The Use of Embolic Protection Devices During Transcatheter Aortic Valve Implantation

Arthur Shiyovich MD[1,2] and Ran Kornowski MD FESC FACC[1,2]

[1]Department of Cardiology, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

ABSTRACT: Aortic stenosis (AS) is a common valvular pathology and is increasing in prevalence. Severe symptomatic AS is associated with serious outcomes if left untreated. Transcatheter aortic valve implantation (TAVI) is an innovative modality, which has revolutionized the treatment of AS. With growing experience and technological upgrades, TAVI has become a valid alternative to surgical valve replacement. However, TAVI is associates with non-negligible risks of mortality, stroke, physical disability, and healthcare expenditures. Furthermore, imaging modalities have shown new ischemic lesions in most patients following TAVI (silent strokes), which might be related to worse subsequent neurocognitive function. Embolic protective devices are emerging as a safe, technically feasible implements to reduce the burden of periprocedural thromboembolism, and have shown promising results of improved clinical outcomes.

IMAJ 2019; 21: 615–619

KEY WORDS: embolic protection device, stroke, thromboembolism, transcatheter aortic valve implantation (TAVI)

Aortic stenosis (AS) is a common valvular pathology among the elderly and its prevalence is expected to increase significantly with aging of the population [1-3]. After symptoms begin to develop, severe AS is associated with approximately 50% mortality during the 2 years following if left untreated [1]. Nevertheless, until approximately one decade ago, many patients went untreated due to high risk for surgical aortic valve replacement (SAVR) [2]. Transcatheter aortic valve implantation (TAVI) is an innovative modality, which emerged over one decade ago and revolutionized the treatment of AS. Approximately 500,000 TAVI procedures have been performed worldwide to date [2]. Furthermore, with growing experience and technological upgrades, TAVI has become a valid alternative in intermediate-risk patients, and it is currently under investigation for low-risk patients [2]. However, TAVI is associates with higher rates of stroke, which increase the risk of mortality, physical disability, and healthcare expenditure, which may be perceived by some patients as "worse than death" [1-4].

Stroke (overt or silent) is a prevalent complication in transcatheter aortic valve implantation patients, often caused by thromboembolism and associated with significantly worse patient outcomes

STROKE CLASSIFICATIONS, INCIDENCE, AND MECHANISMS FOLLOWING TAVI

The definition of stroke following TAVI, and as a result the incidence of stroke, varies significantly in clinical trials. In an effort to unify such discrepancies various definitions have been suggested by professional societies/consortiums [2] ranging from predominantly clinical definitions to wider definitions that include imaging or neuropathological findings, even without evidence of neurological deficiencies (silent stroke).

The landmark Placement of Aortic Transcatheter Valves (PARTNER) clinical trial reported a stroke rate of 5.5% at 30 days and 8.3% at 1 year. Rates were significantly higher than for patients who underwent SAVR (2.4% and 4.3%, respectively) [5]. In inoperable patients, the rate was 6.7% and 10.6% for 30 days and one year, respectively.

Recent clinical trials and registries have reported stroke rates of 1.5–6% (disabling < 2%), which are lower than observed for SAVR [2,3]. The reduction has been attributed to technical and technological improvements. However, those rates may underestimate the true incidence when minor and silent strokes are considered. Studies that included mild to severe strokes and systematic evaluation by neurologists combined with neuroimaging reported rates of up to 28% [2,6]. New ischemic brain lesions post-TAVI were reported in up to 100% of patients using diffusion-weighted magnetic resonance imaging (DW-MRI) [3].

A meta-analysis with pooled results from 25 prospective studies showed new ischemic brain lesions in 77.5% of patients, 95% confidence interval (95%CI) 71.7–83.3 [7]. Multiple lesions were found in 59.5% of patients with 4.2 new lesions per patient, while total and single lesion volume were 437.5 mm^3 (95%CI 286.7–588.3 mm^3) and 78.1 mm^3 (95%CI 56.7–99.5 mm^3), respectively [7]. Importantly, such "silent" lesions were shown to be associated with increased risk of stroke, cognitive decline, and/or dementia [8-10].

