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Transcatheter versus Surgical Aortic Valve Replacement in Patients with Diabetes and Severe Aortic Stenosis at High Risk for Surgery: An Analysis of the PARTNER Trial

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Abstract

Objectives—To determine whether a less invasive approach to aortic valve replacement (AVR) improves clinical outcomes in diabetic patients with aortic stenosis (AS).

Background—Diabetes is associated with increased morbidity and mortality after surgical AVR for AS.

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Methods—Among treated patients with severe symptomatic AS at high-risk for surgery in the PARTNER trial, we examined outcomes stratified by diabetes status of patients randomly assigned to transcatheter or surgical AVR. The primary outcome was all-cause mortality at 1 year.

Results—Among 657 patients enrolled in PARTNER who underwent treatment, there were 275 patients with diabetes (145 transcatheter, 130 surgical). There was a significant interaction between diabetes and treatment group for 1-year all-cause mortality (p=0.048). Among diabetic patients, all-cause mortality at 1 year was 18.0% in the transcatheter group and 27.4% in the surgical group (HR 0.60; 95% CI, 0.36–0.99; p=0.04). Results were consistent among patients treated via transfemoral or transapical routes. In contrast, among non-diabetic patients, there was no significant difference in all-cause mortality at 1 year (p=0.48). Among diabetic patients, the 1-year rates of stroke were similar between treatment groups (3.5% transcatheter vs. 3.5% surgery, p=0.88), but the rates of renal failure requiring dialysis >30 days were lower in the transcatheter group (0% vs. 6.1%, p=0.003).

Conclusions—Among patients with diabetes and severe symptomatic AS at high-risk for surgery, this post-hoc stratified analysis of the PARTNER trial suggests there is a survival benefit, no increase in stroke, and less renal failure from treatment with transcatheter compared to surgical AVR.

Keywords

aortic stenosis; transcatheter aortic valve replacement; diabetes

Introduction

Diabetes mellitus adversely affects morbidity and mortality for all types of cardiovascular diseases (1,2). In patients with aortic stenosis (AS), diabetes is associated with increased hypertrophic remodeling, worse left ventricular function, and worse heart failure symptoms (3,4). Diabetes has also been associated with increased morbidity and mortality after surgical aortic valve replacement, even after adjustment for co-morbidities such as vascular disease and renal dysfunction (5,6). The mechanisms for this additional surgical risk are not completely known, although it is hypothesized that the inflammation, oxidative stress, and reperfusion injury induced by cardioplegia and cardiopulmonary bypass are particularly harmful in the setting of diabetes and hypertrophic ventricular remodeling from chronic pressure overload due to AS, thereby causing adverse short and long-term consequences (7–13). As such, a less invasive method of valve replacement that avoids the injurious effects of cardiopulmonary bypass may lead to improved clinical outcomes among these high-risk patients with diabetes. Accordingly, we examined the clinical outcomes of patients at high risk for surgery enrolled in the PARTNER (Placement of Aortic Transcatheter Valves) trial to evaluate whether outcomes varied according to diabetes status after treatment with transcatheter versus surgical aortic valve replacement (14).

Methods

Study population

The design, inclusion and exclusion criteria, and primary results of the high-risk cohort (Cohort A) of the PARTNER trial have been reported (14). These patients were at high surgical risk as defined by a predicted risk of death of 15% or higher by 30 days after surgery. After evaluation of vascular anatomy, patients were included in either the transfemoral-placement cohort or transapical-placement cohort and randomized to transcatheter therapy with the Edwards-Sapien heart valve system (Edwards Lifesciences, Irvine, California) or surgical aortic valve replacement. Some patients did not undergo their

assigned procedure due to death, refusal, study withdrawal, and/or pretreatment clinical deterioration (14). For the current analysis, we included only patients who were randomized to and received the assigned treatment (as-treated population). The diagnosis of diabetes and other clinical characteristics were determined by the enrolling sites. The study protocol was approved by the institutional review board at each enrolling site and all patients provided written informed consent.

Clinical endpoints

Clinical events including death (all-cause), death (cardiac), repeat hospitalizations, stroke, renal failure, major bleeding, myocardial infarction, and vascular complications were adjudicated by a clinical events committee. The primary end point of the PARTNER trial and our analysis was all-cause death at 1 year. A detailed report of the classification of deaths among the diabetic and non-diabetic patients treated with transcatheter or surgical aortic valve replacement in the transfemoral and transapical placement cohorts is provided in Supplemental Table 1. Repeat hospitalizations were defined as hospitalization resulting from symptoms of aortic stenosis (valve-related deterioration, including heart failure, angina, or syncope) or complications of the valve procedure. Stroke was defined as a focal neurologic deficit lasting ≥24 hours or a focal neurologic deficit lasting <24 hours with imaging findings of acute infarction or hemorrhage. Renal failure events were defined as the need for dialysis of any sort (hemodialysis, CVVHD, peritoneal). Further details on clinical events definitions are provided in Supplemental Table 2. Many of these clinical event definitions are consistent with the VARC-2 definitions (e.g., cardiac death, stroke, and myocardial infarction), but others differ substantially (e.g. renal failure and major bleeding) (15). An independent core laboratory analyzed all echocardiograms (16). The presence and severity of post-procedural prosthesis-patient mismatch and aortic regurgitation were determined according to VARC-2 criteria (15). The Kansas City Cardiomyopathy Questionnaire (KCCQ), a heart failure disease-specific health status measure, was used to assess health status (17,18).

Statistical analysis

Continuous variables are summarized as mean ± SD or medians and quartiles, and were compared using the Student's t-test or Mann-Whitney rank sum test as appropriate. Categorical variables were compared with the chi-square or Fisher exact test. Survival curves for time-to-event variables, based on all available follow-up data, were performed with the use of Kaplan-Meier estimates and were compared between groups with the use of the log-rank test. Cox proportional hazards models were used to calculate hazard ratios and to test for interactions. KCCQ overall summary scores were compared using analysis of covariance to adjust for baseline differences in KCCQ scores between groups. All statistical analyses were performed with SAS software, version 9.2.

Results

Patient population

Among the 699 patients enrolled in the PARTNER trial Cohort A, 657 patients were randomized to and received transcatheter or surgical therapy; 313 patients were treated with surgery and 344 patients were treated with transcatheter therapy. Among the as-treated population, 275 (42%) subjects had diabetes, 145 in the transcatheter group (103 transfemoral, 42 transapical) and 130 in the surgery group (88 transfemoral cohort, 42 transapical cohort). Among the 382 patients without diabetes, 199 were treated with transcatheter valve replacement (137 transfemoral, 62 transapical) and 183 were treated with surgery (133 transfemoral cohort, 50 transapical cohort).

The clinical characteristics and medication usage of patients in the trial with and without diabetes differed in ways that would be expected based on diabetes status (Supplemental Table 3). Within each sub-group of patients (diabetic and non-diabetic patients), the clinical characteristics were generally well-matched between those who received transcatheter versus surgical valve replacement (Table 1 and Supplemental Table 4).

