经导管主动脉瓣置换术后抗栓治疗的现状

吴玲[1] 徐承义[2] 苏晞[1*]

[1]武汉亚心总医院心内科,湖北武汉 430056

[2]武汉亚洲心脏病医院心内科,湖北武汉 430022

关键词 经导管主动脉瓣植入术; 抗血小板治疗; 抗凝血治疗; 维生素 K 拮抗剂; 新型口服抗凝药物

中图分类号 R654.2;R619+.2 **文献标识码** A DOI 10.11768/nkjwzzzz20230115

退行性主动脉瓣狭窄是最常见的瓣膜性心脏病,在老年患者中发生率 2.5% ~7%[1],经导管主动脉瓣置换术(transcatheter aortic valve replacement,TAVR)日益成为代替外科主动脉瓣置换术(surgical aortic valve replacement,SAVR)治疗重度症状性主动脉瓣狭窄(aortic stenosis,AS)的常用方法。TAVR 被确认是具有中高等手术风险的症状性 AS 患者的标准治疗方式[2,3]。最近的 PARTNER 3 与 Evolut 低风险试验两项大型随机试验研究报告,在低危重度 AS 患者中,TAVR 的早期死亡率低于 SAVR,长期死亡率没有差异,这表明 TAVR 的手术指征有望进一步扩大[4~6]。近年来,对患者评估的改进、新一代设备技术和术者更多的经验提高了手术的疗效和安全性。但是,TAVR 术后的血栓栓塞和出血风险仍然是患者术后严重并发症,影响患者的预后[7]。由于进行 TAVR 的患者年龄较高且多存在合并症,情况复杂,为患者制定合适的抗血栓治疗策略,平衡卒中与出血的风险,是目前研究与讨论的重点。

脑卒中与瓣膜血栓形成

脑卒中是 TAVR 术后常见并发症之一,且严重影响患者预后,约 25% 的脑卒中事件在术后的 30d 内发生[8,9]。一项荟萃分析发现外周动脉疾病、颈动脉狭窄等均为 TAVR 术后脑卒中的高危因素,手术入路途径和 TIA 病史为术后脑卒中的独立预测因子[10,11]。在 TAVR 后的不同时间,经导管主动脉瓣血栓形成的表现也不同,早期超声影像上表现可能并不明显,所以跨瓣膜梯度的增加有助于早期识别瓣膜血栓形成[12~14]。在 TAVR 术后急性血栓事件报道较少,但有研究表明,通过对 TAVR 术后患者进行专门的多探测器计算机断层扫描(multiple detector computed tomography,MDCT)随访,瓣膜血栓的发生率高达 7%,亚临床瓣膜血栓形成(subclinical valve thrombosis,SVT)在 5% 到 6% 之间[15,16]。Chakravarty 等[17]报告,与接受双重抗血小板聚集治疗的患者相比,TAVR 术后接受抗凝治疗的患者中,亚临床小叶血栓形成的发生率较低(4% *vs* 15%,$P<0.0001$)。在使用 Edwards Sapien XT 或 Sapien 3 瓣膜 TAVR 术后行 MDCT 扫描的 460 例患者中,TAVR 术后未服用华法林治疗是经导管心脏瓣膜血栓形成的独立预测因素[16]。Rogers 等[18]对低风险患者 TAVR 术后阿司匹林与阿司匹林联合华法林治疗的随机对照研究结果提示,阿司匹林联合华法林可以在短期内预防经导管心脏瓣膜功能障碍且不会出现大量出血。然而,在所有 TAVR 术后的患者中,使用更强的抗血栓治疗方案可能带来的益处是否会超过相关的出血风险,还需要更多的临床研究来证明。

出血事件

TAVR 术后由于血管并发症或心包出血会发生围术期危及生命的大出血事件。TAVR 术后大部分的出血事件在术后 30d 内发生,大约一半的出血事件报告与手术路径相关,经心尖入路与经股动脉入路相比,出血发生率增加 83%,非股动脉入路、女性、慢性肾脏疾病和外周动脉疾病为出血事件的危险因素[19]。在 Partner II 试验中,20.8% 的患者在 30 d 内出现危及生命或致残性出血,而 1 年的累积出血率为 23.2%[20]。Piccolo 等 5 年随访结果显示,31% 的患者发生了重大出血事件;24% 的患者有生命危险或大出血事件的发生。其中 80% 的并发症发生在 1 个月内(早期),且大多与手术穿刺部位有关[21]。普通肝素是 TAVR 围手术期最常用的抗凝剂,比伐卢定可以作为一种替代静脉抗凝药物,特别是在既往有肝素诱导的血小板减少症的患者

