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Original article

Midterm outcome of transcatheter versus surgical aortic valve replacement in low to intermediate risk patients: A meta-analysis of randomized controlled trials

Yanwei Wang (MD)[a,1], Yijiang Zhou (MD)[b,1], Li Zhang (MD, PhD)[b,*], Jianhua Zhu (MS)[b,*]

[a] Department of Cardiology, Ningbo Medical Treatment Center Lihuili Hospital, Ningbo, PR China
[b] Department of Cardiology, The First Affiliated Hospital, Zhejiang University, School of Medicine, Hangzhou, PR China

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ABSTRACT

Background: Current guidelines recommend transcatheter aortic valve replacement (TAVR) in patients with severe symptomatic aortic stenosis (AS) who are not suitable for conventional surgical aortic valve replacement (SAVR). In light of the recent trend in performing TAVR in patients with lower risk profile, we assessed the midterm outcome comparing TAVR and SAVR for the treatment of patients with severe AS at low to intermediate risk.

Methods: PubMed, EBSCO, and Cochrane CENTRAL were systematically searched for randomized controlled trials that reported the clinical outcomes of TAVR versus SAVR in patients at low to intermediate surgical risk with at least 2 years of follow-up. Clinical endpoints including death, acute kidney injury, myocardial infarction, stroke, permanent pacemaker implantation, and life-threatening bleeding events were assessed.

Results: From 2000 to 2017, 4 clinical studies comprising 4355 patients were identified. At 2-year follow-up, TAVR was associated with similar rate of death from any cause (RR 0.86; 95%CI: 0.67–1.10), cardiovascular death (RR 0.88; 95%CI: 0.73–1.06), and stroke (RR 0.97; 95%CI: 0.81–1.15). TAVR reduced incidence of bleeding events (RR 0.45; 95%CI: 0.28–0.73) and acute kidney injury (RR 0.48; 95%CI: 0.25–0.93). However, TAVR was associated with higher rate of permanent pacemaker implantation (RR 3.01; 95%CI: 1.04–8.72).

Conclusion: In patients at low to intermediate surgical risk, midterm clinical outcomes of TAVR were similar to SAVR in survival and stroke rate, superior in reducing life-threatening bleeding, acute kidney injury, and new-onset atrial fibrillation, but inferior in increasing permanent pacemaker implantation.

Introduction

Patients with symptomatic severe aortic stenosis (AS) have a poor prognosis without valve replacement. Although the mainstay of treatment, surgical aortic valve replacement (SAVR), is effective, a portion of patients cannot tolerate the operation. Following the first successful implantation performed by Cribier in 2002 [1], transcatheter aortic valve replacement (TAVR) has become an accepted alternative to SAVR for treating symptomatic severe AS in patients who are unsuitable for surgery or at high risk for procedure-related complications. Guidelines from the European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA) both recommend TAVR in patients with severe symptomatic AS who are not suitable for conventional aortic valve replacement [2,3]. With continuing improvement in TAVR systems and accumulation of procedural experience, there is a clear trend of performing TAVR in patients who are at lower surgical risk [4]. Several observational studies demonstrated that TAVR had a comparable early clinical outcome with SAVR in patients at low to intermediate surgical risk [5,6]. Although previous meta-analyses of randomized controlled trials also showed that TAVR was associated with similar rates of mortality and cardiovascular death in this population, data were confined to short-term outcomes at 1 year [7]. The recent publication of the Surgical Replacement and Transcatheter Aortic

* Corresponding authors at: Department of Cardiology, The First Affiliated Hospital, Zhejiang University, School of Medicine, 79 Qingchun Road, Hangzhou 310003, Zhejiang, PR China.
E-mail addresses: li_zhang@zju.edu.cn (L. Zhang), zjh_john@medmail.com.cn, zjh_john2017@zju.edu.cn (J. Zhu).
[1] These authors contributed equally to this work.

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Valve Implantation (SURTAVI) study confirmed that TAVR with self-expanding valve system was non-inferior to SAVR in patients at intermediate surgical risk at 2 years [8]. We therefore performed an updated systematic review and meta-analysis to examine the midterm clinical outcomes of TAVR compared with SAVR in patients at low to intermediate surgical risk.

Materials and methods

A systematic search was performed in electronic databases including PubMed, EBSCO, and CENTRAL (Cochrane Central Registry of controlled trials) without language limitations. The key words we used included the following terms: "surgical aortic valve replacement", "SAVR", "transcatheter aortic valve replacement", "transcatheter aortic valve implantation", "TAVR", "TAVI", and "aortic valve stenosis". The type of study was restricted to randomized controlled trials (RCT). The references of relevant studies and reviews, editorials, and letters, as well as related conference abstracts were also searched. Eligible studies had to be published as full-length articles in peer-reviewed journals. The study protocol fully adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [9]. Endnote X7.0.1 was used to organize and evaluate the searched studies for inclusion.

Inclusion criteria for our analysis were randomized clinical trials performed in patients with severe aortic valve stenosis at low to intermediate surgical risk, as defined by a mean STS-PROM (Society of Thoracic Surgeons Score Predicted Risk of Mortality) score of 8% or less [10], and/or mean logistic EuroSCORE (LES) I of 15% or less if available [11]. Severe AS is defined as an effective orifice area <1 cm^2 or indexed for body surface area <0.6 cm^2/m^2 and a mean aortic valve gradient >40 mmHg or peak systolic velocity >4 m/s [8,12–14]. Those included in the analysis should compare safety and clinical outcomes between TAVR and SAVR.