Diabetic patients

Stratified analyses based on diabetes status were performed for several important clinical outcomes at 1 year. There was a significant interaction between diabetes status and all-cause mortality (interaction p=0.048) (Figure 1). Among the patients with diabetes, 1 year all-cause mortality was 18.0% in transcatheter-treated patients versus 27.4% in the surgically-treated patients (HR 0.60, 95% CI, 0.36 to 0.99; p=0.044) (Figures 1 and 2a). The Kaplan Meier survival curves for the transfemoral-placement cohort (Figure 2b) and transapical-placement cohort (Figure 2c) demonstrate a consistent relationship of lower all-cause mortality for transcatheter-treated vs. surgically-treated diabetic patients compared with the overall population of diabetic patients (Figure 2a).

At 6 months, all-cause mortality was lower in transcatheter-treated diabetic patients compared to surgically-treated diabetic patients (10.3% vs. 23.4%; HR 0.41, 95% CI, 0.22 to 0.76; p=0.003) (Figure 2a). At 2 years, the survival benefit observed at 6 months and 1 year from transcatheter compared to surgical treatment in diabetic patients was no longer significant (HR 0.76, 95% CI, 0.49 to 1.19; p=0.23) (Supplemental Figure 1a).

The rates of stroke were similar between transcatheter-treated and surgically-treated diabetic patients at 30 days (3.5% vs. 2.4%, p=0.58) and 1 year (3.5% vs. 3.5%, p=0.88) (Table 2). At 1 year, there was a decreased rate of renal failure requiring dialysis with transcatheter compared to surgical therapy (4.2% vs. 10.6%, p=0.05), particularly dialysis lasting greater than 30 days (0.0% vs. 6.1%, p=0.003) (Table 2). Similar to the main trial results, among diabetic subjects there was an increased risk of major bleeding with surgery but an increased risk of major vascular complications with transcatheter therapy at 30 days and 1 year (p<0.05 for all relationships) (Table 2).

Echocardiography, symptoms, and laboratory findings—The incidence of post-operative mild and moderate or severe total aortic regurgitation was higher in diabetic patients treated with transcatheter therapy compared to surgery (Table 3). There was a trend toward a lower incidence of moderate or severe prosthesis-patient mismatch at 30 days with transcatheter therapy, whereas left ventricular mass was lower at 30 days in surgically-treated patients (Table 3). A lower incidence of NYHA class III or IV heart failure symptoms, better quality of life, and longer 6 minute walk distance were observed at 30 days in diabetic patients treated with transcatheter therapy compared to surgery, but there were no significant between-group differences at 6 months or 1 year (Table 4). Post-procedural troponin level and white blood cell count were higher in diabetic subjects treated with surgery compared to transcatheter therapy (Table 3).

Non-diabetic patients

There was no difference in 1 year all-cause mortality in non-diabetic subjects treated with transcatheter versus surgical therapy (Figure 3a); however there was a trend toward increased mortality in the transapical-placement cohort from transcatheter therapy compared to surgery (Figure 3c). A trend toward a higher risk of stroke was observed in non-diabetic patients treated with transcatheter therapy compared to surgery at 1 year (7.6% vs. 2.8%; HR 2.60, 95% CI, 0.94 to 7.22, p=0.056) (Figure 1). The rates of repeat hospitalization and renal failure among non-diabetic patients were similar in the two treatment groups.

Discussion

We report for the first time, in a post-hoc stratified analysis of the high-risk patients enrolled in the PARTNER trial, a differential response to transcatheter versus surgical treatment based on diabetes status. Although the PARTNER trial demonstrated similar rates of death at 1 year in those treated with transcatheter or surgical therapy for the overall population, we found that diabetic patients who were treated with transcatheter aortic valve replacement had a 9% lower absolute risk of 1 year all-cause mortality and a 40% lower hazard of death over the first year after the procedure compared with diabetic patients treated with surgical valve replacement. Furthermore, diabetic patients treated with transcatheter therapy had a similar rate of stroke and lower incidence of renal failure compared with those treated with surgery. These findings have important clinical implications for the treatment of patients with severe AS and diabetes at high risk for surgery.

Clinical Implications

Both transcatheter and surgical valve replacement relieve left ventricular pressure overload from AS by treating the mechanical obstruction of the valve. Among the overall population, the PARTNER trial demonstrated that survival at 1 year was similar with transcatheter and surgical valve replacement for patients with severe symptomatic AS at high risk for surgery. However, there may be sub-groups of patients that will do better with one approach than the other. As we gain more experience with these two treatment options, we will learn how to individualize treatment strategies based on a variety of potential factors to obtain the best clinical results. Our study raises the intriguing possibility that transcatheter valve replacement may be the preferred approach for diabetic patients with severe symptomatic AS who are at high surgical risk.

There is considerable interest in comparing less invasive transcatheter or percutaneous therapies to surgical therapies for a variety of cardiovascular problems including valve disease and coronary, aortic, carotid, and peripheral vascular disease, particularly in diabetic patients (19–23). These comparisons involve differences both in *what* therapy is provided (eg. stent vs. bypass graft) and *how* it is provided (eg. catheter-based vs. open surgery). When comparing transcatheter to surgical aortic valve replacement, there is relatively little difference in *what* therapy is provided. In both cases, the mechanical valve obstruction is treated by the placement of a new valve that relieves the pressure overload on the ventricle. Nonetheless, differences in how well the implanted valve opens the previously restricted orifice (effective orifice area) and how much it leaks could impact outcomes. In contrast, there are more obvious differences in *how* the therapy is provided, which we suspect underlies the difference in survival among diabetic patients between the two treatment groups. In the case of a transcatheter approach there is rapid ventricular pacing with large sheaths introduced into the major vessels and/or heart, whereas with surgery there are the injurious effects of cardiopulmonary bypass, cardioplegia, and reperfusion.

Among diabetic patients, the survival curves between the transcatheter and surgical treatment groups separate soon after valve replacement and continue to move apart until approximately 6 months, after which the curves move modestly toward each other and by 2 years there is no significant difference in survival between the two treatment groups. We hypothesize that this relationship is due to the short-term benefit of a less invasive approach to replace the valve that avoids cardiopulmonary bypass, which is mitigated over time by non-procedure related factors and the known deleterious effects of increased aortic regurgitation after transcatheter valve replacement. In the PARTNER trial, both in the whole population and the sub-group with diabetes, there was a much greater incidence of mild, moderate, and severe aortic regurgitation in the transcatheter treatment group compared to

surgery, which is associated with increased all-cause mortality (24). A potential implication is that if the incidence of aortic regurgitation after transcatheter aortic valve replacement is reduced, the early substantial survival benefit of transcatheter valve replacement in diabetic patients may be sustained beyond the first year.

Other observations from this analysis merit further study. While not the focus of our analysis, the rate of all-cause mortality at 1 year was lower in diabetic patients compared to non-diabetic patients treated with transcatheter therapy. Diabetes is known to adversely affect morbidity and mortality for all types of cardiovascular disease and adversely influence post-procedural outcomes after percutaneous and surgical procedures (1,2,25,26). As such, this result was somewhat surprising. However, it should be noted that there were numerous baseline clinical differences between the diabetic and non-diabetic patients (Supplemental Table 3), which could confound this comparison. In particular and as expected, diabetic patients had a much larger body mass index than non-diabetic patients. In the PARTNER trial, higher body mass index had an independent protective effect in the transcatheter group but not surgical group. This may explain, at least in part, the unexpected observation of lower mortality in diabetic compared to non-diabetic patients in the transcatheter group. This hypothesis-generating observation of an apparent “diabetes paradox” requires further study and careful adjustment for confounders.

