is a great example [7]. Despite the progress in research of TAVR risk today, risk stratification in patients who are considering undergoing TAVR is limited and is based on clinical parameters, fragility assessment, and surgical scoring systems used for surgical aortic valve replacement (SAVR) such as the Society of Thoracic Surgeons risk score and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) [8]. Both tools may provide some insight into TAVR mortality [9] and may highlight the efforts needed to undertake to develop a TAVR-specific risk prediction instrument.

In general, platelets aid in hemostasis and are important in inflammation, thrombosis, and atherogenesis [10,11]. As such, they are integral in adverse cardiovascular events following TAVR [10,11]. To date, platelet count (PC) and mean platelet volume (MPV) have been studied with controversial findings.

Some studies claim that there is a correlation between PC deviations post-TAVR and post-TAVR outcomes [12,13] while others disagree [14]. Gul et al. [10] reported that MPV decreases due to improvement in severe AS, and Magri et al. [11] claimed that baseline MPV value is an independent predictor for short-term life-threatening complications. The relationship between PC, MPV, and TAVR mortality has not been widely studied. PC and MPV may be used as a simple test for clinical and hematologic changes in TAVR. Accordingly, in this study, our objective

**Table 1.** Baseline characteristics

| Variable label | Total cohort |
|---|---|
| TAVR procedure, n | 236 |
| **Demographic characteristics** | |
| Body mass index | 28.8 ± 6.7 |
| Age in years, median (IQR) | 80.5 ± 6.8 |
| Sex: female, n (%) | 135 (57.2%) |
| **Medical co-morbidities** | |
| Diabetes mellitus, n (%) | 109 (46.2%) |
| Dyslipidemia, n (%) | 183 (77.5%) |
| Hypertension, n (%) | 210 (89.0%) |
| Congestive heart failure, n (%) | 70 (29.7%) |
| Chronic obstructive lung disease / interstitial lung disease, n (%) | 29 (12.3%) |
| Chronic kidney disease stages 3–5, n (%) | 63 (26.7%) |
| Cirrhosis, n (%) | 2 (0.8%) |
| Atrial Fibrillation, n (%) | 72 (30.5%) |
| Coronary artery disease, n (%) | 138 (58.5%) |
| Cerebrovascular disease, n (%) | 60 (25.4%) |
| Peripheral vascular disease, n (%) | 21 (8.9%) |
| **Previous cardiac-surgery procedure** | |
| Prior permanent pacemaker, n (%) | 32 (13.6%) |
| Previous percutaneous coronary intervention, n (%) | 114 (48.5%) |
| Previous coronary artery bypass graft, n (%) | 30 (12.7%) |
| Previous valve surgery, n (%) | 6 (2.5%) |
| **Clinical presentation** | |
| Syncope, n (%) | 36 (15.3%) |
| Angina, n (%) | 56 (23.7%) |
| Congestive heart failure, n (%) | 190 (80.5%) |
| **New York Heart Association (NYHA) Class** | |
| 1, n (%) | 34 (14.4%) |
| 2, n (%) | 196 (83.1%) |
| 3/4, n (%) | 4 (1.7%) |
| **Laboratory test** | |
| Pre-TAVR PC 103/mcl, mean ± SD | 222.05 ± 68.20 |
| Pre-TAVR MPV fL, mean ± SD | 8.90 ± 1.08 |
| **Echocardiogram** | |
| Ejection fraction pre-TAVR, mean ± SD | 57.48 ± 11.26 |
| **TAVR procedure status,** n (%) | |
| Elective | 183 (77.5%) |
| Urgent/Emergent | 53 (22.5%) |
| Society of thoracic surgery risk score, mean ± SD | 4.2 ± 2.6 |
| **TAVR device** | |
| Self-expandable, n (%) | 202 (85.5%) |
| Balloon-expandable, n (%) | 34 (14.5%) |
| **Follow-up, months, mean ± SD** | 24.05 ± 12.14 |

HR = hazard ratio, IQR = interquartile range,
MPV = mean platelet volume, SD = standard deviation,
TAVR = transcatheter aortic valve replacement

was to examine whether PC and MPV levels predicted 1-year all-cause mortality rates in post-TAVR patients.

