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Comprehensive Analysis of Mortality Among Patients Undergoing TAVR

Results of the PARTNER Trial

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ABSTRACT

BACKGROUND Patients with severe aortic stenosis (AS) who were deemed too high risk or inoperable for conventional aortic valve replacement (AVR) in the PARTNER (Placement of Aortic Transcatheter Valves) trial were randomized to transcatheter aortic valve replacement (TAVR) versus AVR (PARTNER-A arm) or standard therapy (PARTNER-B arm).

OBJECTIVES This study compared when and how deaths occurred after TAVR versus surgical AVR or standard therapy.

METHODS The PARTNER-A arm included 244 transfemoral (TF) and 104 transapical (TA) TAVR patients, and 351 AVR patients; the PARTNER-B arm included 179 TF-TAVR patients and 179 standard therapy patients. Deaths were categorized as cardiovascular, noncardiovascular, or uncategorizable, and were characterized by multiphase hazard modelling.

RESULTS In the PARTNER-A arm, the risk of death peaked after randomization in the TA-TAVR and AVR groups, falling to low levels commensurate with the U.S. population within 3 months. Early risk was less in TF-TAVR patients, resulting in initial superior survival; between 12 and 18 months, risk increased, such that within 2 years, TF-TAVR and AVR patients had similar survival rates. Cardiovascular, noncardiovascular, and uncategorizable deaths for TF-TAVR were 37%, 43%, and 20%, respectively, versus 22%, 41%, and 37%, respectively, for TA-TAVR and 33%, 43%, and 24%, respectively, for AVR. In the PARTNER-B arm, risk with standard therapy was 60% per year; TF-TAVR reduced risk to 20% per year, resulting in 0.5 years of life added within 2.5 years.

CONCLUSIONS In inoperable AS patients, TAVR substantially reduced the risk of cardiovascular death. In high-risk patients, TA-TAVR and AVR were associated with elevated peri-procedural risk more than with TF-TAVR, although cardiovascular death was higher after TF-TAVR. Therefore, TF-TAVR should be considered the standard of care for severely symptomatic inoperable patients or those at high risk of noncardiovascular mortality after conventional surgery. (THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valve Trial; NCT00530894) (J Am Coll Cardiol 2014;64:158–68) © 2014 by the American College of Cardiology Foundation.

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Symptomatic aortic stenosis (AS) has a dismal prognosis. Despite this, up to two-thirds of patients with severe AS do not undergo surgical aortic valve replacement (AVR) due to their comorbidities (1–6). Thus, after some small, but promising feasibility studies and trials, the applicability of transcatheter aortic valve replacement (TAVR) for these high-risk patients has evolved rapidly (6–10). The 2-armed randomized PARTNER (Placement of Aortic Transcatheter Valves) trial was designed to test the procedure for safety and effectiveness. Patients in the PARTNER-A arm were considered high risk for surgery; patients in the PARTNER-B arm were considered inoperable.

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This detailed analysis reports on deaths among patients in both trial arms, including those that occurred between randomization and the procedure, focusing on when and how the deaths occurred (11–14).

METHODS

PATIENTS. A total of 3,105 patients were presented to a Web-based review panel for potential inclusion in the PARTNER trial. All patients were required to have a Society of Thoracic Surgeons (STS) score of >10%, unless comorbidities that were not part of the score assessment were present (e.g., radiation heart disease, cirrhosis, or porcelain calcification of the aortic arch without a distal landing site for a replacement graft). Patients were required to have an aortic valve area <0.8 cm^2 and either a mean transaortic gradient of >40 mm Hg or a transvalvar velocity of >4.0 m/s (11–14). High-risk patients were required to have a >15% probability of 30-day mortality, as deemed by the surgeon, irrespective of the STS score.

Of the reviewed patients, 699 were considered high risk for open surgery (PARTNER-A), and 358 were considered inoperable (PARTNER-B). Before randomization, a determination was made as to whether each patient was suitable for the transfemoral (TF) or the transapical (TA) approach. Of PARTNER-A patients, 348 were randomized to TAVR—244 to a TF approach (TF-TAVR) and 104 to a TA approach (TA-TAVR) (depending on vascular access)—and 351 were randomized to AVR (12).

The inoperable PARTNER-B subset was defined as those patients who were deemed by 2 cardiac surgeons as having a >50% probability of death or irreversible severe morbidity after AVR (11). Of PARTNER-B patients, 179 were randomized to TF-TAVR and 179 to standard therapy (medical management with or without balloon aortic valvotomy).

Baseline patient characteristics were similar among subsets of both PARTNER-A and PARTNER-B arms (11–14). The trial was approved by the U.S. Food and Drug Administration and the institutional review board at each participating center. Additional trial details are described in earlier publications (11–14). All patients who underwent TAVR received the Edwards Sapien valve (Edwards Lifesciences, Irvine, California).

ENDPOINTS. The primary endpoint was all-cause mortality from time of randomization (intent-to-treat). The Online Appendix provides analyses of as-treated mortality in PARTNER-A. Secondary endpoints were categories and subcategories of deaths.

All-cause mortality. Median follow-up was 2 years for PARTNER-A patients, and 10% of the survivors were followed for more than 3 years; 1,154 patient-years of follow-up were available for analyses. Median follow-up was 1.3 years for PARTNER-B patients, and 10% of the survivors were followed for more than 3.2 years; 541 patient-years of follow-up were available for analyses. All time-related depictions were truncated at 2.5 years. Mortality information was current as of April 25, 2012.