Possible Mechanisms

Diabetes is characterized by a milieu of hyperglycemia, insulin resistance, and increased nonesterified fatty acids, which contribute to oxidative stress, lipotoxicity, advanced glycation end products, and altered calcium handling and substrate metabolism (11). Surgical valve replacement involves cardioplegia, cardiopulmonary bypass, and reperfusion injury, which may cause more inflammation, oxidative stress, and myocardial ischemia/injury than with the rapid ventricular pacing performed during transcatheter therapy (7–10,12,13). In diabetic patients, this may intensify an already existing deleterious myocardial and systemic environment, which may have important short and long-term adverse consequences for cardiac performance and clinical outcomes after valve replacement. Recently, Sinning et al. demonstrated that the development of systemic inflammatory response syndrome during the first 48 hours after transcatheter aortic valve replacement is associated with increased 30-day and 1-year mortality (27). We speculate that surgical valve replacement may be associated with an increased incidence of systemic inflammatory response syndrome compared to transcatheter replacement. Consistent with this possibility, the 24 hour post-procedure blood analyses drawn in the PARTNER trial showed higher levels of white blood cells in patients with diabetes after surgical compared to transcatheter valve replacement. The 24 hour post-procedure cardiac enzyme levels were also higher in the diabetic patients treated with surgery, suggesting increased ischemic injury compared to a transcatheter approach. Other mechanisms whereby transcatheter therapy may confer a survival benefit in diabetic patients include less prosthesis-patient mismatch and less post-procedural renal failure requiring dialysis, both of which have a known adverse impact on clinical outcomes (16,24). However, ultimately the mechanisms underlying the survival benefit from a transcatheter valve replacement in diabetic patients require further investigation, including the impact of insulin and/or oral diabetic medical treatments and how the metabolic syndrome and diabetes separately and in combination influence outcomes in diabetic patients undergoing transcatheter or surgical valve replacement.

Limitations

Our study has several limitations to consider when interpreting the results and potential implications. Most importantly, diabetes status was not a pre-specified sub-group analysis

and, as such, these results should be considered hypothesis generating and need to be confirmed in future studies. However, given the relatively low power to demonstrate superiority of transcatheter replacement over surgical replacement in a sub-group analysis, the statistically significant survival benefit is noteworthy and should encourage further evaluation. Second, the diagnosis of diabetes was determined by enrolling sites and was not verified by other mechanisms. However, the differences observed between diabetic and non-diabetic patients in the PARTNER trial with respect to baseline clinical characteristics and medication usage are consistent with those that would be expected based on the presence or absence of diabetes. Furthermore, we do not have reliable information on diabetic medication usage (insulin and/or oral medications) nor access to data on the severity or duration of diabetes, microvascular complications, or glucose control. How each of these factors contributes to the treatment effect of transcatheter versus surgical aortic valve replacement will require further study. However, by including patients with mild (recent onset, diet controlled or oral medications only) as well as severe (long-standing, requiring insulin) diabetes, we were less likely to disprove the null hypothesis that survival would be similar between the transcatheter and surgical treatment groups.

Conclusion

Diabetes is associated with increased morbidity and mortality in patients with AS undergoing surgical valve replacement. In a post-hoc stratified analysis of the PARTNER trial in which high-risk patients were randomized to transcatheter or surgical aortic valve replacement, we found that diabetic patients had a survival benefit at 1 year with no increased risk of stroke and less renal failure when treated with transcatheter valve replacement compared to surgery. These results suggest that transcatheter aortic valve replacement may be the preferred treatment approach for patients with AS and diabetes who are high-risk for surgery. Confirmation of these findings, particularly in lower risk populations, is needed as well as insights into the underlying mechanisms for the observed survival benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

AS	aortic stenosis
AVR	aortic valve replacement
DM	diabetes mellitus / diabetic
KCCQ	Kansas City Cardiomyopathy Questionnaire
NDM	non-diabetic
NYHA	New York Heart Association
PARTNER	Placement of Aortic Transcatheter Valves trial

SAVR	surgical aortic valve replacement
TA	transapical
TAVR	transcatheter aortic valve replacement
TF	transfemoral

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006; 355:251–269. [PubMed: 16855265]
2. Mak KH, Topol EJ. Emerging concepts in the management of acute myocardial infarction in patients with diabetes mellitus. J Am Coll Cardiol. 2000; 35:563–588. [PubMed: 10716456]
3. Lindman BR, Arnold SV, Madrazo JA, et al. The adverse impact of diabetes mellitus on left ventricular remodeling and function in patients with severe aortic stenosis. Circ Heart Fail. 2011; 4:286–292. [PubMed: 21357546]
4. Falcao-Pires I, Hamdani N, Borbely A, et al. Diabetes mellitus worsens diastolic left ventricular dysfunction in aortic stenosis through altered myocardial structure and cardiomyocyte stiffness. Circulation. 2011; 124:1151–1129. [PubMed: 21844073]
5. Halkos ME, Kilgo P, Lattouf OM, et al. The effect of diabetes mellitus on in-hospital and long-term outcomes after heart valve operations. Ann Thorac Surg. 2010; 90:124–130. [PubMed: 20609762]
6. Smith RL 2nd, Herbert MA, Dewey TM, et al. Does body mass index affect outcomes for aortic valve replacement surgery for aortic stenosis? Ann Thorac Surg. 2012; 93:742–756. [PubMed: 22284305]
7. Ascione R, Caputo M, Gomes WJ, et al. Myocardial injury in hypertrophic hearts of patients undergoing aortic valve surgery using cold or warm blood cardioplegia. Eur J Cardiothorac Surg. 2002; 21:440–456. [PubMed: 11888760]
8. Cavalca V, Sisillo E, Veglia F, et al. Isoprostanes and oxidative stress in off-pump and on-pump coronary bypass surgery. Ann Thorac Surg. 2006; 81:562–577. [PubMed: 16427852]
9. Wan S, DeSmet JM, Barvais L, Goldstein M, Vincent JL, LeClerc JL. Myocardium is a major source of proinflammatory cytokines in patients undergoing cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1996; 112:806–811. [PubMed: 8800171]
10. Dybdahl B, Wahba A, Lien E, et al. Inflammatory response after open heart surgery: release of heat-shock protein 70 and signaling through toll-like receptor-4. Circulation. 2002; 105:685–790. [PubMed: 11839622]
11. Poornima IG, Parikh P, Shannon RP. Diabetic cardiomyopathy: the search for a unifying hypothesis. Circ Res. 2006; 98:596–605. [PubMed: 16543510]
12. Suleiman MS, Hancock M, Shukla R, Rajakaruna C, Angelini GD. Cardioplegic strategies to protect the hypertrophic heart during cardiac surgery. Perfusion. 2011; 26(Suppl 1):48–56. [PubMed: 21933822]
13. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. Chest. 1997; 112:676–692. [PubMed: 9315800]
14. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011; 364:2187–2298. [PubMed: 21639811]
15. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012; 60:1438–1454. [PubMed: 23036636]
16. Hahn RT, Pibarot P, Stewart WJ, et al. Comparison of Transcatheter and Surgical Aortic Valve Replacement in Severe Aortic Stenosis: A Longitudinal Study of Echocardiography Parameters in Cohort A of the PARTNER Trial (Placement of Aortic Transcatheter Valves). J Am Coll Cardiol. 2013; 61:2514–2521. [PubMed: 23623915]

17. Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). J Am Coll Cardiol. 2012; 60:548–558. [PubMed: 22818074]