We excluded studies that were nonhuman, or with a mean STS risk score $>8\%$ or LES I $\geq 15\%$. Studies with duplicate publications, outcomes of interest neither clearly reported nor impossible to extract or calculate, or follow-up duration less than 2 years, were also excluded.

The efficacy endpoints of the analysis include: (a) death from any cause, (b) cardiovascular death, (c) acute kidney injury, (d) myocardial infarction (MI), (e) stroke, (f) aortic-valve re-intervention, (g) life-threatening bleeding, (h) new permanent pacemaker implantation and, (i) new-onset or worsening atrial fibrillation (AF). The definitions of above endpoints, including cardiovascular death, acute kidney injury, MI, stroke, life-threatening bleeding, and new-onset or worsening AF were according to the updated Valve Academic Research Consortium-2 Consensus (VARC-2) [15]. The definition of life-threatening bleeding was: (1) fatal bleeding, (2) bleeding in a critical organ, (3) bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery, (4) overt source of bleeding with drop in hemoglobin of ≥ 5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥ 4 units [15].

Two investigators independently assessed reports for eligibility at title and/or at abstract level, with divergences resolved by a third reviewer; studies that met inclusion criteria were selected for further analysis. The risk of bias was evaluated by the same two reviewer authors, in accordance with The Cochrane Collaboration methods [16].

Meta-analysis was performed using the Review Manager 5.3 software (*The Nordic Cochrane Centre, Copenhagen*). Reported event frequencies were used to calculate risk ratio (RR) with 95% confidence intervals (CI). Heterogeneity of the trial results was quantified with the chi^2 heterogeneity statistic, with inconsistency assessed by means of I^2. Results were reported as the p-value of the chi^2 test ($p < 0.05$ for heterogeneous results) and percentage of the I^2. Heterogeneity was quantified as low, moderate, or high based on I^2 values of 25%, 50%, and 75%, respectively. A random effects or a fixed effect model was used based on associated heterogeneity. Since the random effects model provides more conservative and robust results, it was used when $I^2 > 50\%$. To study the relevance of such publication bias, funnel plots were constructed plotting the trial results against their precision.

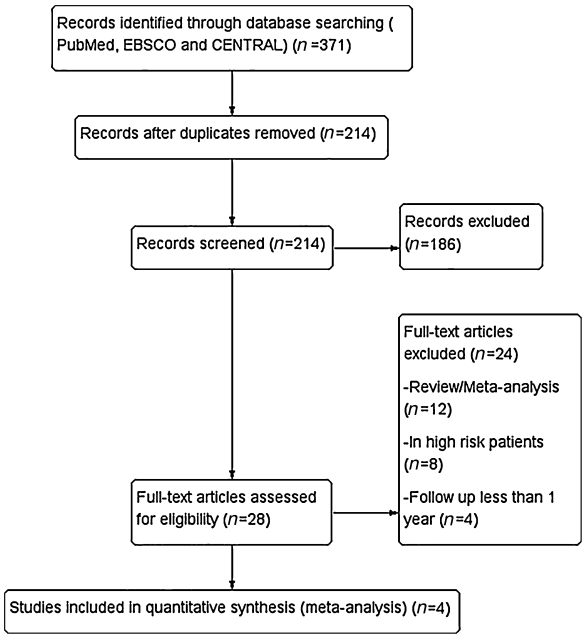

Fig. 1. Flowchart of study selection.

Results

After deduplication, screening of titles and abstracts, and full text review based on inclusion and exclusion criteria, 4 studies involving 4355 patients qualified for the analysis [8,14,17,18] (Fig. 1). The detailed characteristics of the included studies are shown in Table 1. Studies varied in publication year and types of valves. In general, total number of participants treated with TAVR was 2222 (50.1%). Self-expanding valves such as CoreValve and Evolut R (Medtronic Inc., Minneapolis, MN, USA) were used in 53.3% of patients, whereas the balloon-expandable Edwards SAPIEN valve (Edwards Lifescience, Irvine, CA, USA) was used in 46.7% of patients. There were no significant differences between the two groups with regard to baseline characteristics such as age, gender, presence of diabetes mellitus, coronary artery disease (CAD), prior MI, prior percutaneous coronary intervention (PCI), prior cerebrovascular accident, or proportion of stage III-IV New York Heart Association (NYHA) scores. Quality assessment is presented in Fig. 2.

At 2-year follow-up, 305 of the 2222 (13.7%) patients undergoing TAVR and 323 of 2133 (15.1%) patients randomized to SAVR died (RR 0.86; 95%CI: 0.67–1.10; $p = 0.22$; $I^2 = 54\%$). Rate of cardiovascular death was 8.87% for TAVR and 10.08% for SAVR, without significant difference (RR 0.88; 95%CI: 0.73–1.06; $p = 0.17$; $I^2 = 0\%$). There were also no detectable differences in incidence of stroke (RR 0.90; 95%CI: 0.73–1.10; $p = 0.31$; $I^2 = 13\%$) or myocardial infarction (RR 0.99; 95%CI: 0.70–1.39; $p = 0.93$) between the two groups (Fig. 3). As to the safety endpoints, TAVR was associated with a lower rate of life-threatening bleeding (RR 0.45; 95%CI: 0.28–0.73; $p = 0.001$), acute kidney injury (RR 0.48;