Categorization of deaths. The PARTNER Trial Clinical Events Committee reviewed documentation concerning every death that occurred after randomization, initially blinded according to randomized group, then unblinded. Each death was

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
AVR = surgical aortic valve replacement
CL = confidence limit
STS = Society of Thoracic Surgeons
TA = transapical
TAVR = transcatheter aortic valve replacement
TF = transfemoral

research grant support from Medtronic and St. Jude Medical; and consulting fees from Edwards Lifesciences, Medtronic, Sorin, and Entourage. Dr. Guyton has received consultant fees from Medtronic. Dr. Thourani has received consulting fees from Edwards Lifesciences, Sorin Medical, St. Jude Medical, and DirectFlow. Dr. Pichard has received consulting fees and has been a proctor from Edwards Lifesciences. Dr. Herrmann has received consulting fees from St. Jude Medical and Paieon; has received research support from Edwards Lifesciences, Medtronic, and St. Jude; and holds equity in Microinterventional Devices. Dr. Williams has received consulting fees from Edwards Lifesciences and Medtronic. Dr. Babaliaros has received consulting fees from DirectFlow and St. Jude Medical. Ms. Akin is employed by Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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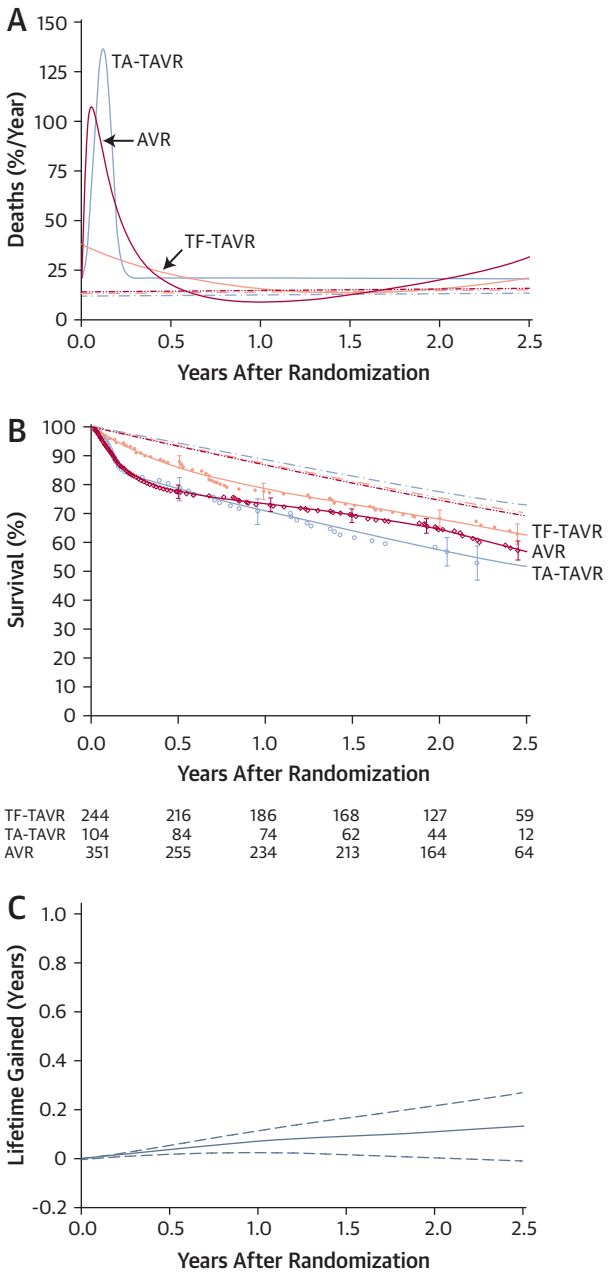

FIGURE 1 All-Cause Mortality in PARTNER-A

(A) Instantaneous risk of death after transcatheter aortic valve replacement (TAVR) performed either transapically (TA) **(blue)** or transfemorally (TF) **(salmon)**, and surgical aortic valve replacement (AVR) **(red)**. For reference, **fine dash-dot-dash lines** represent risk of death in an age-, sex-, and race-matched U.S. population. **(B)** Survival stratified by randomized groups. Each symbol represents a death, **vertical bars** are 68% confidence limits (CL) equivalent to ±1 SE, and **numbers beneath the horizontal axis** are patients remaining at risk. **Solid lines** represent parametric survival estimates. **Fine dash-dot-dash lines** represent survival of an age-, sex-, and race-matched U.S. population. **(C)** Estimated lifetime gained by TF-TAVR over AVR. This represents the integrated difference between TF-TAVR and AVR survival curves in Figure 1B. **Dashed lines** form a 90% confidence band.

placed into 1 of 3 categories: 1) clearly cardiovascular in cause, mechanism, and circumstance (mode of death); 2) clearly noncardiovascular in cause, mechanism, and circumstance; or 3) not clearly classifiable as 1 or the other of these 2 categories. Two of the authors (N.B. and L.G.S.) reviewed the medical records of uncategorizable patients, often finding they were elderly and frail, and failed to thrive. This admixture of unfavorable demographic characteristics, and cardiovascular and noncardiovascular comorbidities, as well as circumstances that surround many deaths in hospice care and skilled nursing facilities, made it impossible to classify these deaths as clearly cardiovascular or noncardiovascular, despite extensive documentation.

Cardiovascular deaths were further subcategorized as due to heart failure, sudden death, stroke, arrhythmia, myocardial infarction, noncerebral hemorrhage, endocarditis of prosthetic study valve, arterial disease, vascular complications, other, or unknown. Noncardiovascular deaths were further subcategorized as due to infection, cancer, renal disease, accident, pulmonary disease, other, or unknown. Two of the authors (N.B. and L.G.S.) reviewed the deaths for potential valve-related causes and performed a more detailed evaluation of the "other" subcategory.

