

· 临床研究 ·

不同双重抗血小板治疗时间对药物洗脱支架极晚期血栓患者预后的影响

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【摘要】目的 分析药物洗脱支架(DES)术后发生极晚期支架内血栓(VLST)的患者接受双重抗血小板治疗(DAPT)的情况,探讨不同DAPT持续时间对患者远期预后的影响。**方法** 2006年1月至2013年2月,首都医科大学附属北京朝阳医院心脏中心共完成3945例急诊冠状动脉造影,入选经急诊造影证实为VLST的患者。根据随访期间是否仍持续使用DAPT,将患者分为持续DAPT组和对照组。比较两组患者的临床资料、造影及介入治疗资料以及抗血小板药物治疗情况。临床主要不良心血管事件(MACE)包括随访期间的非致死性心肌梗死(MI),再发支架内血栓(ST),靶血管重建率(TVR)以及死亡。探讨不同DAPT持续时间对患者远期预后的影响,并分析随访期间发生MACE的预测因素。**结果** 共计有62例VLST患者纳入研究,其中男性55例,女性7例,年龄41~82(58.6 ± 10.2)岁。VLST距第1次DES置入时间为12.5~84(38.7 ± 18.1)个月。住院期间脑出血死亡1例,存活的61例患者随访5~88(32.1 ± 19.1)个月。随访期间,又有17例患者出现MACE,Kaplan-Meier生存率分析提示无事件生存率为45.1%。末次随访时,坚持持续DAPT的患者38例,其中5例(13.2%)发生MACE,事件发生率明显低于对照组(54.2%, $P=0.001$)。根据是否发生MACE事件将所有患者分为两组,Cox单因素分析提示再次置入第一代DES[危害率(hazard ratio, HR): 2.69, $P=0.04$]和持续DAPT(HR: 0.25, $P=0.01$)为远期随访中MACE相关的预测因素。而多因素Cox分析则提示仅有持续DAPT是随访期间不发生MACE的唯一预测因素(HR: 0.30, 95% CI: 0.09~0.97, $P=0.04$)。**结论** DES术后VLST患者远期预后情况欠佳,事件发生率较高。坚持DAPT可能有助于减少远期不良事件的发生。

【关键词】 药物洗脱支架; 支架内血栓; 抗血小板治疗; 随访

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Effect of duration for dual antiplatelet therapy on long-term prognosis in patients with very late stent thrombosis after drug eluting stent implantation

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【Abstract】 Objective To study the application of dual antiplatelet therapy (DAPT) in the patients with very late stent thrombosis (VLST) after implantation of drug-eluting stent (DES), and to determine the effect of different durations of DAPT on long-term prognosis of these patients. **Methods** All of the patients with angiographically defined VLST out of 3945 patients undergoing emergent coronary angiography in our heart center from January 2006 to February 2013 were recruited in this study. The patients were divided into 2 groups according to whether receiving continuous DAPT after implantation. The clinical data, angiographic results and interventional data were compared between the 2 groups. Major adverse cardiac events (MACE) including nonfatal myocardial infarction (MI), recurrence of stent thrombosis (ST), target vessel revascularization (TVR), and death in all causes were compared to determine the different durations of DAPT on the prognosis. Predictors of MACE during long-term follow-up were confirmed in these patients. **Results** Sixty-two patients were enrolled, consisting of 55 males and 7 females, with age from 41 to 82 (58.6 ± 10.2) years. The time from first implantation of DES to occurrence of VLST was from 12.5 to 84 (38.7 ± 18.1) months. One patient died in hospital due to cerebral hemorrhage. The other 61 patients survived to discharge, and MACE occurred in 17 patients of

them during follow-up of 5 to 88 (32.1 ± 19.1) months. Kaplan-Meier survival analysis showed the estimated MACE-free survival was 45.1%. Compared with the patients without continuous DAPT ($n = 24$, 13/24, 54.2%), the MACE rate was obviously lower in those with continuous DAPT ($n = 38$, 5/38, 13.2%, $P = 0.001$). Based on the occurrence of MACE, univariate Cox analysis revealed the independent predictors for MACE-free were re-implantation of the first-generation of DES [hazard ratio (HR): 2.69, $P = 0.04$] and continuous DAPT (HR: 0.25, $P = 0.01$) during our long-term follow-up. Multivariate COX analysis indicated that continuous DAPT was the only predictor for MACE-free (HR: 0.30, 95% CI: 0.09 to 0.97, $P = 0.04$). **Conclusion** Long-term outcomes for DES patients having VLST are unfavorable, with high incidence of MACE. So, continuous DAPT should be prescribed to prevent long-term MACE.

【Key words】 drug eluting stent; stent thrombosis; anti-platelets therapy; follow-up

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与金属裸支架 (bare metal stent, BMS) 比较, 药物洗脱支架 (drug-eluting stent, DES) 可以明显降低支架内再狭窄率和血管重建率^[1,2], 因此, 目前DES在临床实践中已经得到了广泛应用, 而且适应证不断拓宽^[3]。但是, 在临床实践中, DES置入以后的极晚期支架内血栓 (very late stent thrombosis, VLST) 病例亦日益增多^[4-6]。而目前专门针对VLST患者的远期随访研究少见, 这些患者双重抗血小板治疗 (dual antiplatelet therapy, DAPT) 的合适持续时间亦尚未确定。本研究将专门分析DES术后发生VLST的患者接受DAPT的情况, 探讨不同DAPT持续时间对这些患者远期预后的影响。