More than 50% of all strokes following TAVI occur within the first 24 hours [11] as the leading mechanism is thrombo-

embolism. Actually embolic material was observed in 99% of cases by an embolic protection device (EPD) [12]. This finding is also supported by studies that used transcranial Doppler as surrogate marker for periprocedural embolization (detected by transient high intensity signals) and showed especially high load of embolization during valve deployment and positioning [3,13]. The embolic material captured by the EPDs is comprised of thrombus, calcium debris, tissue elements, and foreign materials [2,3] and is believed to originate mainly from the atherosclerotic thoracic aorta, calcific aortic valve, and the equipment used during the procedure. Although several procedure-related (e.g., total time of delivery catheter time in the patient's body, rapid pacing during valvuloplasty, valve repositioning, and balloon pre-dilatation) and patient-related factors (e.g., prior stroke, degree of aortic valve calcification, peripheral artery disease, and chronic kidney disease) were reported to be associated with increased risk of periprocedural stroke, currently there are no efficient tools to accurately predict such an event [3].

Since the majority of the periprocedural neurologic events seem to be embolic, resulting from mechanical interactions of the TAVI apparatus with the native valve and vessel walls, the use of EPDs to capture or deflect thromboembolic material during the procedure has a strong logical foundation. The main EPDs studied to date can be mechanistically divided into deflectors and filters [Table 1]. The filters includes the Sentinel™ (Boston Scientific, Corp., USA) and Embol-X (Edwards Lifesciences, Irvine, CA, USA). The Sentinel contains filters positioned in the brachiocephalic trunk and the left common carotid. Embol-X is a single aortic filter deployed in the ascending aorta before the aortic puncture in a setting of trans-aortic TAVI. The deflectors, include the TriGuard (Keystone Heart, Herzliya, Israel) and Embrella (Edwards Lifesciences, Irvine, CA, USA) devices, which are positioned along the external curvature protecting the innominate artery, left common carotid and the left subclavian artery (only TriGuard) deflecting the embolized material toward the descending aorta. Various EPDs that are under development or at the first-in-man study stage exist [Table 1] and include potentially promising devices such designed to provide full body circumferential aortic protection [13].

The evolving technology of embolic protection devices is safe and technically feasible during the transcatheter aortic valve implantation procedure without significantly increasing procedural time

MAIN RESULTS OF EPDS IN CLINICAL STUDIES

The currently available data regarding EPDs are collected from a series of observational studies and five randomized studies as well and several meta-analyses with different combinations of the studies.

The Embrella was evaluated in the non-randomized multicenter PROTAVI-C trial [14] (n=52; 41 with the Embrella device and 11 without). The system was successfully deployed in all patients without any complications. New brain lesions by DW-MRI were found in 100% of patients in both groups; however, lower volume of ischemic lesions was found in the EPD group compared to the control group ($P = 0.003$).

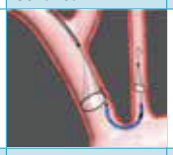
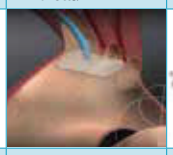
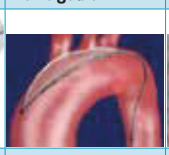
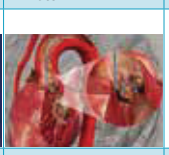
The Embol-X was evaluated in a single center, prospective, single-blinded randomized study in which 30 patients were assigned to undergo TAVI with the device (n=14) or without it (n=16) [15]. There were no neurologic events in this study. Evaluation with post-procedural DW-MRI showed a non-significant decrease in the rate of new brain lesions (50% vs. 69%, respectively) and lesion volume (88 ± 60mm^3 vs. 168 ± 217 mm^3, respectively) was found in the device group, yet the study was underpowered for efficacy.

The DEFLECT III trial [16] was a prospective multi-center randomized trial (n=85) that evaluated the TriGuard EPD. Study participants underwent neurocognitive evaluation and DW-MRI at baseline, pre-discharge, and 30 days following TAVI. Successful device placement was reported in 89% of cases. The safety endpoint (death, stroke, major bleeding, acute kidney injury stage 2/3, major vascular complication) occurred in 21.7% of the EPD group vs. 30.8% of the control group ($P = 0.34$). Furthermore, patients in the EPD group had fewer new ischemic brain lesions at 30 days (26.9 vs. 11.5%) and exhibited fewer new neurologic deficits according to the National Institutes of Health Stroke Scale (NIHSS) (3.1 vs. 15.4%) as well as showing improved Montreal Cognitive Assessment (MoCA) scores, better performance on a delayed memory task ($P = 0.028$) at discharge, and greater increase in recovery of normal MoCA score (> 26) at 30 days compared with the control group.