DATA ANALYSIS. All analyses were performed using SAS statistical software (SAS version 9.2, SAS, Inc., Cary, North Carolina). The starting point for all analyses of death was time of randomization. Survival after randomization was estimated nonparametrically by the Kaplan-Meier estimator and parametrically by a multiphase, temporal decomposition hazard model (15). Parametric modeling resolved a number of phases of instantaneous risk of an event (hazard function), mathematical equations used to characterize these phases, and values of shaping parameters.

For reference, U.S. Life Tables (National Center for Health Statistics, Hyattsville, Maryland) were used to construct conditional survival and risk of death according to each patient's age, sex, and race. These individual survival estimates were averaged across time to yield matched population-based expected survival and hazard curves. Years gained by 1 therapy versus another were calculated by the difference between survival curves, integrated across time (16).

Categories of death represented competing risks. Nonparametric estimates and confidence limits (CLs) of competing risks used the methods described by Anderson et al. (17). Parametric estimates were

obtained by numerical integration of the individual parametric hazard estimates for each competing risk. **Presentation.** Actuarial and instantaneous risk of death estimates are accompanied by asymmetric confidence intervals equivalent to ±1 SE (68% confidence coefficient). The integrated difference between survival curves is accompanied by 90% confidence bands to obtain a similar visual interpretation as an overlapping 68% CL (16). Comparisons of causes of death among the randomized groups were made using a chi-square test of independence. Fisher's exact test was used when comparing 2 groups with a cell frequency <5.

RESULTS

OVERALL RISK OF DEATH. The PARTNER-A Trial. At the date of the last follow-up (April 25, 2012), 275 PARTNER-A patients had died, 20 of them between randomization and the procedure (Online Fig. 9). Instantaneous unadjusted risk of death peaked early after randomization in both AVR and TA-TAVR groups, falling within 3 to 6 months to a low level commensurate or better than that of the matched U.S. population estimates (**Fig. 1A**). Seventeen deaths occurred before the procedure in the AVR group (4.8%) and 1 in the TA-TAVR group (1.0%). The magnitude and longer duration of the early hazard in the AVR group was partly related to these deaths before surgery during the more prolonged interval between randomization and the procedure (median 9 days, with a lengthy right tail) compared with either TAVR subgroup (median 7 days, with a shorter right tail) (Online Fig. 11). In contrast to an early peaking hazard, risk after randomization to TF-TAVR was only modestly elevated after the date of randomization, and gradually fell over the first year of follow-up to levels similar to that of the other 2 groups. Two deaths occurred before the procedure (0.8%). This pattern of early risk resulted in separation of the TF-TAVR survival curves from the survival curves of AVR and TA-TAVR (**Fig. 1B**).

After approximately 3 months, instantaneous risk became constant in the TA-TAVR subgroup, but gradually rose after approximately 1.5 years in the TF-TAVR group and after approximately 1 year in the AVR group. This resulted in nearly parallel survival curves for TA-TAVR and TF-TAVR, with survival of the AVR group between them. TF and TA subsets of the AVR group had similar temporal risk profiles (Online Fig. 1). A total of 0.13 years (90% CL: −0.008 to 0.27) of lifetime was gained within 2.5 years by the TF-TAVR group over the AVR group (**Fig. 1C**), 0.22 years (90% CL: 0.025 to 0.41) by the TF-TAVR group over the TA-TAVR group (Online Fig. 2), and 0.087 years (90% CL: −0.102 to 0.28) by the AVR group over the TA-TAVR group (Online Fig. 3).