## PATIENTS AND METHODS

A single-center retrospective cohort study was conducted at the Tzafon Medical Center. The study was approved by our institutional research ethics board (IRB ID0099-14-POR).

### DATA SOURCES

We used data collected from the Tzafon Medical Center TAVR registry. The TAVR database contains demographics, co-morbidities, and procedural variables from our center. Data were collected from the medical charts and procedure technical reports of all patients who underwent TAVR at our institution.

### PATIENT SELECTION

We included all 236 sequential patients who underwent TAVR at Tzafon Medical Center from 1 June 2015 to 31 August 2018.

### PLATELETS AND MPV MEASUREMENT

Blood tests for serum PC and MPV are routinely assessed in all TAVR patients before the TAVR procedure, immediately after the procedure, and 24 hours after the procedure. Blood samples were drawn from the antecubital fossa or other accessible veins, such as the dorsal hand vein, and the blood was collected to chilled EDTA tubes. PC and MPV were assessed by the ADVIA 2120i (Manufactured by Siemens, Germany).

### OUTCOME VARIABLES

Our primary clinical outcome was the 1-year all-cause mortality post-TAVR procedure. Mortality was defined as death from any cause within the first year post-TAVR, starting from the day of the TAVR procedure. All-cause mortality was determined retrospectively for all patients by hospital chart review and by matching identification numbers of patients with the Israeli National Population Register.

### ADDITIONAL CO-VARIATES

Demographic, clinical echocardiogram, and laboratory data were abstracted from the patient records. Chronic kidney disease (CKD) stages 3–5 was defined as GFR 59 ml/min/1.73 $m^2$ and below. Discharge diagnoses and complications during the hospitalization were determined and recorded by the attending physicians based on clinical information, echocardiogram imaging, and laboratory tests.

### STATISTICAL ANALYSIS

Statistical analyses were performed using Statistical Package for the Social Sciences software version 18 (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as frequency (percentage), and continuous variables were presented as mean ±

**Table 2.** Univariate and multivariable analysis, 1-year mortality post-TAVR

| **Univariate analysis** | | |
|---|---|---|
| **Parameter** | **HR (95%CI)** | ***P*-value** |
| Age | 0.987 (0.941–1.035) | 0.584 |
| Sex: female | 0.607 (0.312–1.18) | 0.141 |
| Body mass index | 0.968 (0.918–1.022) | 0.243 |
| Congestive Heart Failure | 1.485 (0.576–3.827) | 0.413 |
| Dyslipidemia | 0.972 (0.442–2.139) | 0.944 |
| Diabetes mellitus | 1.254 (0.646–2.433) | 0.504 |
| Pulmonary hypertension pre-TAVR | 1.290 (0.772–2.156) | 0.332 |
| Pulmonary Hypertension post-TAVR | 1.563 (1.132–2.159) | 0.007 |
| Hypertension | 0.957 (0.338–2.710) | 0.934 |
| Lung disease | 1.625 (0.675–3.914) | 0.279 |
| Chronic kidney disease stages 3–5 | 3.723 (1.914–7.244) | < 0.001 |
| Coronary artery disease | 1.064 (0.541–2.092) | 0.858 |
| Atrial fibrillation | 1.978 (1.180–3.315) | 0.010 |
| Cerebrovascular disease | 2.101 (1.068–4.132) | 0.031 |
| Peripheral vascular disease | 2.283 (0.948–5.501) | 0.066 |
| MPV pre-TAVR | 1.304 (0.993–1.711) | 0.056 |
| MPV post-TAVR | 1.157 (0.844–1.585) | 0.364 |
| MPV 24-hours after TAVR | 1.343 (1.059–1.703) | 0.015 |
| PC pre-TAVR | 0.999 (0.994–1.004) | 0.611 |
| PC post-TAVR | 1.001 (0.995–1.007) | 0.81 |
| PC 24-hours after TAVR | 0.998 (0.992–1.003) | 0.417 |
| Elective TAVR | 0.573 (0.281–1.17) | 0.127 |
| Ejection fraction % pre-TAVR | 0.971 (0.944–0.999) | 0.04 |
| Ejection Fraction % post-TAVR | 0.969 (0.94–0.998) | 0.039 |
| Peak gradient post-TAVR | 1.003 (0.996–1.04) | 0.894 |
| Mitral regurgitation post-TAVR | 1.486 (0.898–2.460) | 0.123 |
| Paravalvular leak post-TAVR | 2.001 (1.029–3.894) | 0.041 |
| **Multivariable Cox regression** | | |
| Chronic kidney disease stages 3–5 | 3.287 (1.640–6.588) | 0.001 |
| Atrial fibrillation | 1.951 (1.045–3.641) | 0.036 |
| MPV 24-hours after TAVR | 1.372 (1.049–1.796) | 0.021 |
| Ejection fraction % post-TAVR | 0.971 (0.939–1.003) | 0.078 |