The MISTRAL-C trial [17] was a prospective multicenter randomized 1:1 trial (n=65) that assessed the Claret Medical Sentinel® Cerebral Protection System (Sentinel System, USA). Patients underwent neurocognitive evaluation and DW-MRI before and 5–7 days following the procedure. Significant debris were retrieved from all the devices used in the study. The study found fewer (73 vs. 87%) and smaller (95 vs. 197 mm^3) new brain lesions in the device versus the control group, yet statistical significance was not reached. A significant reduction in the rate of patients with multiple brain lesions (20 vs. 0%, $P = 0.03$) and lower cognitive impairment (4 vs. 27%, $P = 0.017$) was observed in the EPD group.

The CLEAN-TAVI [18] trial was a single-center randomized 1:1 trial (n=100) using the Claret device. The device was successfully placed in 92% of patients without periprocedural complications reported. The EPD group was associated with a significant reduction of new cerebral lesions in the protected territories (4 vs. 10, $P < 0.001$) and in the entire brain (8 vs. 16, $P = 0.002$). Volume of these lesions was also lower in the EPD group (466 vs. 800 mm^3, $P = 0.02$). Clinical stroke rate and neurocognitive outcomes did not differ between the two groups.

Table 1. Embolic protection devices (including under-investigation)

	Sentinel	TriGuard	Embrella	Embol-X	Point-guard	Emblok	Emboliner	ProtEmbo
Illustration								
Manufacturer	Claret Medical (Boston Scientific, Corp., USA)	Keystone Heart, Herzliya, Israel	Edwards Lifesciences, Irvine, CA, USA	Edwards Lifesciences, Irvine, CA, USA	Transverse Medical Inc., USA	Innovative Cardiovascular Solutions, Grand Rapids, MI, USA	Emboline Inc., Santa Cruz, CA, USA	Protembis GmbH, Germany
Approach	Right radial	Femoral	Radial/brachial	Aortic	Femoral	Femoral	Femoral	Left radial
Delivery	6F	8F	6F	17F	10F	11F	9F	6F
Coverage*	Partial	Full	Partial	Full	Full	Full	Full	Full
Mechanism of action	Capture	Deflection	Deflection	Capture	Deflection	Capture	Capture	Deflection
Pore size µm	140	115X145	100	120	105	125	150	60
Main trials	MISTRAL-C CLEAN-TAVI SENTINEL PROTECT-TAVI (ongoing)	DEFLECT I DEFLECT II DEFLECT III REFLECT/TRIFLECT (planned)	PROTAVI-C	Tao-EMBOLX	CENTER Trial (ongoing)	European study (ongoing)	SafePass trial (planned)	PROTEMBO SF Trial (ongoing)
EU/US Regulatory status	CE Mark/FDA approved	CE Mark/ investigational	CE Mark	Investigational	Investigational	Investigational	Investigational	Investigational

*Partial, covers two branches: left common carotid artery and left subclavian artery

The SENTINEL trial (n=363) [12] is the largest and most important randomized study with EPD to date. The Claret device was successfully implanted in all of the patients and obtained embolic material almost universally (99%). The major adverse cardiac and cerebrovascular events rate (7.3%) was non-inferior to the performance goal (18.3%, *P* noninferior < 0.001) and not statistically different from that of the control group (9.9%, *P* = 0.41). The rate of stroke at 30 days was numerically lower in the device group (5.6% vs. 9.1%, *P* = 0.25). New lesion volume was 42% lower in the study group, yet the results were not statistically significant (*P* = 0.33). Neurocognitive function was similar in the control and device patients, yet there was correlation between lesion volume and neurocognitive decline (*P* = 0.0022). A recent sub-analysis showed a significant treatment effect with 63% stroke reduction during the periprocedural (≤ 72 hours) time frame (3.0 vs. 8.2%, *P* = 0.05) [19]. Based on these finding, this device received FDA approval as well as a reimbursement code in the United States.