18. Arnold SV, Spertus JA, Lei Y, et al. Use of the Kansas City Cardiomyopathy Questionnaire for monitoring health status in patients with aortic stenosis. Circ Heart Fail. 2013; 6:61–77. [PubMed: 23230306]

19. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med. 2011; 364:1395–1406. [PubMed: 21463154]

20. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med. 2012; 367:2375–2484. [PubMed: 23121323]

21. Chaitman BR, Rosen AD, Williams DO, et al. Myocardial infarction and cardiac mortality in the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial. Circulation. 1997; 96:2162–2270. [PubMed: 9337185]

22. Bavaria JE, Appoo JJ, Makaroun MS, et al. Endovascular stent grafting versus open surgical repair of descending thoracic aortic aneurysms in low-risk patients: a multicenter comparative trial. J Thorac Cardiovasc Surg. 2007; 133:369–377. [PubMed: 17258566]

23. Brott TG, Hobson RW 2nd, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010; 363:11–23. [PubMed: 20505173]

24. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012; 366:1686–1695. [PubMed: 22443479]

25. Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Circulation. 1996; 94:1818–1825. [PubMed: 8873655]

26. Bucerius J, Gummert JF, Walther T, et al. Impact of diabetes mellitus on cardiac surgery outcome. Thorac Cardiovasc Surg. 2003; 51:11–16. [PubMed: 12587082]

27. Sinning JM, Scheer AC, Adenauer V, et al. Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. Eur Heart J. 2012; 33:1459–1568. [PubMed: 22285582]

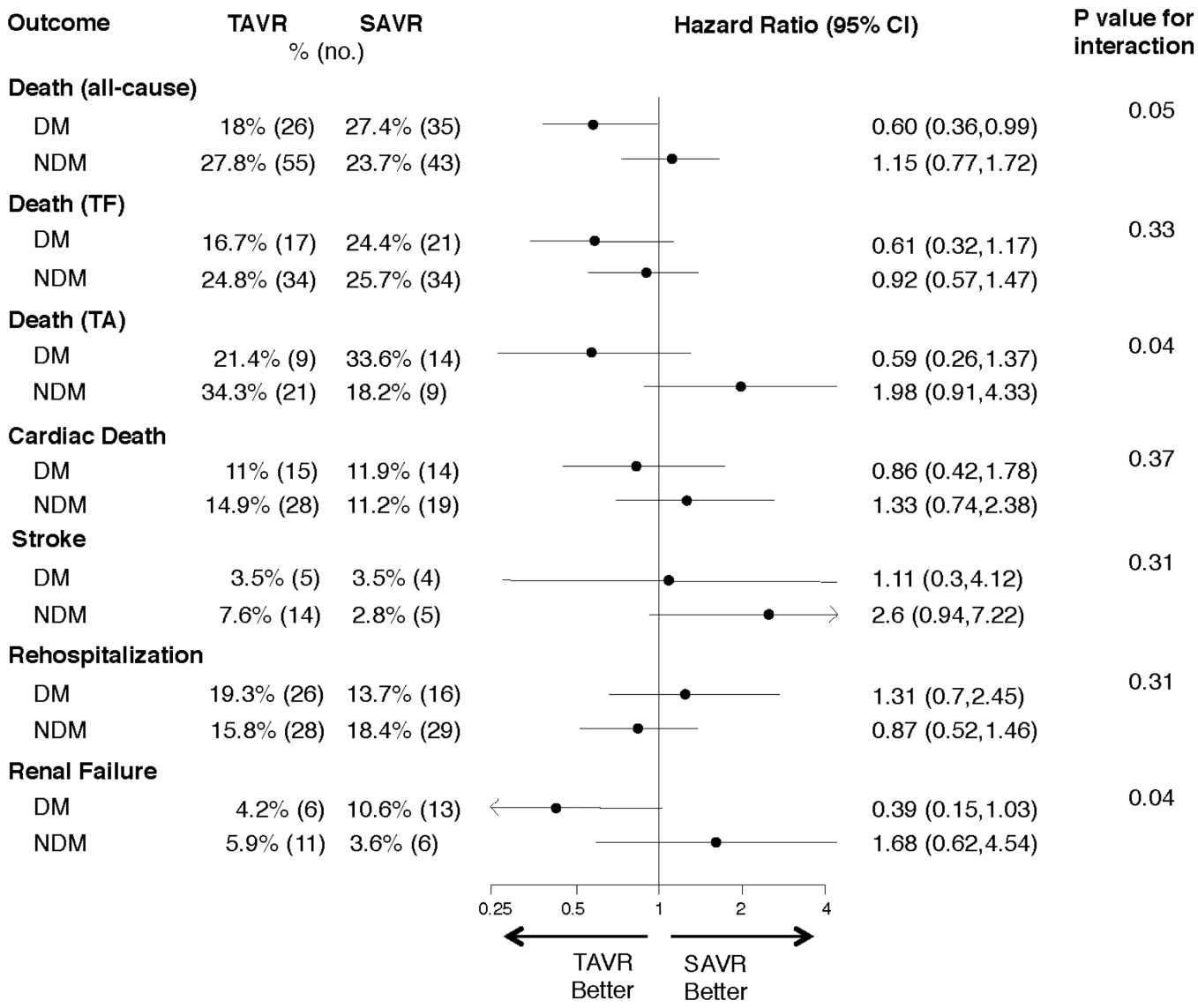
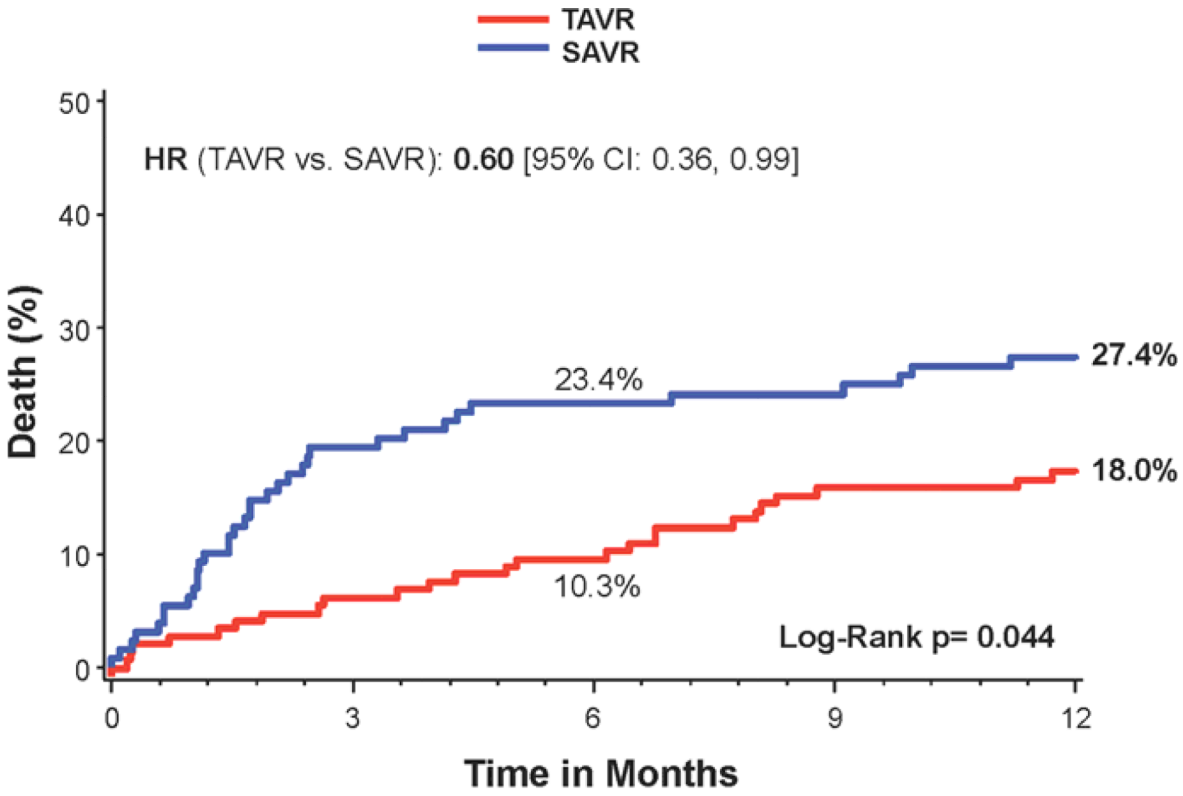