95%CI = 95% confidence interval, HR = hazard ratio, MPV = mean platelet volume, TAVR = transcatheter aortic valve replacement

standard deviation (SD) or median ± interquartile range (IQR). The Friedman Test was performed to assess differences in the levels of the primary parameters, MPV and PC, pre-TAVR, immediately after the procedure, and 24 hours post-TAVR.

One-year mortality following the TAVR procedure was estimated using the Kaplan–Meier method, with a 95% confidence interval (95%CI). Incidence rates were calculated from life tables. The log-rank test was used to test whether the differences in survival times between patients with MPV and PC lower or equal to the median and patients with MPV and PC >higher than median levels at 24-hour post-TAVR procedure.

To further evaluate the independent predictors of mortality, we performed a univariable Cox regression analysis. Using the backward Cox regression model, we utilized a backward variable elimination process. We began by assessing the statistical significance of the univariate association between each covariate and outcome. All covariates that had a univariate statistical significance of < 0.01 were forced into a multivariable model. Backward variable elimination was then used to develop a parsimonious regression model. Variables with adjusted statistical significance of < 0.1 were retained in the final model. Hazard ratio (OR) with a 95%CI and *P*-values were derived from the Wald chi-square test. Linear regression analysis was conducted to assess the relationship between the delivery system of the valve implanted (self-expandable/balloon-expandable) and MPV levels, which showed no correlation.

A receiver-operating characteristic (ROC) curve was calculated for lower than or equal to the median or higher than the median of the primary parameters. The results were significant predictors of all-cause mortality. Sensitivity and specificity were computed for median of primary parameters using the median as the cutoff point. *P*-value < 0.05 was considered statistically significant.

## RESULTS

We included all 236 sequential patients who underwent TAVR at Tzafon Medical Center during our study period. Baseline characteristics of the total cohort are found in table 1. In the total cohort, the mean follow-up time was 24.05 ± 12.14 months. The median age was 80.5 years (IQR ± 6.8) and 57.2% of patients were female. Most of the patients had elective procedures 77.5%, with a higher rate of self-expandable versus balloon-expandable valve implantation (85.5% vs. 14.5%, respectively). Mean ± SD ejection fraction pre-TAVR was 57.5% ± 11.3%.

Median MPV 24-hour post-TAVR was 9 fL (IQR 8.5–9.8), median PC 24-hour post-TAVR was 175 103/mcL (IQR 138–227). The Kaplan–Meier survival analysis and log-rank test [Figure 1] revealed that patients with MPV levels higher than the median MPV at 24-hour post-TAVR had lower 1-year survival rates compared to patients with equal or lower than the median MPV levels at 24-hour post-TAVR (log-rank test, chi-square = 5.488, $P < 0.019$). The overall mortality rate 1-year post-TAVR was 14.5% (n=34), 25 patients had MPV levels above the median. PC median did not predict mortality.