* 通信作者:苏晞,E-mail:yaxin_suxi@163.com,湖北省武汉市江岸区京汉大道 753 号

中[22]。Barawan 等[23]认为,TAVR 术后使用鱼精蛋白拮抗肝素治疗可以显著降低术后 30 d 内危及生命和主要出血并发症的发生率。

抗血小板聚集治疗

在没有口服抗凝药物(oral anticoagulation,OAC)适应证的情况下,TAVR 术后患者常规采用双联抗血小板聚集药物治疗(dual antiplatelet therapy,DAPT)方案(阿司匹林联合氯吡格雷 3 ~ 6 个月)。2011 年,Ussia 等[24]首次提出 TAVR 术后抗血小板药物治疗(single antiplatelet therapy,SAPT)的可行性和安全性。近年来研究表明,在 TAVR 术后,与 DAPT 相比,SAPT 降低了重大或危及生命的事件的风险,同时不增加心肌梗死或中风的风险[25,26]。最近 Brouwer 等[27]对 TAVR 术后且无长期抗凝适应证的患者进行的一项随机对照研究显示,在术后 12 个月随访中,SAPT 组心血管原因死亡、非手术相关出血、任何原因引起的中风或心肌梗死等复合终点事件也明显低于 DAPT 组(23.0% *vs* 31.1%;P = 0.04)。在 4 项共包括 1086 名患者的随机对照试验的荟萃分析中,SAPT 组患者的生命危险或大出血发生率较低(5.4% *vs* 10.6%;P = 0.01),SAPT 组和 DAPT 组在全因死亡率、心肌梗死和脑卒中的发生率无明显差异[28]。但是,Hirofumi 等[29]的一项回顾性研究表明,TAVR 术后 1 年服用 DAPT 治疗可明显降低术后 1 年内脑血管事件死亡率,这表明短期使用 DAPT 治疗可降低 TAVR 术后的长期心血管死亡率。所以,在缺乏足够有效的随机试验的情况下,TAVR 术后是否可采用 SAPT 治疗还需要谨慎决定。

抗凝治疗

心房颤动是心脏手术后死亡、中风和充血性心力衰竭的主要预测因素[30],重度主动脉瓣狭窄患者常常合并心房颤动,且术后新发房颤也是 TAVR 常见的并发症之一。Romain 等[31]对 FRANCE-2 登记中的数据分析表明,无论是术前就患有心房颤动还是术后新发,两者均明显增加术后患者的死亡率。新发心房颤动增加了死亡风险和脑血管事件,术前就已存在的心房颤动与 TAVR 术后出血独立相关[32,33]。因此,选择合适的治疗方案平衡卒中与出血风险显得尤为重要。2017 年美国心脏病学会/美国心脏协会(American College of Cardiology/American Heart Association,ACC/AHA)在指南更新中推荐,无高出血风险的患者在 TAVR 术后的前 3 个月内使用维生素 K 拮抗剂(VKA,IIB 类推荐)[34],TAVR 术后合并房颤的患者,首选单独口服抗凝治疗,有 OAC 适应证的患者,联合 VKA 和抗血小板治疗的死亡、出血和中风发生率明显高于单纯 VKA[35,36]。

新型口服抗凝剂(new OAC,NOAC)在预防非瓣膜性房颤患者血栓栓塞并发症方面已被证明是安全有效的,阿哌沙班是一种新型 NOAC,被证明优于 VKA,并优于阿司匹林预防非瓣膜性心房颤动栓塞性卒中[37,38]。Seeger 等[39]的一项单中心登记中,随访 30d 和 12 个月结果显示,服用阿哌沙班的房颤患者与接受 VKA 治疗的房颤患者相比,早期安全终点、卒中发生率均更低。近来,Krishnaswamy 等[40]提出对于合并多种并发症(如糖尿病、冠心病、高血压或其他血管疾病)、出血风险及卒中风险均高的患者,可以考虑 TAVR 和左心耳封堵术同时进行,以降低患者术后因长期口服抗凝药导致的出血风险。当然,这种联合治疗策略可能不是对所有患者均是必要的,这可能是未来研究的一个热点。