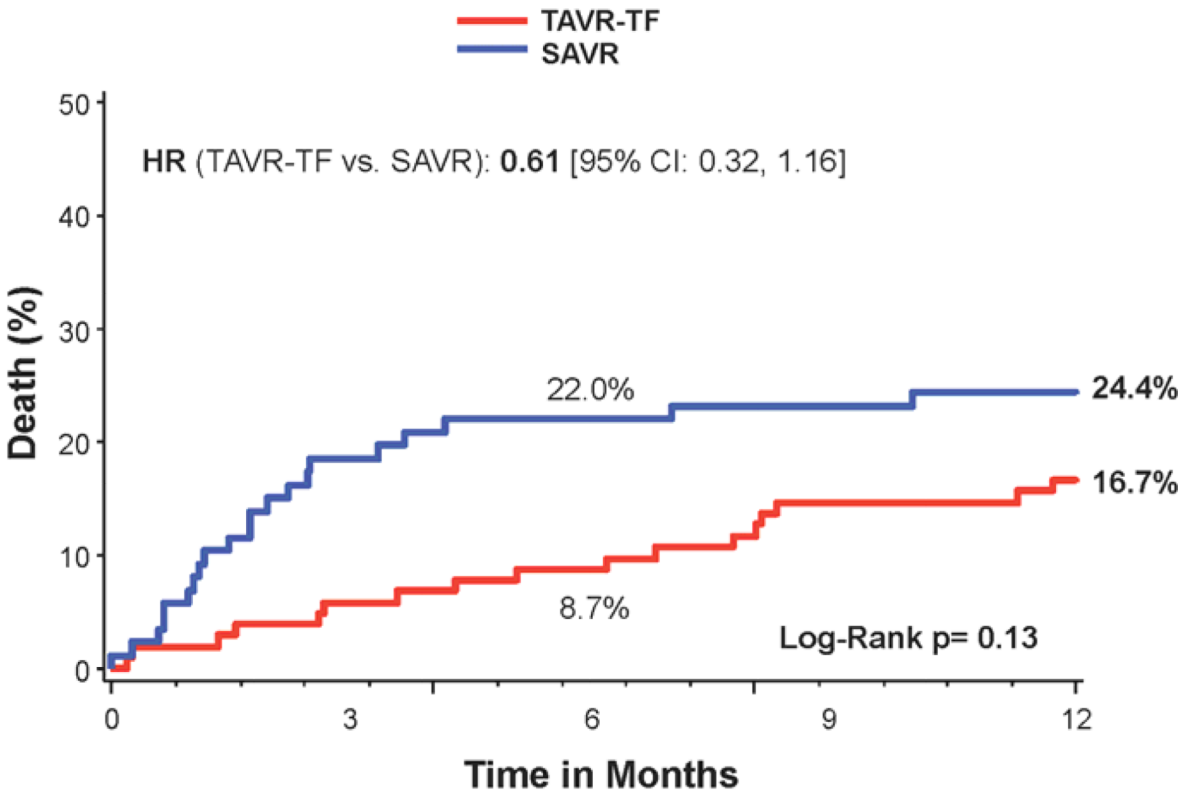
Figure 1. Clinical outcomes stratified by diabetes in the high risk cohort of the PARTNER trial

Cox proportional hazards models were used to evaluate the hazard ratios for patients with (DM) and without (NDM) diabetes for the clinical outcomes shown and the interaction between diabetes status and treatment for each clinical outcome. Abbreviations: TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; DM, diabetes mellitus; NDM, non-diabetes mellitus; TF, transfemoral; TA, transapical.