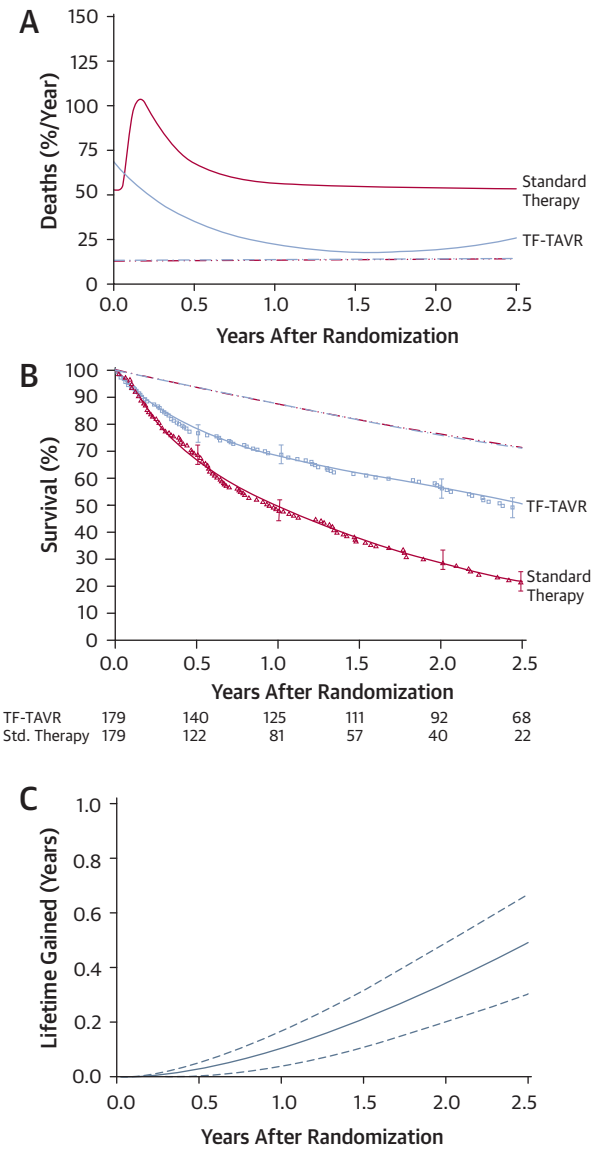

FIGURE 2 All-Cause Mortality in PARTNER-B

(A) Instantaneous risk of death among patients randomized to standard therapy **(red)** or TF-TAVR **(blue)**. Format is as in **Figure 1A**. **(B)** Survival stratified by randomized groups. Format is as in **Figure 1B**. **(C)** Estimated lifetime gained by TF-TAVR over standard therapy. This represents the integrated difference between TF-TAVR and standard therapy survival curves in **Figure 2B**. **Dashed lines** form a 90% confidence band. Abbreviations as in **Figure 1**.

The PARTNER-B Trial. At the date of last follow-up, 237 PARTNER-B patients had died, 2 between randomization and TF-TAVR (1.1%). For patients randomized to TF-TAVR, the pattern of instantaneous risk of death paralleled that of TF-TAVR for PARTNER-A patients, although at a somewhat higher level (Fig. 2A). Those randomized to standard therapy, however, exhibited an early peak—possibly related to balloon aortic valvotomy—that was prolonged beyond 6 months and merged with a constant hazard that was considerably higher than that after TF-TAVR, and higher than that expected for the general population. Thus, survival diverged between the 2 trial arms within 30 to 60 days, and the gap widened thereafter (Fig. 2B). The net lifetime added by TF-TAVR over standard therapy was 0.50 years (90% CL: 0.30 to 0.67) (Fig. 2C).

Reference to general population. Instantaneous risk of death early after randomization was considerably higher among all intervention groups than that referenced to an age-, sex, and race-matched population life table (Online Fig. 4A). As a result, survival was immediately less than that expected of the general population (Online Fig. 4B). However, between 6 and 18 months, risk of death rapidly decreased in these groups to near or below the level expected for the general population. Thereafter, risk of death began to rise above that of the general population. This temporal pattern of risk contrasted with standard therapy patients, who remained at considerably higher risk than that of the general population throughout the 2.5 years of follow-up.

CARDIOVASCULAR VERSUS NONCARDIOVASCULAR DEATHS. The PARTNER-B Trial. Among PARTNER-A patients, death was categorized as cardiovascular in 89 patients, noncardiovascular in 118, and uncategorizable in 68 (Table 1, Online Table 1). Instantaneous risk of cardiovascular death peaked earlier after randomization to TF-TAVR than to AVR (Fig. 3A). Instantaneous risk of noncardiovascular death also peaked after randomization, but the peak was higher and earlier in the AVR group than in either the TA-TAVR or TF-TAVR groups (Fig. 3B, Online Figs. 5A to 5C). Of deaths between randomization and procedure, 2 in the TF-TAVR group were cardiovascular (arrhythmia and heart failure), and 1 death in the TA-TAVR group was uncategorizable (Online Appendix). Of the 17 deaths in the AVR group, 8 were cardiovascular (2 arrhythmia, 4 heart failure, 2 sudden), 5 were noncardiovascular (2 infection, 1 renal failure, 1 encephalopathy, 1 necrotic bowel), and 4 were uncategorizable.

TABLE 1 Categorization of Deaths in PARTNER-A Patients

Mode of Death	TF-TAVR N	TF-TAVR n (%)	TA-TAVR N	TA-TAVR n (%)	AVR N	AVR n (%)	p Value
Cardiovascular	33		10		46		
Heart failure		13 (39)		4 (40)		16 (35)	0.90
Sudden death		9 (27)		1 (10)		12 (26)	0.50
Arrhythmia		1 (3)		3 (30)		5 (11)	0.05
Stroke		5 (15)		0 (0)		7 (15)	0.40
Noncerebral hemorrhage		1 (3)		1 (10)		2 (4.3)	0.60
Myocardial infarction		1 (3)		0 (0)		1 (2.2)	0.80
Prosthetic valve endocarditis		0 (0)		1 (10)		1 (2.2)	0.20
Peripheral arterial disease or abdominal aortic aneurysm		1 (3)		0 (0)		0 (0)	0.40
Vascular complication		1 (3)		0 (0)		0 (0)	0.40
Other		1 (3)		0 (0)		1 (2.2)	0.80
Unknown		0 (0)		0 (0)		1 (2.2)	0.60
Noncardiovascular	39		19		60		
Infection/sepsis		15 (38)		7 (37)		28 (47)	0.60
Renal disease		6 (15)		0 (0)		6 (10)	0.20
Malignancy		4 (10)		1 (5.3)		8 (13)	0.60
Accidental		3 (7.7)		0 (0)		1 (1.7)	0.20
Respiratory		3 (7.7)		7 (37)		9 (15)	0.02
Other		8 (20)		2 (10)		7 (12)	0.50
Unknown		0 (0)		2 (11)		1 (1.7)	0.05
Uncategorizable	18		17		33		

AVR = surgical aortic valve replacement; TA-TAVR = transapical transcatheter aortic valve replacement; TF-TAVR = transfemoral transcatheter aortic valve replacement.