The use of embolic protection devices during transcatheter aortic valve implantation was shown to significantly reduce the burden of cerebral embolism as well as signal improved clinical outcomes

Several meta-analyses combining results from multiple studies using different devices showed consistent reductions in total lesion volume, a number of new ischemic lesions [7,20,21], or volume per lesion as well as improvement in neurocognitive scores upon discharge (e.g., MoCA, NIHSS) [20] with the use of EPD during TAVI. However a reduction in the hard clinical outcomes (i.e., mortality or stroke) was not consistently shown in these analyses. A meta-analysis that included eight studies (n=1,285) [22] found a significant reduction in the rate of stroke at 30 days with the use if EPDs (odds ratio [OR] 0.55, 95% confidence interval [95%CI] 0.31–0.98, *P* = 0.04); however, this result was driven mainly by a single nonrandomized study (Seeger et al. [23]) and was not confirmed when the randomized trials where considered separately. An additional recent meta-analysis that included five randomized controlled trials (RCTs) (n=643) [21] found a reduction in the composite endpoint of all-cause mortality and stroke at 30 days with EPDs (OR 0.54; 95%CI 0.30–0.98). Most studies failed to identify patients that are at particular risk for developing stroke events following TAVI. Thus, a comprehensive approach toward the adoption of EPDs seems to be advisable rather than more restricted/selective utilization strategy.

NEW EMBOLIC PROTECTION DEVICES

With the rapidly growing rate of TAVI procedures worldwide, complications and particularly ischemic events are receiving increasing attention; hence, the market of EPDs is expected to exceed US$1.8 billion by 2024 (Global Market Insights, Inc.). Thus many companies are focusing on brain protection strategies and devices during left heart catheter based procedures, and TAVI in particular. Examples of novel EPDs [Table 1] under preliminary stages of development include Point-Guard™

(Transverse Medical Inc., USA), which includes a filter mesh wrapped around a flexible nitinol frame and a supporting extension at its distal end. Its isolation zone supports stable positioning and minimized device migration and decoupling. This device is designed to provide complete coverage of the great arch vessels, full perimeter edge and sidewall conformity, and isolated stabilization against the superior curve of the aortic arch while maximizing blood flow to the brain and debris filtration.

The Emblok system (Innovative Cardiovascular Solutions, Grand Rapids, MI, USA) is an EPD designed to offer full circumferential aortic protection. The system includes an embolic filter and a pigtail catheter, advanced simultaneously through a single femoral puncture. The system opens inside the aorta following positioning and uses a 125 μm pore to catch embolic debris while allowing blood passage.

The Emboliner embolic protection catheter (Emboline Inc., Santa Cruz, CA, USA) is designed to provide full body protection by capturing and removing both cerebral and non-cerebra emboli (full body protection). Human studies are planned for 2018.

The ProtEmbo cerebral protection system (Protembis GmbH, Germany) includes a low-profile design that is delivered by radial access and designed to deflect embolic debris larger than 60 μm (pore size) from all the supraaortic vessels, downstream.

COST EFFECTIVENESS

Generally, there is a paucity of data regarding healthcare expenditure associated with stroke following TAVI as well as cost-effectiveness estimations for the use of EPDs. However, such a periprocedural stroke has previously been estimated to increase the costs of the index hospitalization by approximately US$25,000 followed by a subsequent annual cost increase of up to $60,000 if the patient is discharged with a moderate disability [24,25]. It has been [20] estimated that the number needed to treat (NNT) to prevent one stroke or death with an EPD is 22 patients. Considering the cost of the Sentinel device (US$2800), roughly US$61,600 has to be spent to prevent one stroke or death.

The clinical use of EPDs in Israel became more common in 2018, and dozens of successful cases were performed in the first year. Nonetheless, the procedure lacks the health basket reimbursement authorization, thus, its approval and implementation is restricted or even forbidden in most TAVI centers, which is a status that calls for a drastic change to prevent periprocedural strokes.