Number at risk

TAVR	145	135	129	119	117
SAVR	130	103	97	95	91



Number at risk

TAVR-TF	103	97	93	86	84
SAVR	88	70	67	65	64

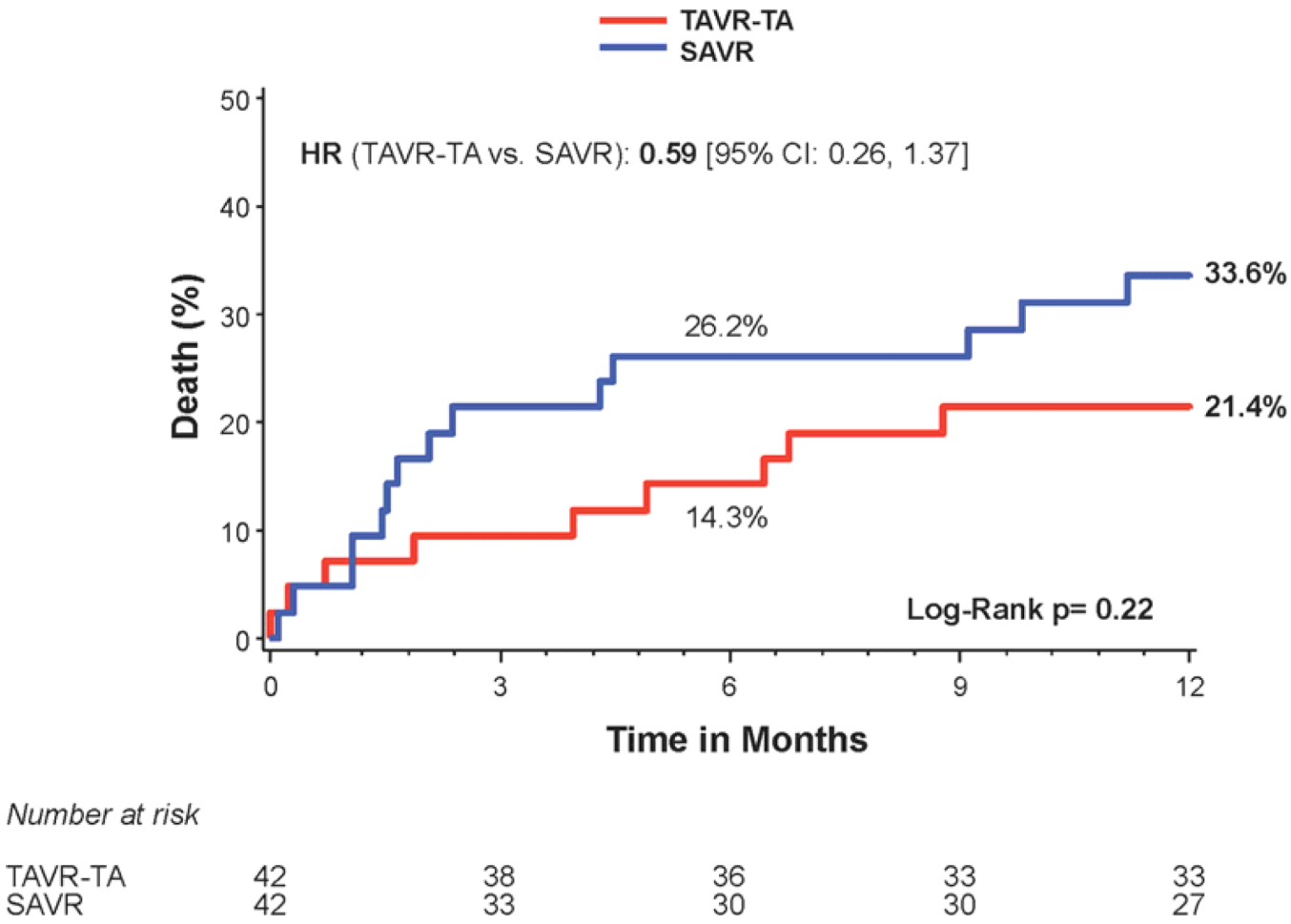
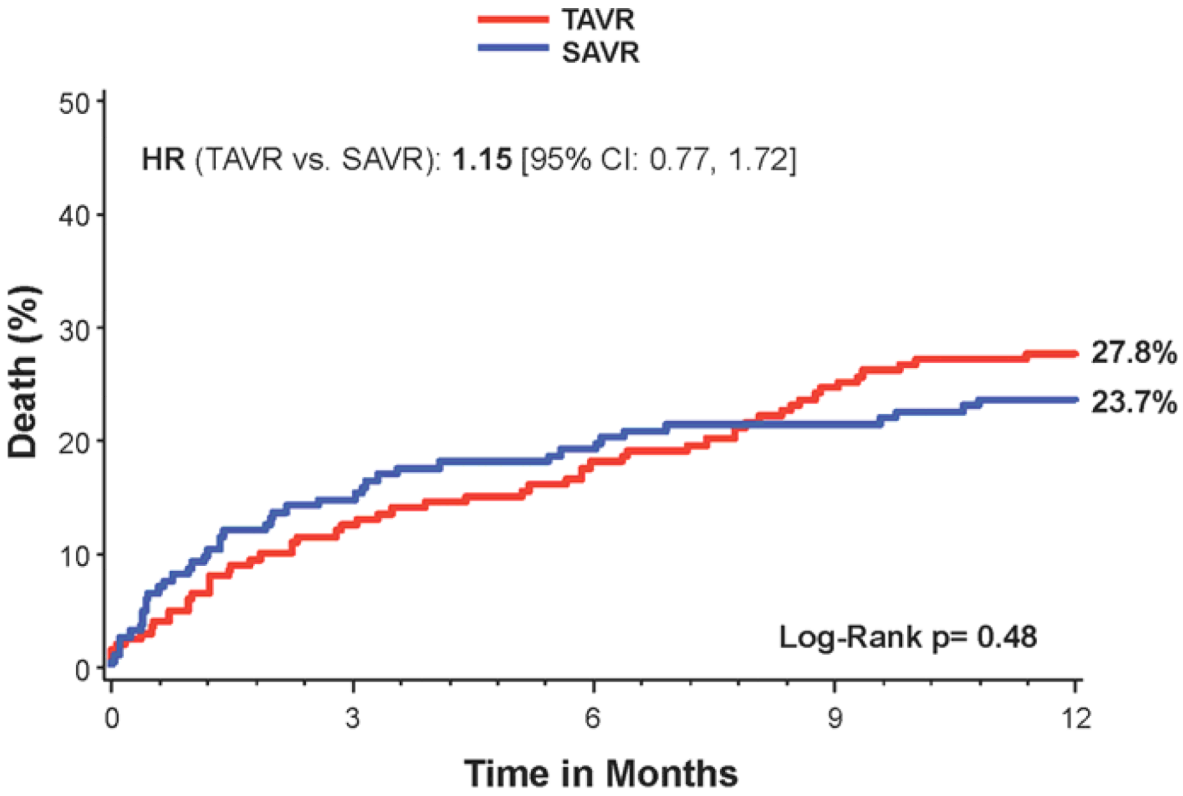


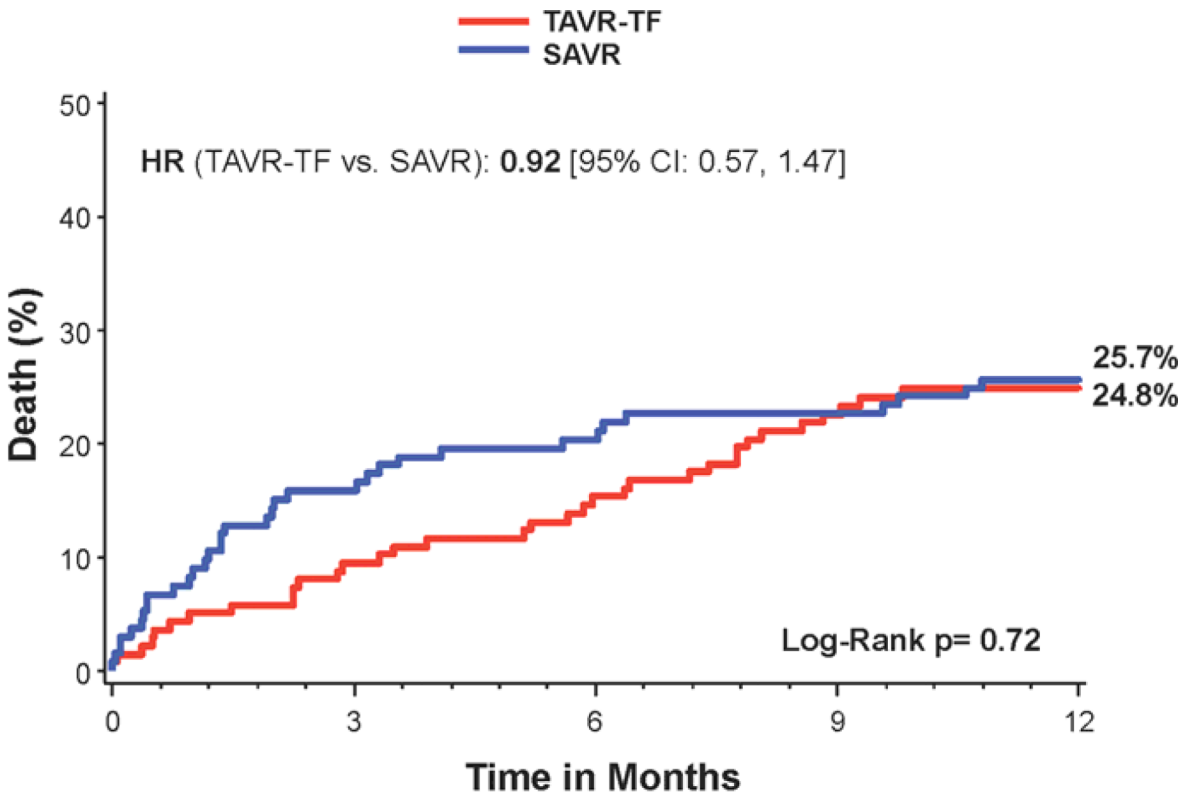
Figure 2. Time-to-event curves for diabetic patients for 1-year death from any cause

One-year time-to-event curves are shown for diabetic patients for death from any cause in the as-treated population of the PARTNER trial (treated with either transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR)). The curves are shown for all diabetic patients (A), those in the transfemoral (TF) cohort (B), and those in the transapical (TA) cohort (C). The event rates were calculated with the use of Kaplan-Meier methods and compared with the use of the log-rank test.