The PARTNER-B Trial. Among PARTNER-B patients, death was categorized as cardiovascular in 107 patients, noncardiovascular in 53, and uncategorizable in 77 (Table 1, Online Table 2). Instantaneous risk of cardiovascular death during standard therapy remained elevated well above risk after randomization to TF-TAVR (Fig. 4A, Online Figs. 6A and 6B). Risk of cardiovascular death peaked early after TF-TAVR, fell to lower levels within approximately 6 months, and gradually rose after approximately 1 year, similar to that observed in PARTNER-A patients (Online Fig, 7A). Although risk of noncardiovascular death peaked after randomization to TF-TAVR, the general level of risk was similar to that of standard therapy (Fig. 4B) and noncardiovascular death in PARTNER-A patients (Online Fig. 7B). One death between randomization and intended TF-TAVR was due to heart failure, and 1 was uncategorizable.

SUBCATEGORIES OF CARDIOVASCULAR DEATH. The 2 most common subcategories of cardiovascular death among PARTNER patients were heart failure and sudden death (Tables 1 and 2). Risk of death from heart failure after TAVR or AVR peaked early

after the procedure (Fig. 5A), unlike that for sudden death (Fig. 5B). In PARTNER-B patients, the risk was more protracted, but risk of death from heart failure remained elevated during standard therapy (Fig. 6A). Risk of sudden death occurred at a low level among patients randomized to an aortic valve intervention in both PARTNER-A and PARTNER-B. However, risk was considerably higher and remained elevated in patients randomized to standard therapy (Fig. 6B).

SUBCATEGORIES OF NONCARDIOVASCULAR DEATH. The most common subcategories of noncardiovascular death among PARTNER patients were infection, respiratory complications, and malignancies (Tables 1 and 2). There were 24 noncardiovascular deaths in the "other" category: 8 from neurological events, 2 from multisystem organ failure, 5 from liver failure, 7 from gastrointestinal complications, and 2 from uncertain noncardiovascular causes (Table 3).

Close examination of clinical source documents from PARTNER-B patients whose deaths could not be categorized showed that they were later deaths that occurred in nursing homes or hospices, were associated with old age, frailty, or failure to thrive, and could not be further characterized.

DEVICE-RELATED DEATHS. No device failure occurred in either PARTNER-A or -B. In the entire PARTNER study, there were 4 deaths from endocarditis, all involving a prosthetic valve (Tables 1 and 2). There were no deaths from hemolysis; only 1 patient experienced documented hemolysis, and that was after AVR.

DISCUSSION

OVERALL RISK OF DEATH. Temporal Pattern of Risk. The instantaneous risk of death (hazard function) following intervention is initially high, then falls to a low level before gradually rising (Central Illustration). This "bathtub-shaped" risk following open cardiac surgical procedures has been observed for several decades (15,18–20). Clinical management of patients after surgery mirrors this pattern of risk: intensive care, step-down unit, regular nursing floor, and discharge to a nearby hotel or home. Nevertheless, the period of higher risk extends well beyond initial hospitalization, as was found in the present study. This corresponds with elevated risk of hospital readmissions soon after hospital discharge.

However, an important novel finding is that early risk after randomization to TF-TAVR in PARTNER-A and -B was substantially lower than after TA-TAVR or AVR. Thus, an advantage of a percutaneous approach is a reduction of peri-procedural risk, particularly noncardiovascular risk.

The shape of the elevated early hazard phase is not typical of that previously found for surgical intervention, in that it peaks for the surgical cohorts. Generally, risk is highest immediately after a procedure, then falls steeply. The explanation lies in the nature of this intent-to-treat analysis. The interval between randomization and the procedure has a lengthy "right tail" of up to several weeks or months. The peaking early hazard phase is a result, as demonstrated when an "as treated" analysis of instantaneous risk is performed (Online Fig. 12A): the peak disappears, and risk starts high immediately after the procedure. Thereafter, the contour of the

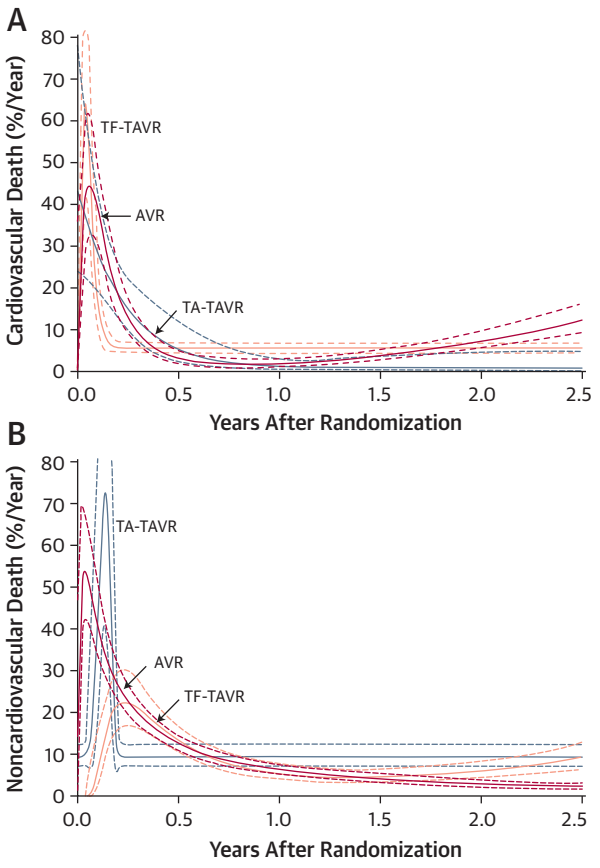

FIGURE 3 Instantaneous Risk of Cardiovascular and Noncardiovascular Death After TAVR Performed Either TA or TF Versus Surgical AVR in PARTNER-A

Format is as in Figure 1A, except that **dashed lines** enclosing the solid parametric hazard estimates form a 68% confidence band. **(A)** Cardiovascular death. **(B)** Noncardiovascular death. **Blue** = TA; **salmon** = TF; **red** = AVR. Abbreviations as in Figure 1.