尚在进行的临床研究

目前正在进行的随机对照试验研究在不同的 TAVR 术后患者中服用 NOAC 与抗血小板或 VKA 治疗的有效性和安全性。GALILEO 试验(clinical trials. gov NCT 02556203)目的是以利伐沙班为基础的抗凝治疗策略与目前推荐的以抗血小板治疗为基础的策略相比,是否可以降低 TAVR 术后血栓栓塞并发症的风险[41]。ATLANTIS 试验(clinical trials. gov NCT 02664649)为证明以阿哌沙班为基础的治疗策略与推荐标准治疗策略比较的优越性[42]。ENVISAGE 试验(clinical trials. gov NCT 02943785)比较房颤患者 TAVR 术后选择依度沙班联合抗血小板药物与 VKA 联合抗血小板药物治疗方案的有效性[43]。ADAPT-TAVR 试验(clinical trials. gov NCT 03284827)分为依度沙班组与 DAPT 组,以比较在预防 TAVR 术后瓣膜血栓和脑栓塞事件的优劣性[44]。

参 考 文 献

1 Mozaffarian D, Benjamin EJ, Go AS, et al. Executive summary: heart disease and stroke statistics——2016 update: a report from the American heart association[J]. Circulation, 2016, 133(4): 447-454.

2 Marcantuono R, Gottschee J, Burke-Julien M, et al. Rationale development implementation and initial results of a fast-track protocol for transfemoral transcatheter aortic valve replacement (TAVR)[J]. Catheter Cardiovasc Interv, 2015, 85(4): 648-654.

3 Cribier A. The development of transcatheter aortic valve replacement (TAVR)[J]. Glob Cardiol Sci Pract,2016,2016(4):e201632.

4 Braghiroli J,Kapoor K,Thielhelm TP,et al. Transcatheter aortic valve replacement in low-risk patients: a review of PARTNER 3 and evolut low risk trials[J]. Cardiovasc Diagn Ther. 2020,10(1):59-71.

5 Mack MJ,Leon MB,Thourani VH,et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients[J]. N Engl J Med,2019,380(18):1695-1705.

6 Popma JJ,Deeb GM,Yakubov SJ,et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients[J]. N Engl J Med. 2019,380(18):1706-1715.

7 Muralidharan A,Thiagarajan K,Van Ham R,et al. Meta-analysis of perioperative stroke and mortality in transcatheter aortic valve implantation[J]. Am J Cardiol. 2016,118(7):1031-1045.

8 Mangieri A,Montalto C,Poletti E,et al. Thrombotic versus bleeding risk after transcatheter aortic valve replacement: JACC review topic of the week[J]. J Am Coll Cardiol. 2019,74(16):2088-2101.

9 Vranckx P,Windecker S,Welsh RC,et al. Thrombo-embolic prevention after transcatheter aortic valve implantation[J]. Eur Heart J,2017,38(45):3341-3350.

10 Hatfield SA,Nores MA, James TM,et al. Predictors and outcomes of stroke after transcatheter aortic valve replacement[J]. J Card Surg. 2020,35(1):21-27.

11 Goel K,Nkomo VT,Slusser JP,et al. Relationship between procedural characteristics and cerebrovascular events after transcatheter aortic valve replacement[J]. Open Heart,2018,5(2):e000816.

12 Puri R, Auffret V, Rodés-Cabau J. Bioprosthetic valve thrombosis [J]. J Am Coll Cardiol. 2017,69(17):2193-2211.

13 Ng ACT,Holmes DR,Mack MJ,et al. Leaflet immobility and thrombosis in transcatheter aortic valve replacement[J]. Eur Heart J,2020,41(33):3184-3197.

14 Mirsadraee S,Sellers S,Duncan A,et al. Bioprosthetic valve thrombosis and degeneration following transcatheter aortic valve implantation (TAVI)[J]. Clin Radiol,2021,76(1):39-47.

15 Dangas GD,Weitz JI,Giustino G,et al. Prosthetic heart valve thrombosis[J]. J Am Coll Cardiol. 2016,68(24):2670-2689.

16 Hansson NC, Grove EL, Andersen HR, et al. Transcatheter aortic valve thrombosis: incidence predisposing factors and clinical implications[J]. J Am Coll Cardiol,2016,68(19):2059-2069.

17 Chakravarty T, Sondergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study[J]. Lancet. 2017,389(10087):2383-2392.

18 Rogers T,Shults C,Torguson R,et al. Randomized trial of aspirin versus warfarin after transcatheter aortic valve replacement in low-risk patients[J]. Circ Cardiovasc Interv. 2021,14(1):e009983.

19 Kapadia SR,Krishnaswamy A. Bleeding and transcatheter aortic valve replacement[J]. J Am Coll Cardiol. 2019,74(22):2768-2770.

20 Webb JG,Mack MJ,White JM,et al. Transcatheter aortic valve implantation within degenerated aortic surgical bioprostheses: PARTNER 2 valve-in-valve registry[J]. J Am Coll Cardiol,2017,69(18):2253-2262.