### UNIVARIABLE COX REGRESSION ANALYSIS

The results of the univariable cox regression analysis are presented in Table 2. MPV levels fL 24-hour post-TAVR that were greater than the cohort median were the strongest predictors of 1-year mortality with a hazard ratio (HR) 1.343, 95%CI 1.059–1.703, $P = 0.015$. Other mortality predictors were CKD stages

**Figure 1.** The Kaplan–Meier survival analysis and log-rank test

MPV = mean platelet volume, TAVR = transcatheter aortic valve replacement

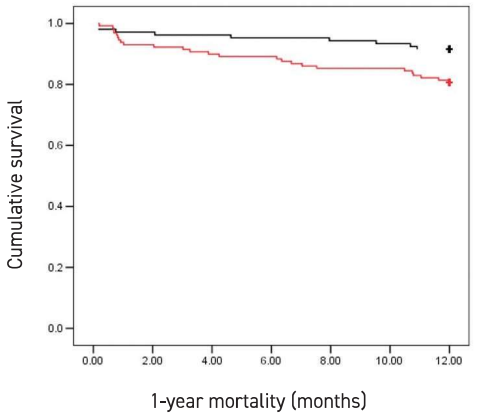
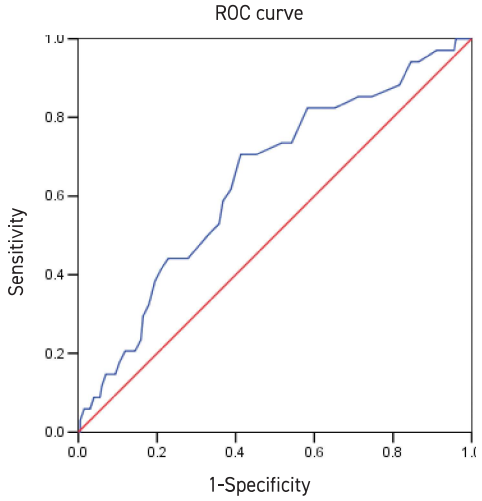



**Figure 2.** The ROC curves for 24-hours post-TAVR median MPV fL

MPV = mean platelet volume, ROC = receiver operating characteristic, TAVR = transcatheter aortic valve replacement




3–5 (HR 3.723, 95%CI 1.914–7.244, *P* = 0.001), paravalvular leak (PVL) post-TAVR (classified as mild, moderate, or severe [15,16]) (HR 2.001, 95%CI 1.029–3.894, *P* = 0.041), atrial fibrillation (AF) (HR 1.978, 95%CI 1.180–3.315, *P* 0.010), pulmonary hypertension (PHTN) post-TAVR (HR 1.563, 95%CI 1.132–2.159, *P* = 0.007), cerebrovascular disease (CVD) (HR 2.101, 95%CI 1.068–4.132, *P* = 0.031), ejection fraction (EF) pre-TAVR (HR 0.972, 95%CI 0.944–0.999, *P* = 0.04), and EF post-TAVR (HR 0.969, 95%CI 0.94–0.998, *P* = 0.039).

Age, sex, body mass index (BMI), congestive heart failure (CHF), dyslipidemia (DLP), diabetes mellitus (DM), PHTN pre-TAVR, hypertension, lung disease, coronary artery disease (CAD), peripheral vascular disease (PVD), MPV pre-TAVR, MPV immediately after TAVR, PC pre-TAVR, PC post-TAVR, PC 24 hours after TAVR, peak gradient post-TAVR, and mitral regurgitation (MR) post-TVAR were not significant.