RECOMMENDATIONS

TAVI has become the treatment of choice for many patients with severe symptomatic AS, and the volumes of TAVI procedures have increased worldwide while indications continue to expand toward younger and lower risk patients. Although the incidence of periprocedural stroke has shown a trend of decline over the last decade, it is still non-negligible and certainly clinically significant, while cerebral thromboembolism seems to be almost universal. The clinical consequences of such embolization is probably underexplored and hence remains uncertain; however. significant signals support that they correlate with worse long-term neuropsychological outcomes. The evolving technology of EPDs is safe and technically feasible during the TAVI procedure without significantly increasing procedural time.

Thus far, EPDs have been evaluated in relatively few small and underpowered studies, which showed quite consistently a reduction of the burden of cerebral embolism during TAVI. However, decline in hard clinical outcomes, such as mortality or stroke, were not clearly demonstrated, probably due to insufficient power of the clinical trials. Nevertheless, several recent reports (meta- and sub-analyses) have shown significant signals geared toward improvements in such hard adverse outcomes with the use of EPDs versus without them. We encourage further investigation of the efficacy of EPDs in large RCTs to accurately delineate and substantiate their role in TAVI.

CONCLUSIONS

Considering the well-proven safety of the EPDs and the unpredicted nature and the devastating consequences of periprocedural stroke or the probable negative long-term consequences of "silent" cerebral embolism, we strongly believe that the use of EPDs should routinely be considered in all TAVI candidates and among all clinical indications. Furthermore we anticipate that newer and improved EPDs with greater efficacy and safety should emerge in the near future, further supporting their use during TAVI.

Correspondence
Dr. R. Kornowski
Dept. of Cardiology, Rabin Medical Center (Beilinson Campus), Petah Tikva 49100, Israel
Phone: (972-3) 937-7107
Fax: (972-3) 924-9850
email: ran.kornowski@gmail.com

References

1. Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very severe aortic stenosis. *Circulation* 2010, 121 (1): 151-6.
2. Lansky A, Ghare MI, Tchetche D, Baumbach A. TAVI and the brain: update on definitions, evidence of neuroprotection and adjunctive pharmacotherapy. *EuroIntervention* 2018, 14 (AB): AB53-63.
3. Shiyovich A, Kornowski R. Neuroprotective measures throughout the TAVI pathway. *Minerva Cardioangiol* 2019; 67 (1): 39-56.
4. Steinvil A, Benson RT, Waksman R. Embolic protection devices in transcatheter aortic valve replacement. *Circ Cardiovasc Interv* 2016; 9 (3): e003284.
5. Smith CR, Leon MB, Mack MJ, et al; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011, 364 (23): 2187-98.
6. Messe SR, Acker MA, Kasner SE, et al. Stroke after aortic valve surgery: results from a prospective cohort. *Circulation* 2014, 129 (22): 2253-61.
7. Pagnesi M, Martino EA, Chiarito M, et al. Silent cerebral injury after transcatheter aortic valve implantation and the preventive role of embolic protection devices: a systematic review and meta-analysis. *Int J Cardiol* 2016, 221: 97-106.