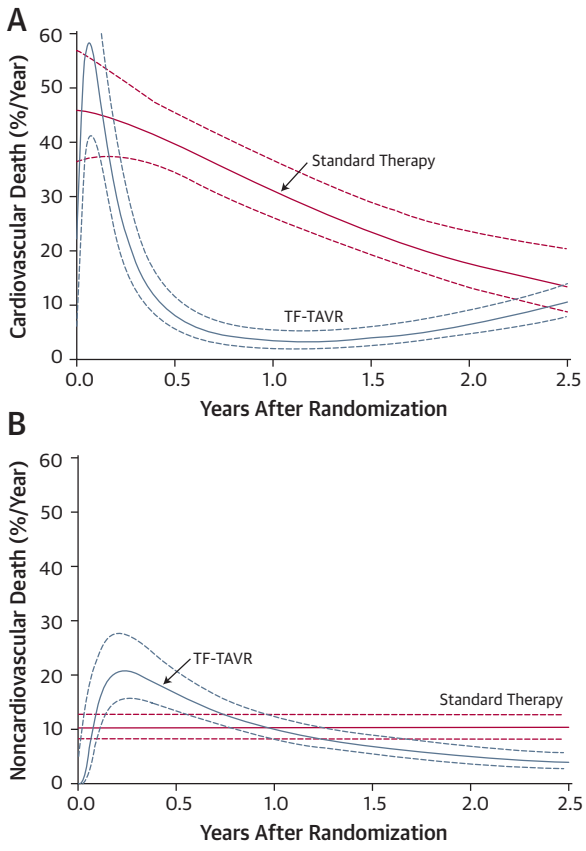

FIGURE 4 Instantaneous Risk of Cardiovascular and Noncardiovascular Death After TF-TAVR Versus Standard Therapy in PARTNER-B

Format is as in Figure 3A. **(A)** Cardiovascular death. **(B)** Noncardiovascular death. Abbreviations as in Figure 1.

TABLE 2 Categorization of Deaths in PARTNER-B Patients

Mode of Death	Standard Therapy N	Standard Therapy n (%)	TF-TAVR N	TF-TAVR n (%)	p Value
Cardiovascular	67		40		
Heart failure		34 (51)		13 (33)	0.07
Sudden death		21 (31)		4 (10)	0.02
Arrhythmia		4 (6)		1 (2.5)	0.60
Stroke		4 (6)		7 (18)	0.10
Noncerebral hemorrhage		2 (3)		0 (0)	0.50
Myocardial infarction		0 (0)		2 (5)	0.14
Prosthetic valve endocarditis		0 (0)		2 (5)	0.14
Peripheral arterial disease/ abdominal aortic aneurysm		0 (0)		1 (2.5)	0.40
Vascular complication		0 (0)		3 (7.5)	0.05
Other		1 (1.5)		2 (5)	0.60
Unknown		1 (1.5)		5 (12)	0.02
Noncardiovascular	21		32		
Infection/sepsis		7 (33)		10 (31)	>0.90
Renal disease		3 (14)		3 (9.4)	0.70
Malignancy		4 (19)		4 (13)	0.70
Accidental		0 (0)		2 (6.3)	0.50
Respiratory		3 (14)		5 (16)	>0.90
Other		1 (4.8)		6 (19)	0.20
Unknown		3 (14)		2 (6.3)	0.40
Uncategorizable	47		30		

Abbreviations as in Table 1.

hazard function is similar to the depiction shown in Figure 1A.

In addition, the magnitude of early risk after randomization to AVR reflects 4.8% mortality in this group before surgery. This contrasts with 0.9% mortality between randomization and TAVR in the combined PARTNER trial arms. In observational surgical studies that nearly always commence at operation, deaths before planned surgery are rarely reported. This is in contrast to inception cohort studies, such as randomized trials and some studies on managing congenital heart disease (21). Bavaria et al. (22) reported a 12% mortality between referral for TAVR and procedure in their program, and others reported even higher mortality for patients screened for possible valve replacement (23,24).

Relation to risk in the general population. After early high risk falls to its lowest level, risk of death is commensurate with that of the age-, sex-, and race-matched general population. Thereafter, it gradually begins to rise above that expected in the general population. In these elderly patients, this rise is also accelerated beyond that expected in the general population. Patient demographic characteristics, comorbidities, and new health problems (e.g., strokes) likely contribute to the post-recovery increase in risk. These contrast sharply with the rates observed after surgical reports of AVR, for which instantaneous risk of death is progressively less than that of the general population as patient age increases (20), which is probably due to the selection of lower risk patients for conventional heart surgery.

Value of intervention. Survival results of the PARTNER-B randomized trial reported previously (11–14), and evaluated further in this study, demonstrate that inoperable patients treated by TF-TAVR have markedly improved overall survival compared with standard therapy. This was true despite all of the conditions, valve- and non-valve-related, that led to the consensus about inoperability. In this group, TF-TAVR provided, on average, a half-year of added lifetime within 2.5 years of randomization. Hence, TF-TAVR should be considered the standard of care for inoperable patients with anticipated longevity

commensurate with, or better than, that of the general population.