### MULTIVARIABLE COX REGRESSION ANALYSIS

All covariates that had the univariate statistical significance of < 0.01 were retained in the backward multivariable model. HR with 95%CI and *P*-values were derived from the Wald chi-square test [Table 2]. In the final model, which included all step 1 variables, median MPV 24-hour post-TAVR was strongly associated with 1-year mortality (HR 1.372, 95%CI 1.049–1.796, *P* = 0.02). Other predictors of mortality were CKD stages 3–5 (HR 3.287, 95%CI 1.640–6.588, *P* = 0.001), and AF (HR 1.951, 95%CI 1.045–3.641, *P* = 0.36). EF post-TAVR was not significant.

The ROC curves for 24-hour post-TAVR median MPV are presented in Figure 2. The AUC was 0.641 (95%CI 0.542–0.739, *P* = 0.009) when stratified by 24-hour post-TAVR median MPV. A cutoff of median MPV ≤/> 8.95 fL 24-hour post-TAVR had a sensitivity of 73.5% and specificity of 52%.

## DISCUSSION

In our population-based study of TAVR patients, we found that among all the parameters we assessed, MPV level 24-hour post-TAVR was the strongest independent predictor of 1-year all-cause mortality rate in post-TAVR patients. We found that MPV levels higher than the 24-hour post-TAVR median had higher mortality rates (cutoff median of 8.95 fL, 75.3% sensitivity, 52% specificity).

The use of TAVR in the last decade has increased dramatically, exceeding SAVR, which has contributed to the decrease in complications and mortality due to valve replacement, as shown in the PARTNER trials [4]. However, the 1-year mortality remains high [5,17], which emphasizes the need to explore possible predictors of TAVR outcomes to enable the selection of patients who would most benefit from TAVR [17]. Several studies have suggested blood biomarkers as possible predictors of TAVR morbidity and mortality, with the most studied being BNP, creatinine kinase myocardial band, C-reactive protein, cardiac troponin, growth differentiation factor-15, high on-treatment platelet reactivity, and MPV [5]. Medranda and colleagues [7] observed 1297 severe symptomatic AS patients who underwent TAVR and concluded a suggestion that baseline BNP can be a non-invasive, impartial instrument to classify the patients need to be closely monitored post-TAVR.

We aimed to improve the knowledge of TAVR-relevant blood biomarkers and to strengthen the available risk stratification. The most frequent complication following TAVR is a hemostatic imbalance, which can present as thromboembolic or bleeding events [18]. Both thromboembolic and bleeding events

are related to the turbulent flow caused by AS and the presence of the bioprosthetic valve beside the native tissue [18]. Since PC and MPV can be markers of hemostatic imbalance, we sought to determine whether there was a correlation between PC or MPV and 1-year mortality to improve patient evaluation in patients requiring close monitoring.

Our primary finding was that 24-hour post-TAVR MPV levels higher than the median are a strong predictor of 1-year all-cause mortality. Platelet size is measured by MPV, representing platelet activation and homeostatic efficacy [11,12], with higher MPV values indicating large and active platelets [5,19,20], thus suggesting increased thrombotic activity and reduced bleeding rate [11,12]. Studies presenting high values of MPV in AS patients attributed this finding to the shear stress in turbulent flow seen following TAVR [21,22]. Our primary findings were supported by Slavka and co-authors [19]. They found that higher MPV correlates with vascular mortality and ischemic heart disease. Gul et al. [10] found that MPV decreased following TAVR due to improvement in severe AS. Since literature about the relation between TAVR and MPV is scarce, it is difficult to compare our results to previous studies, which mainly focused on short-term outcomes, in contrast to our objective of 1-year all-cause mortality. Magri et al. [11] analyzed a cohort of 330 TAVR patients, measuring only baseline MPV and PC at admission and focusing on combined safety endpoint (CSEP) at 30 days, which included all-cause mortality and other parameters. The authors stated that baseline MPV was an independent predictor of CSEP at 30-days, but a univariate analysis found the association of MPV with strictly all-cause mortality was statistically not significant ($P = 0.17$) [11]. In our univariate analysis, baseline MPV was indeed statistically not significant ($P = 0.056$), but MPV 24-hour post-TAVR was found to be significant ($P = 0.015$). The difference in the results can be explained by the fact that Magri et al. [11] analyzed only baseline MPV and not post-TAVR. The possibility exists that platelet activation by the endothelial damage and turbulent flow caused by the prosthesis implantation may increase MPV. Magri et al. also found that MPV levels above their MPV cutoff point of 10.75 fL (58% sensitivity, 54% specificity) were associated with lower CSEP rates [11]. This finding is in stark contrast to our results, which demonstrated that MPV levels higher than the 24-hour post-TAVR median of 8.95 fL (75.3% sensitivity, 52% specificity) had higher mortality rates. This discrepancy may be explained by the fact that Magri et al. studied short-term outcomes with CSEP at 30 days post-TAVR [11] in contrast to 1-year all-cause mortality, which was investigated in our study.