Number at risk

TAVR	199	173	162	149	143
SAVR	183	154	146	142	138



Number at risk

TAVR-TF	137	124	116	106	103
SAVR	133	111	105	102	98

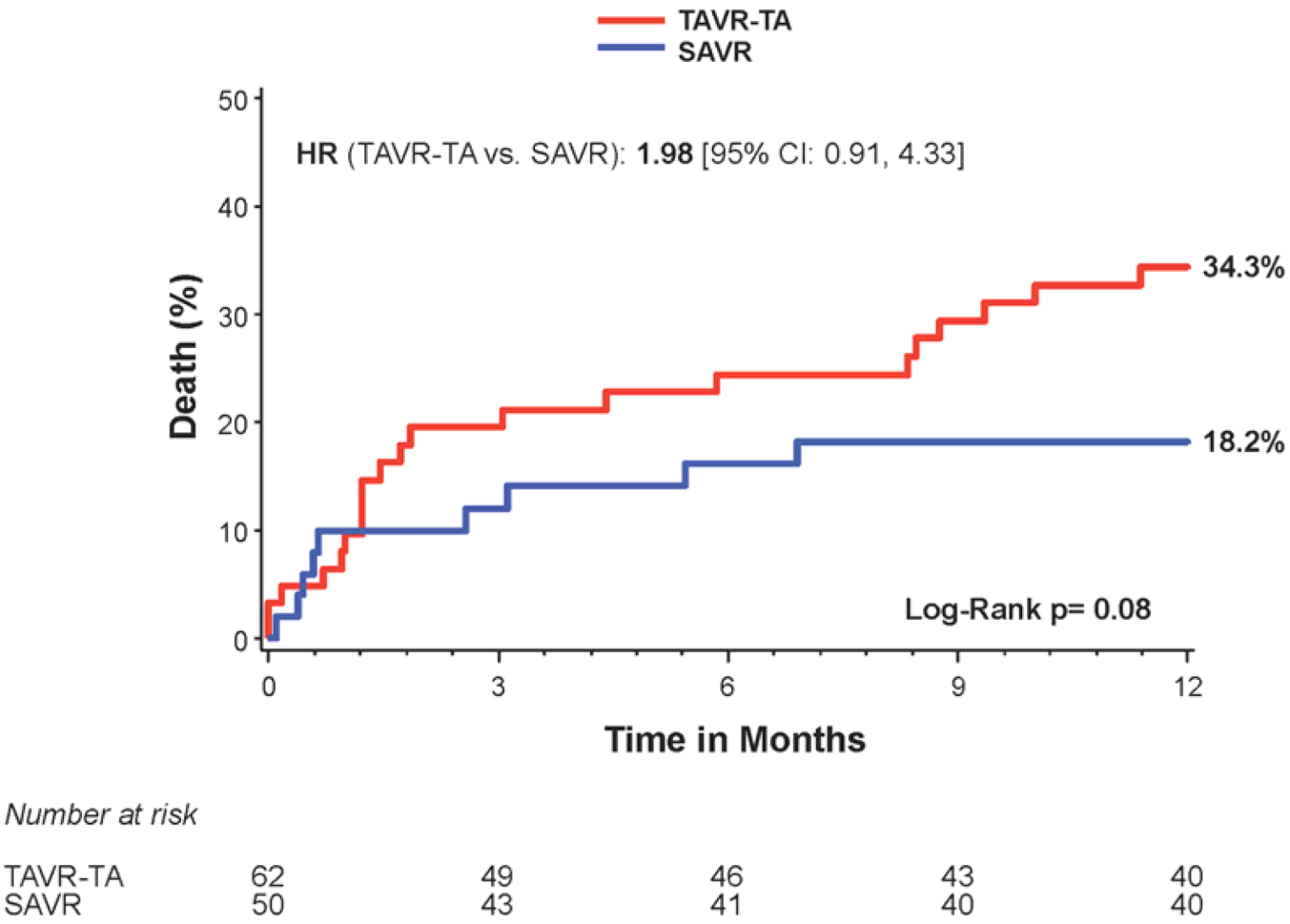


Figure 3. Time-to-event curves for non-diabetic patients for 1-year death from any cause

One-year time-to-event curves are shown for non-diabetic patients for death from any cause in the as-treated population of the PARTNER trial (treated with either transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR)). The curves are shown for all patients without diabetes (A), those in the transfemoral (TF) cohort (B), and those in the transapical (TA) cohort (C). The event rates were calculated with the use of Kaplan-Meier methods and compared with the use of the log-rank test.

Table 1

Clinical Characteristics of the Diabetic Subjects in the High Risk Cohort of the PARTNER Trial

	TAVR-DM n=145	SAVR-DM n=130	p-value
Demographic and Clinical Data			
Age	81.8 ± 7.5	82.4 ± 6.8	0.47
Female (%)	35%	39%	0.57
Body mass index	30.1 ± 7.7	28.8 ± 6.6	0.13
Body surface area	1.93 ± 0.24	1.89 ± 0.23	0.20
STS Score	12.2 ± 3.4	11.8 ± 3.1	0.31
STS >10	80%	80%	1.0
Logistic EuroSCORE	28.3 ± 16	28.3 ± 16	0.99
Hyperlipidemia	86%	86%	0.99
Smoking	55%	55%	0.88
Hypertension	95%	95%	0.73
NYHA class 4	55%	57%	0.68
Angina	29%	22%	0.21
Coronary disease	82%	84%	0.70
Prior myocardial infarction	29%	30%	0.88
Prior percutaneous coronary intervention	35%	35%	0.95
Prior coronary artery bypass surgery	51%	54%	0.64
Stroke or TIA (last 6–12 months)	30%	32%	0.70
Carotid disease	32%	27%	0.40
Peripheral vascular disease	48%	43%	0.41
Porcelain aorta	0.7%	0.0%	1.0
Pulmonary hypertension	44%	45%	0.89
Major arrhythmia	40%	49%	0.16
Permanent pacemaker	26%	28%	0.68
Renal disease (creatinine ^{3}2)	23%	26%	0.60
Liver disease	3.4%	3.1%	0.43
Chronic obstructive lung disease	48%	42%	0.26
Oxygen dependent	9%	9%	0.94
Anemia	74%	64%	0.10
Transfemoral cohort	71%	68%	0.55
Baseline Cardiac Medications			
βblockers	68%	67%	0.91
ACE-inhibitors	40%	39%	0.79
Angiotensin II receptor blockers (ARBs)	16%	22%	0.17
ACE-inhibitors or ARBs	52%	57%	0.45
Calcium channel blockers	26%	22%	0.44

	TAVR-DM n=145	SAVR-DM n=130	p-value
Statins	73%	65%	0.13
Diuretics	76%	68%	0.13
Nitrates	15%	10%	0.26
Anti-arrhythmics	26%	30%	0.41
Aspirin	77%	61%	0.003
Anti-platelet (other than aspirin)	26%	23%	0.64

Abbreviations: TAVR, transcatheter aortic valve replacement; DM, diabetes mellitus; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgery; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme.