21 Piccolo R,Pilgrim T,Franzone A,et al. Frequency timing and impact of access-site and non-access-site bleeding on mortality among patients undergoing transcatheter aortic valve replacement[J]. JACC Cardiovasc Interv. 2017,10(14):1436-1446.

22 Scott B,Tam CW,Moon RS. Transfemoral transcatheter aortic valve replacement in a patient with heparin-induced thrombocytopenia:intraoperative anticoagulation management with bivalirudin[J]. J Cardiothorac Vasc Anesth,2015,29(6):1603-1605.

23 Al-Kassou B,Kandt J,Lohde L,et al. Safety and efficacy of protamine administration for prevention of bleeding complications in patients undergoing TAVR[J]. JACC Cardiovasc Interv,2020,13(12):1471-1480.

24 Ussia GP,Scarabelli M,Mulè M,et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation[J]. Am J Cardiol. 2011,108(12):1772-1776.

25 Rodés-Cabau J,Masson JB,Welsh RC,et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve: the ARTE (aspirin versus aspirin + clopidogrel following transcatheter aortic valve implantation) randomized clinical trial[J]. JACC Cardiovasc Interv. 2017,10(13):1357-1365.

26 Jimenez Diaz VA,Tello-Montoliu A,Moreno R,et al. Assessment of platelet REACtivity after transcatheter aortic valve replacement: the RE-AC-TAVI Trial[J]. JACC Cardiovasc Interv. 2019,12(1):22-32.

27 Brouwer J,Nijenhuis VJ,Delewi R,et al. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation[J]. N Engl J Med,2020,383(15):1447-1457.

28 Elbadawi A,Thakker R,Abuzaid AA,et al. Single anti-platelet versus dual antiplatelet therapy after transcatheter aortic valve implantation: a meta-analysis of randomized trials[J]. Am J Cardiol,2021,140:152-154.

29 Hioki H,Watanabe Y,Kozuma K,et al. Short-term dual anti-platelet therapy decreases long-term cardiovascular mortality after transcatheter aortic valve replacement[J]. Heart Vessels 2020,1:3.

30 De Backer O,Butt JH,Wong YH,et al. Early and late risk of ischemic stroke after TAVR as compared to a nationwide background population[J]. Clin Res Cardiol,2020,109(7):791-801.

31 Chopard R,Teiger E,Meneveau N,et al. Baseline characteristics and prognostic implications of pre-existing and new-onset atrial fibrillation after transcatheter aortic valve implantation: results from the FRANCE-2 registry[J]. JACC Cardiovasc Interv, 2015, 8(10):1346-1355.

32 Siontis GCM,Praz F,Lanz J,et al. New-onset arrhythmias following transcatheter aortic valve implantation: a systematic review and meta-analysis[J]. Heart,2018,104(14):1208-1215.

33 Wang J,Yu W,Jin Q,et al. Risk factors for post-TAVI bleeding according to the VARC-2 bleeding definition and effect of the bleeding on short-term mortality: a meta-analysis[J]. Can J Cardiol,2017,33(4):525-534.

(下转第 60 页)