Regarding platelet count, previous studies have demonstrated that PC decline following TAVR is a common phenomenon [5,12,23,24]. The PC decline, explained by platelet activation and thus consumption [6,10-12,20], may be an outcome of endothelial damage caused by prosthesis implantation, fibrinogen binding on metallic armatures, and shear stress modification due to prosthesis implantation, which occurs throughout the TAVR procedure [12].

However, there is disagreement in the literature regarding whether PC correlates with post-TAVR outcomes. While some claim that the degree of PC decline following TAVR is an independent predictor of TAVR outcomes [12,13], others showed no direct correlation between the two [14]. Our study found PC to have no statistical significance predicting TAVR long-term mortality.

Our study should be interpreted in several contexts. First, while it has a fair number of patients, it was a retrospective single-center study. Second, our primary outcome of interest was all-cause mortality, and we could not separate cardiac versus non-cardiac mortality causes. Moreover, in this study we did not investigate other major adverse cardiovascular events (MACE) such as acute myocardial infarction, or stroke. Future studies should investigate the relationships between MPV levels and other MACE parameters.

## CONCLUSIONS

Using a serum MPV level 24-hours post-TAVR cutoff of 8.95 fL may better identify patients who require future closer clinical follow-up to reduce mortality rates post TAVR.

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**Courage is the price that life exacts for granting peace. The soul that knows it not, knows no release from little things.**

Amelia Earhart (1897–1937), American aviation pioneer and author, the first female aviator to fly solo across the Atlantic Ocean

**If you want to build a ship, don't drum up people together to collect wood and don't assign them tasks and work, but rather teach them to long for the endless immensity of the sea.**

Antoine de Saint-Exupery (1900–1944), French writer, poet, journalist, and pioneering aviator

**Capsule**

## Genetic stabilization of attenuated oral vaccines against poliovirus types 1 and 3

Vaccination with Sabin, a live attenuated oral polio vaccine (OPV), results in robust intestinal and humoral immunity and has been key to controlling poliomyelitis. As with any RNA virus, OPV evolves rapidly to lose attenuating determinants critical to the reacquisition of virulence resulting in vaccine-derived, virulent poliovirus variants. Circulation of these variants within underimmunized populations leads to further evolution of circulating, vaccine-derived poliovirus with higher transmission capacity, representing a significant risk of polio re-emergence. A new type 2 OPV (nOPV2), with promising clinical data on genetic stability and immunogenicity, recently received authorization from the World Health Organization for use in response to circulating vaccine-derived poliovirus outbreaks. **Yeh** et al. reported the development of two additional live attenuated vaccine candidates against type 1 and 3 polioviruses. The candidates were generated by replacing the capsid coding region of nOPV2 with that from Sabin 1 or 3. These chimeric viruses show growth phenotypes similar to nOPV2 and immunogenicity comparable to their parental Sabin strains but are more attenuated. The experiments in mice and deep sequencing analysis confirmed that the candidates remained attenuated and preserved all the documented nOPV2 characteristics concerning genetic stability following accelerated virus evolution. Importantly, these vaccine candidates were highly immunogenic in mice as monovalent and multivalent formulations and may contribute to poliovirus eradication.

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