CARDIOVASCULAR AND NONCARDIOVASCULAR DEATHS. After an early phase of high risk attributable mainly to cardiovascular deaths, risk of cardiovascular death was substantially reduced in patients randomized to AVR by either TAVR or AVR compared with those randomized to standard therapy. In contrast, the risk of noncardiovascular death was only modestly greater in those randomized to standard therapy, because of the comorbidities that made them inoperable. As might be anticipated, after the early phase of risk, inoperable PARTNER-B patients randomized to TF-TAVR did not do as well as high risk PARTNER-A patients randomized to TF-TAVR. However, the increased risk of death was related to a higher risk of noncardiovascular death.

Although device failure did not occur in either PARTNER-A or -B, peri-valvar leakage or central regurgitation could increase the risk of heart failure, endocarditis, stroke, hemolysis, and death. An increased risk of death related to peri-valvar leakage has been documented (13), but the etiology needs to be evaluated further.

SUBCATEGORIES OF CARDIOVASCULAR AND NONCARDIOVASCULAR DEATHS. After valve insertion, the primary mode of death was acute or subacute heart failure as documented for surgical AVR (19). It was curious that risk of death in heart failure gradually diminished among patients randomized to standard therapy. There were an insufficient number of patients who crossed over to TAVR or AVR to account for this; however, the uncategorizable deaths might explain this trend (Online Figs. 8A to 8F). This could also be due to a Darwinian phenomenon: over time, those individuals whose survival was most sensitive to their heart disease were eliminated early from the population, leaving a more robust group.

Although sudden death still occurred occasionally after TAVR and AVR, it continued unabated at nearly 10% per year among patients randomized to standard therapy. Thus, AVR distinctly reduced risk of sudden death and heart failure death.

STUDY LIMITATIONS. Although this was a randomized trial with nearly complete follow-up, blinded adjudication of adverse events, and meticulous assessment, minor factors might have influenced the outcomes. Comorbid variables were generally well-balanced, but there were small differences of unknown clinical consequence (11–14). Treated TAVR patients might have been followed and managed more intensively, because this was not a blinded treatment study. Clearly, these patients represented a selected population who underwent rigorous screening. Only one-third of screened patients were enrolled (11), and approximately 12% of patients presented to the Web-based review panel for potential inclusion were eventually randomized. Whether these results could be generalized to patients at institutions beyond those participating in this trial is not known.

It was beyond the scope of this study to translate added lifetime from TAVR over standard therapy to quality-adjusted life years (25), a necessary step in assessing cost effectiveness of treatments. In addition, we did not perform a multivariable analysis of death to identify risk factors for both early and late deaths in the various patient subsets. Thus, we did not address the possibility that some patients benefitted more than others from intervention. These are subjects of forthcoming investigations.

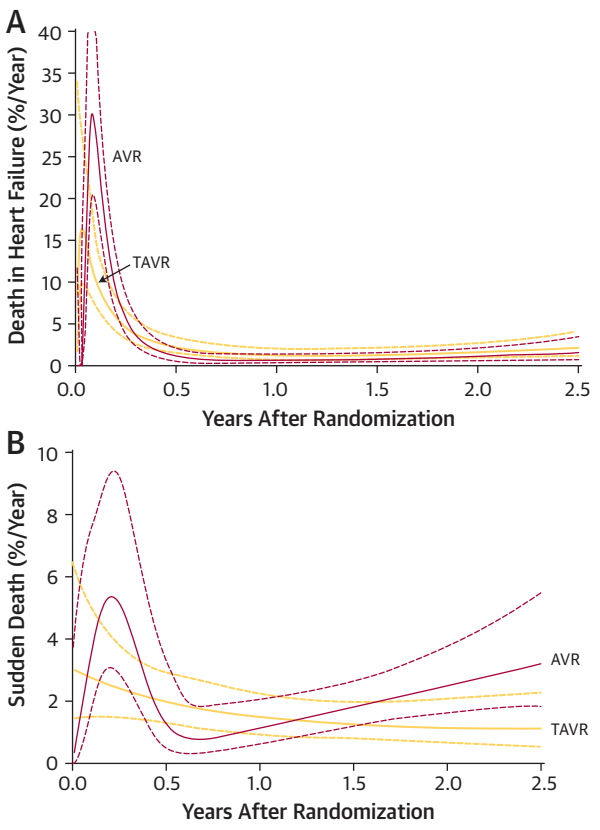

FIGURE 5 Subcategories of Cardiovascular Death After TAVR or Surgical AVR in PARTNER-A

Format is as in Figure 3A. **(A)** Risk of death in heart failure. **(B)** Risk of sudden death. Abbreviations as in Figure 1.

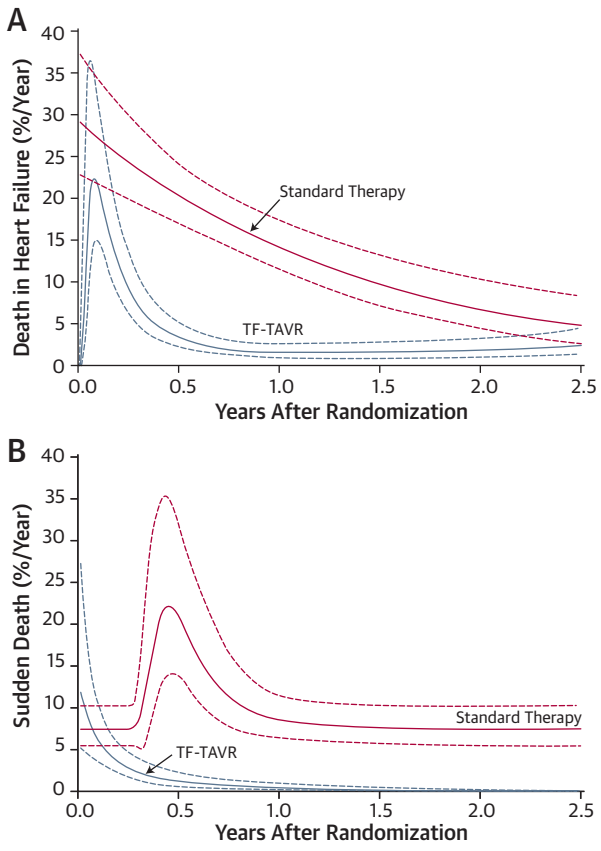

FIGURE 6 Subcategories of Cardiovascular Death After TF-TAVR or Standard Therapy in PARTNER-B

Format is as in Figure 1B. **(A)** Risk of death in heart failure. **(B)** Risk of sudden death. Abbreviations as in Figure 1.