Table 2

Clinical Outcomes in Diabetic Patients in the High Risk Cohort of the PARTNER Trial

Clinical Outcome	TAVR-DM n=145 % (no.)	SAVR-DM n=130 % (no.)	Hazard Ratio (95% CI)	p-value
30 days				
Death (all-cause)	3.4% (5)	6.2% (8)	0.56 [0.18,1.70]	0.29
Death (all-cause), TF cohort	1.9% (2)	6.9% (6)	0.28 [0.06,1.39]	0.09
Death (all-cause), TA cohort	7.1% (3)	4.8% (2)	1.51 [0.25,9.07]	0.65
Death (cardiac)	1.4% (2)	3.2% (4)	0.44 [0.08,2.42]	0.33
Repeat hospitalizations	5.0% (7)	8.0% (10)	0.61 [0.23,1.60]	0.31
Stroke (any)	3.5% (5)	2.4% (3)	1.50 [0.36,6.27]	0.58
Major bleeding	11.1% (16)	22.3% (29)	0.48 [0.26,0.88]	0.01
Vascular complications (major)	11.7% (17)	2.3% (3)	5.10 [1.50,17.4]	0.003
Myocardial infarction	0.0% (0)	0.8% (1)	---	0.29
Renal failure (dialysis required)	3.5% (5)	7.8% (10)	0.44 [0.15,1.30]	0.12
Dialysis lasting >30 days	0.0% (0)	3.2% (4)	---	0.03
1 year				
Death (all-cause)	18.0% (26)	27.4% (35)	0.60 [0.36,0.99]	0.04
Death (all-cause), TF cohort	16.7% (17)	24.4% (21)	0.61 [0.32,1.16]	0.13
Death (all-cause), TA cohort	21.4% (9)	33.6% (14)	0.59 [0.26,1.37]	0.22
Death (cardiac)	8.0% (11)	8.3% (10)	0.89 [0.38,2.11]	0.80
Repeat hospitalizations	19.3% (26)	13.7% (16)	1.32 [0.71,2.45]	0.39
Stroke (any)	3.5% (5)	3.5% (4)	1.11 [0.30,4.12]	0.88
Major bleeding	15.1% (21)	26.9% (34)	0.52 [0.30,0.89]	0.01
Vascular complications (major)	11.7% (17)	2.3% (3)	5.10 [1.50,17.4]	0.003
Myocardial infarction	0.0% (0)	0.8% (1)	---	0.29
Renal failure (dialysis required)	4.2% (6)	10.6% (13)	0.39 [0.15,1.03]	0.05
Dialysis lasting >30 days	0.0% (0)	6.1% (7)	---	0.003

The event rates were calculated with the use of Kaplan-Meier methods.

Abbreviations: TF, transfemoral; TA, transapical; others as in Table 1.

Table 3

Echocardiographic and Laboratory Data in Diabetic Patients in the High Risk Cohort of the PARTNER Trial

	TAVR-DM	SAVR-DM	p-value
Echocardiography			
Ejection fraction			
Baseline	51.7 ± 14.0	52.7 ± 11.7	0.53
30 days	54.1 ± 11.1	53.7 ± 10.8	0.78
LV Mass			
Baseline	304 ± 86	289 ± 88	0.18
30 days	294 ± 86	256 ± 78	0.002
Prosthesis-patient mismatch (moderate or severe)			
30 days	46.9%	60.7%	0.07
Moderate/severe mitral regurgitation			
Baseline (%)	14.2%	15.6%	0.75
30 days	15.4%	14.6%	0.86
Mild total aortic regurgitation			
Baseline (%)	48.9%	35.2%	0.02
30 days	52.8%	9.3%	<0.0001
6 months (%)	54.1%	5.5%	<0.0001
Moderate/severe total aortic regurgitation			
Baseline (%)	6.4%	13.6%	0.05
30 days	9.6%	1.0%	0.007
6 months (%)	9.0%	1.4%	0.052
Laboratory Values			
Troponin I			
Baseline	0.04 (0.02, 0.08)	0.05 (0.03, 0.10)	0.12
24 hours post-procedure	0.78 (0.20, 3.62)	4.47 (2.04, 10.40)	<0.001
Creatinine			
Baseline	1.30 (1.00, 1.60)	1.25 (1.00, 1.60)	0.85
30 days	1.21 (1.00, 1.59)	1.29 (0.94, 1.84)	0.80
White blood cells			
Baseline	6.9 (5.9, 8.2)	6.7 (5.7, 8.1)	0.35
24 hours post-procedure	10.2 (8.6, 12.4)	11.7 (9.9, 15.4)	0.056
30 days	7.0 (6.0, 8.0)	7.3 (6.2, 9.8)	0.04
Hemoglobin			
Baseline	11.6 (10.7, 12.8)	11.9 (10.6, 13.0)	0.40
24 hours post-procedure	10.0 (9.2, 11.1)	9.9 (8.8, 11.4)	0.89
30 days	11.2 (10.5, 12.1)	11.0 (10.0, 11.9)	0.13

Data reported as mean ± SD or median (25^{th}, 75^{th} percentiles) and includes all subjects with data at the specified time.

Abbreviations: LV, left ventricle; ULN, upper limit of normal; others as in Table 1.

Patient-prosthesis mismatch (moderate or severe) = Effective orifice area index ≤0.85 cm^2/m^2

Table 4

Symptoms, Quality of Life, and 6 Minute Walk in Diabetic Patients in the High Risk Cohort of the PARTNER Trial.

	TAVR-DM	SAVR-DM	p-value
NYHA class III/IV			
Baseline	95%	94%	0.63
Discharge / 7 days	40%	60%	0.003
30 days	21%	40%	0.002
6 months	18%	11%	0.18
1 year	13%	10%	0.58
KCCQ			
Baseline			
Number of subjects with KCCQ data	n=139	n=120	
Overall summary score	39.5 ± 23.1	44.3 ± 20.3	0.08
30 days			
Number of subjects with KCCQ data	n=123	n=100	
Overall summary score adjusted for baseline score	64.9 (60.6, 69.2)	55.3 (50.4, 60.1)	0.004
6 months			
Number of subjects with KCCQ data	n=118	n=87	
Overall summary score adjusted for baseline score	68.9 (64.7, 73.0)	72.3 (67.5, 77.1)	0.29
1 year			
Number of subjects with KCCQ data	n=108	n=83	
Overall summary score adjusted for baseline score	68.2 (64.0, 72.3)	72.7 (67.8, 77.6)	0.17
6 minute walk			
Baseline			
Could not perform	41%	39%	0.81
Distance walked (m)*	175 ± 116	180 ± 103	0.77
30 days			
Could not perform	42%	50%	0.19
Distance walked (m)	208 ± 111	159 ± 97	0.01
6 months			
Could not perform	35%	32%	0.60
Distance walked (m)	238 ± 115	236 ± 115	0.92
1 year			
Could not perform	28%	32%	0.47
Distance walked (m)	190 ± 98	226 ± 113	0.06

Data reported as mean ± SD, median (25^{th}, 75^{th} percentiles), or %.

*Excluding those who could not perform the 6 minute walk.

Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; others as in Table 1.