8. Gupta A, Giambrone AE, Gialdini G, et al. Silent brain infarction and risk of future stroke: a systematic review and meta-analysis. *Stroke* 2016, 47 (3): 719-25.
9. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke* 2003, 34 (5): 1126-9.
10. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003, 348 (13): 1215-22.
11. Mohammed Imran G, Alexandra L. Understanding neurologic complications following TAVR. *Interv Cardiol* 2018, 13 (1): 27-32.
12. Kapadia SR, Kodali S, Makkar R, et al. Protection against cerebral embolism during transcatheter aortic valve replacement. *J Am Coll Cardiol* 2017, 69 (4): 367-77.Demir OM, Iannopollo G, Mangieri A, et al. The role of cerebral embolic protection devices during transcatheter aortic valve replacement. *Front Cardiovasc Med* 2018, 5: 150.
13. Rodes-Cabau J, Kahlert P, Neumann FJ, et al. Feasibility and exploratory efficacy evaluation of the Embrella Embolic Deflector system for the prevention of cerebral emboli in patients undergoing transcatheter aortic valve replacement: the PROTAVI-C pilot study. *JACC Cardiovasc Interv* 2014, 7 (10): 1146-55.
14. Wendt D, Kleinbongard P, Knipp S, et al. Intraaortic protection from embolization in patients undergoing transaortic transcatheter aortic valve implantation. *Ann Thorac Surg* 2015, 100 (2): 686-91.
15. Lansky AJ, Schofer J, Tchetche D, et al. A prospective randomized evaluation of the TriGuard HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. *Eur Heart J* 2015, 36 (31): 2070-8.
16. Van Mieghem NM, van Gils L, Ahmad H, et al. Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial. *EuroIntervention* 2016, 12 (4): 499-507.
17. 18.Haussig S, Mangner N, Dwyer MG, et al. Effect of a cerebral protection device on brain lesions following transcatheter aortic valve implantation in patients with severe aortic stenosis: the CLEAN-TAVI randomized clinical trial. *JAMA* 2016, 316 (6): 592-601.
18. FDA Executive Summary. De Novo request for Claret Medical, Inc.'s Sentinel® Cerebral Protection System based on data from the SENTINEL Study, February 23, 2017. [Available from https://www.fda.gov/media/102952/download].
19. Giustino G, Sorrentino S, Mehran R, Faggioni M, Dangas G. Cerebral embolic protection during TAVR: a clinical event meta-analysis. *J Am Coll Cardiol* 2017, 69 (4): 465-6.
20. Wang N, Phan K. Cerebral protection devices in transcatheter aortic valve replacement: a clinical meta-analysis of randomized controlled trials. *J Thorac Dis* 2018, 10 (3): 1927-35.
21. Testa L, Latib A, Casenghi M, Gorla R, Colombo A, Bedogni F. Cerebral protection during transcatheter aortic valve implantation: an updated systematic review and meta-analysis. *J Am Heart Assoc* 2018; 7 (10). pii: e008463.
22. Seeger J, Gonska B, Otto M, Rottbauer W, Wohrle J. Cerebral embolic protection during transcatheter aortic valve replacement significantly reduces death and stroke compared with unprotected procedures. *JACC Cardiovasc Interv* 2017, 10 (22): 2297-303.
23. Arnold SV, Lei Y, Reynolds MR, et al. Costs of periprocedural complications in patients treated with transcatheter aortic valve replacement: results from the Placement of Aortic Transcatheter Valve trial. *Circ Cardiovasc Interv* 2014; 7 (6): 829-36.
24. Armijo G, Nombela-Franco L, Tirado-Conte G. *Front Cardiovasc Med* 2018 31; 5: 104.

Capsule

An islet cell reaches out

Blood glucose levels in mammals are controlled by the coordinated activity of several distinct hormone-secreting cells within pancreatic islets. These include beta cells, which release insulin; alpha cells, which release glucagon; and delta cells, which release somatostatin. Delta cells are integral because their release of somatostatin suppresses hormone secretion by the other cell types. At the islet level, how delta cells accomplish this has been unclear, as they are relatively rare.

In a study of mice, **Arrojo e Drigo** and colleagues found the answer lies in the characteristic cytoplasmic projections of the delta cells called filipodia. These projections contain secretory machinery, and their dynamic nature allows delta cells to contact distant beta and alpha cells and control their activity.

Nat Commun 2019; 10: 3700

Eitan Israeli

Capsule

Challenging assumptions in immunogenicity

Cancers with lower mutation rates, such as pediatric acute lymphoblastic leukemia (ALL), have not shown high immunotherapy response rates, possibly because there are fewer neoepitopes for T cells to recognize. To better understand anti-tumor responses, **Zamora** and colleagues examined samples from pediatric patients with ALL. They predicted peptide neoepitopes that could bind patients' human leukocyte antigen for presentation to T cells and generated tetramers. Somewhat surprisingly, almost all the predicted peptides were recognizable by patient T cells and induced functional responses in vitro. Thus, low mutation burden tumors should not be assumed to be immunogenically silent, as they could respond to checkpoint blockade or other T cell–targeted therapies.

Sci Transl Med 2019; 11: eaat8549

Eitan Israeli

"A great book should leave you with many experiences, and slightly exhausted at the end. You live several lives while reading it"

William Styron (1925–2006), novelist