Similarly, the effects of balloon aortic valvotomy and crossover in the standard therapy group were not examined.

Although death was a hard endpoint, categorization of the circumstances surrounding each death, particularly the mechanism of death, was subjective, and the data were incomplete. Few autopsies were performed to identify possible mechanisms. This resulted in a substantial proportion of deaths deemed as uncategorizable.

Procedural aspects of TAVR, peri-operative neurological events, and vascular access site issues were the focus of previous reports. This study did not specifically address these problems and their possible effects on mortality (26-30).

CONCLUSIONS

In inoperable AS patients, TAVR substantially reduced risk of cardiovascular death. In high-risk patients, TA-TAVR and AVR were associated with elevated periprocedural risk more than TF-TAVR, particularly for noncardiovascular death, although early risk of cardiovascular death was higher with TF-TAVR. Therefore, TF-TAVR should be considered the standard of care for eligible inoperable patients with severe symptomatic AS or at high risk of noncardiovascular mortality after conventional surgery.

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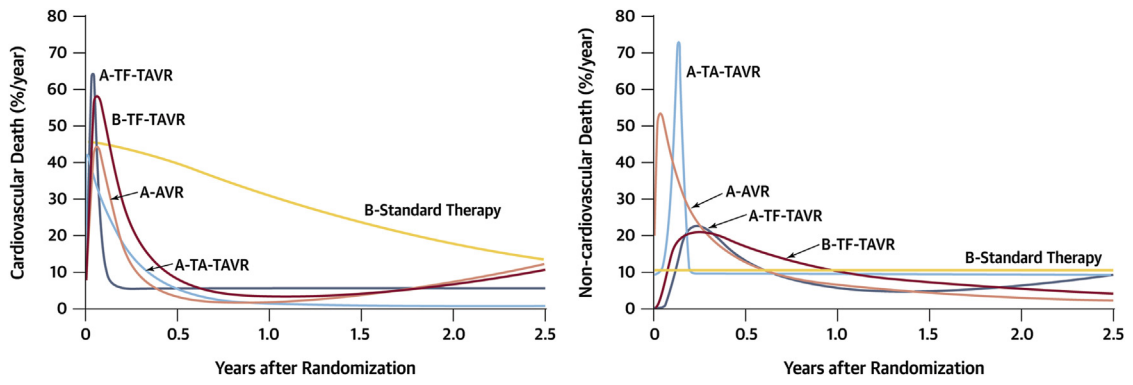
TABLE 3 Other Noncardiovascular Deaths

	PARTNER-A				PARTNER-B		
Mode of Death	TF-TAVR (N = 8)	TA-TAVR (N = 2)	AVR (N = 7)	p Value	Standard (N = 1)	TF-TAVR (N = 6)	p Value
Neurological	3 (38)	1 (50)	2 (29)	0.80	0 (0)	2 (33)	>0.90
Dementia	1	1	0		0	1	
Intracranial hemorrhage	1	0	0		0	0	
Encephalopathy	0	0	2		0	0	
Parkinsonism	0	0	0		0	1	
Other	1	0	0		0	0	
Gastrointestinal	2 (25)	0 (0)	2 (29)	0.70	1 (100)	2 (33)	>0.90
Bleed	1	0	1		1	1	
Bowel obstruction	1	0	1		0	0	
Necrotic bowel	0	0	0		0	1	
Multisystem organ failure	0 (0)	1 (50)	1 (14)	0.20	0 (0)	0 (0)	>0.90
Liver failure	2 (25)	0 (0)	2 (29)	0.70	0 (0)	1 (17)	>0.90
Uncertain	1 (12)	0 (0)	0 (0)	>0.90	0 (0)	1 (17)	>0.90

Values are n (%).
Abbreviations as in Table 1.



CENTRAL ILLUSTRATION **Composite Instantaneous Risk of Cardiovascular and Noncardiovascular Death in PARTNER-A and -B**

AVR = aortic valve replacement; TA = transapically; TAVR = transcatheter aortic valve replacement; TF = transfemorally.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: After an early high-risk phase following the procedures, the risk of cardiovascular death was lower in patients undergoing TAVR or surgical AVR than those managed without valve replacement. In high-risk patients, TAVR should therefore be considered for severely symptomatic inoperable patients or those at high risk of noncardiovascular mortality after surgical AVR.

TRANSLATIONAL OUTLOOK 1: Registry studies could provide insight into the generalizability of the benefit of TAVR to patients with severe aortic stenosis outside the context of a randomized trial.

TRANSLATIONAL OUTLOOK 2: Additional studies are needed to reveal risk factors for early and late mortality after TAVR and identify patients such as those with cardiac cachexia (characterized by low body mass index and hypoalbuminemia) for whom intervention may be futile.

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KEY WORDS aortic stenosis, causes of death, TAVR

APPENDIX For supplemental tables and figures, please see the online version of this article.