27 Kumagai T, Rahman F, Smith AM. The microbiome and radiation induced-bowel injury: evidence for potential mechanistic role in disease pathogenesis[J]. Nutrients, 2018, 10(10): 1405.
28 Fujimoto K, Kimura Y, Allegretti JR, et al. Functional restoration of bacteriomes and viromes by fecal microbiota transplantation[J]. Gastroenterology, 2021, 160(6): 2089-2102. e12.
29 Hayase E, Jenq RR. Role of the intestinal microbiome and microbial-derived metabolites in immune checkpoint blockade immunotherapy of cancer[J]. Genome Med, 2021, 13(1): 107.
30 Davar D, Zarour HM. Facts and hopes for gut microbiota interventions in cancer immunotherapy[J]. Clin Cancer Res, 2022 Oct 14; 28(20): 4370-4384.
31 Yang L, Ning Q, Tang SS. Recent advances and next breakthrough in immunotherapy for cancer treatment[J]. J Immunol Res, 2022, 18, 2022: 8052212.
32 Gaikwad S, Agrawal MY, Kaushik I, et al. Immune checkpoint proteins: Signaling mechanisms and molecular interactions in cancer immunotherapy[J]. Semin Cancer Biol, 2022, 86(Pt 3): 137-150.
33 Killock D. Immunotherapy: gut bacteria modulate responses to PD-1 blockade[J]. Nat Rev Clin Oncol, 2018, 15(1): 6-7.
34 Temraz S, Nassar F, Kreidieh F, et al. Hepatocellular carcinoma immunotherapy and the potential influence of gut microbiome[J]. Int J Mol Sci, 2021, 22(15): 7800.
35 Davar D, Dzutsev AK, McCulloch JA, et al. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients[J]. Science, 2021, 371(6529): 595-602.
36 Lu Y, Yuan X, Wang M, et al. Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies[J]. J Hematol Oncol, 2022, 15(1): 47.
37 Frankel AE, Coughlin LA, Kim J, et al. Metagenomic shotgun sequencing and unbiased metabolomic profiling identify specific human gut microbiota and metabolites associated with immune checkpoint therapy efficacy in melanoma patients[J]. Neoplasia, 2017, 19(10): 848-855.
38 Patel P, Poudel A, Kafle S, et al. Influence of microbiome and antibiotics on the efficacy of immune checkpoint inhibitors[J]. Cureus, 2021, 13(8): e16829.
39 Zhang J, Wu K, Shi C, et al. Cancer immunotherapy: fecal microbiota transplantation brings light[J]. Curr Treat Options Oncol, 2022, 23(12): 1777-1792.
40 Ahmed J, Kumar A, Parikh K, et al. Use of broad-spectrum antibiotics impacts outcome in patients treated with immune checkpoint inhibitors[J]. Oncoimmunology, 2018, 20; 7(11): e1507670.
41 Ueda K, Yonekura S, Ogasawara N, et al. The impact of antibiotics on prognosis of metastatic renal cell carcinoma in Japanese patients treated with immune checkpoint inhibitors[J]. Anticancer Res, 2019, 39(11): 6265-6271.

(2022-10-08 2023-01-20 修回)

(上接第 55 页)

34 Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines[J]. J Am Coll Cardiol, 2017, 70(2): 252-289.
35 Conrotto F, D'Ascenzo F, Bianco M, et al. Is oral anticoagulation effective in preventing transcatheter aortic valve implantation failure? A propensity matched analysis of the Italian Transcatheter balloon-Expandable valve Registry study[J]. J Cardiovasc Med (Hagerstown), 2020, 21(1): 51-57.
36 Abdul-Jawad Altisent O, Durand E, Munoz-García AJ, et al. Warfarin and antiplatelet therapy versus warfarin alone for treating patients with atrial fibrillation undergoing transcatheter aortic valve replacement[J]. JACC Cardiovasc Interv, 2016, 9(16): 1706-1717.
37 Tsai CT, Liao JN, Chen SJ, et al. Non-vitamin K antagonist oral anticoagulants versus warfarin in AF patients ≥ 85 years[J]. Eur J Clin Invest, 2021, 51(6): e13488.
38 Alexander KP, Brouwer MA, Mulder H, et al. Outcomes of apixaban versus warfarin in patients with atrial fibrillation and multi-morbidity: Insights from the ARISTOTLE trial[J]. Am Heart J, 2019, 208(1): 123-131.
39 Seeger J, Gonska B, Rodewald C, et al. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement[J]. JACC Cardiovasc Interv, 2017, 10(1): 66-74.
40 Krishnaswamy A, Wazni O, Kapadia SR. Left atrial appendage occlusion for patients with transcatheter aortic valve replacement mitraClip percutaneous coronary intervention and ablation for atrial fibrillation: optimizing long-term patient outcomes[J]. Card Electrophysiol Clin, 2020, 12(1): 117-124.
41 Windecker S, Tijssen J, Giustino G, et al. Trial design: rivaroxaban for the prevention of major cardiovascular events after transcatheter aortic valve replacement: rationale and design of the GALILEO study[J]. Am Heart J, 2017, 184(1): 81-87.
42 Collet JP, Berti S, Cequier A, et al. Oral anti-Xa anticoagulation after trans-aortic valve implantation for aortic stenosis: the randomized ATLANTIS trial[J]. Am Heart J, 2018, 200(1): 44-50.
43 Van Mieghem NM, Unverdorben M, Valgimigli M, et al. Edoxaban versus standard of care and their effects on clinical outcomes in patients having undergone transcatheter aortic valve implantation in atrial fibrillation-rationale and design of the ENVISAGE-TAVI AF trial[J]. Am Heart J, 2018, 205(1): 63-69.
44 Park H, Kang DY, Ahn JM, et al. Rationale and design of the A-DAPT-TAVR trial: a randomised comparison of edoxaban and dual antiplatelet therapy for prevention of leaflet thrombosis and cerebral embolisation after transcatheter aortic valve replacement[J]. BMJ Open, 2021, 5, 11(1): e042587.

(2021-03-19 收稿 2022-09-01 修回)