1 对象与方法

1.1 研究对象及分组

2006年1月至2013年2月, 共计3945例患者在首都医科大学附属北京朝阳医院心脏中心接受急诊冠状动脉造影, 将经急诊造影证实为VLST的患者纳入研究。VLST的定义采用美国学术研究联合会 (American Academic Research Association, ARC) 标准^[7], 均为造影证实明确的血栓, 且血栓距离首次DES置入时间 > 1年。通过电话联系患者或家属, 门诊及住院医疗记载历次随访。根据随访期间是否仍持续使用DAPT, 将患者分为持续DAPT组 (38例) 和对照组 (24例)。对比分析两组的临床资料, 造影及介入治疗资料和抗血小板治疗情况。

1.2 定义

主要不良心血管事件 (major adverse cardiovascular events, MACE) 包括心肌梗死 (myocardial infarction, MI)、再发支架内血栓 (stent thrombosis, ST)、靶血管血运重建术和死亡。再发ST定义为造影证实的明确ST^[7]。急性心肌梗死 (acute myocardial infarction, AMI) 定义为心脏生物标志物 (肌钙蛋白) 增高或增高后降低, 同时伴有心肌缺血症状和心电图改变^[8]。标准DAPT, 指患者服用阿司匹林

(aspirin) 100mg, 1次/d, 以及氯吡格雷 (clopidogrel) 75mg, 1次/d。第一代DES包括永久涂层的西罗莫司洗脱支架 (sirolimus-eluting stent, SES) 和紫杉醇洗脱支架 (paclitaxel-eluting stent, PES), 新一代DES包括: 涂层可降解DES, 无涂层DES, 佐他莫司洗脱支架 (zotarolimus-eluting stent, ZES) 和依维莫司洗脱支架 (everolimus-eluting stent, EES)^[9-11]。

1.3 统计学处理

使用SPSS17.0统计软件进行统计学分析。计量资料以均数 ± 标准差或中位数表示, 计数资料以百分率表示, 分别行t检验和 χ^2 检验 (必要时精确概率法)。采用COX回归分析VLST后再发MACE的危险因素, 先采用单因素分析, $P < 0.05$ 的因素纳入多因素分析。采用Kaplan-Meier分析用于估算累计生存率。双侧P值 < 0.05时表明差异具有统计学意义。

2 结果

2.1 患者发生VLST时的基线临床资料

共计有62例患者符合ARC定义的明确支架内血栓标准和VLST标准, 其中男性55例, 女性7例, 年龄41~82 (58.6 ± 10.2) 岁。VLST距第1次DES置入时间为12.5~84 (38.7 ± 18.1) 个月。

所有患者均发生AMI, 其中前壁心肌梗死46例 (74.2%), 下壁梗死9例 (14.5%), 侧壁2例 (3.2%), 非ST段抬高型心肌梗死5例 (8.1%)。心功能Killip分级1级和2级分别为41例 (66.1%) 和17例 (27.4%), 3级2例 (3.2%), 心源性休克 (Killip 4级) 2例 (3.2%)。VLST发生时, 仅应用阿司匹林的患者41例, 仅服用氯吡格雷的患者1例, 仍接受DAPT的患者5例, 停用所有抗血小板治疗15例。患者发生VLST时的基线临床资料见表1。

2.2 患者造影及介入治疗资料

在第1次PCI中, 有54例患者置入第1代DES,

包括52例永久涂层的SES和1例PES, 1例SES + PES。另有2例DES具体类型不详, 结合第1次PCI时间和家属描述, 也可确定为第1代DES。6例置入第2代DES, 其中3例置入涂层可降解SES, 2例ZES, 1例EES。

表1 患者基线临床资料
Table 1 Clinical characteristics of patients

Item	Continuous DAPT group (n = 38)	Control group (n = 24)	P
Male[n(%)]	34 (89.5)	21 (87.5)	1.000
Age(years, $\bar{x} \pm s$)	58.2 $\pm$ 9.82	59.2 $\pm$ 10.9	0.703
Time from first PCI to occurrence of VLST (months, $\bar{x} \pm s$)	37.2 $\pm$ 18.4	41.1 $\pm$ 17.7	0.413
Duration of follow-up (months, $\bar{x} \pm s$)	30.2 $\pm$ 20.8	33.8 $\pm$ 17.0	0.465
VLST occurred before 2007[n(%)]	2 (5.3)	6 (25.0)	0.047
Region of MI (ST segment elevation in anterior wall) [n(%)]	27 (71.1)	19 (79.2)	0.561
Risk factors[n(%)]			
Hypertension	17 (44.7)	16 (66.7)	0.120
Diabetes mellitus	13 (34.2)	4 (16.7)	0.156
Hyperlipidemia	19 (50.0)	11 (45.8)	0.799
Smoking	29 (76.3)	16 (66.7)	0.560
Killip class of 1-2[n(%)]	36 (94.5)	22 (91.7)	0.637
LVEF(%), $\bar{x} \pm s$)	58.3 $\pm$ 13.0	51.9 $\pm$ 9.1	0.040
Peak value of cTnI ($\mu\text{g/L}$, $\bar{x} \pm s$)	78.7 $\pm$ 75.2	68.8 $\pm$ 70.2	0.607

DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention; VLST: very late stent thrombosis; MI: myocardial infarction; LVEF: left ventricular ejection fraction; cTnI: cardiac troponin I

造影显示靶血管为左主干的1例(1.6%), 左前降支(LAD)47例(75.8%), 左回旋支3例(4.8%), 右冠状动脉11例(17.7%)。7例患者置入主动脉球囊反搏, 分别仅有3例和2例患者接受血管内超声和光学相干断层显像检查。60例患者造影后接受急诊PCI治疗, 其中1例PCI干预失败后保守治疗; 14例仅行单纯球囊扩张和(或)血栓抽吸治疗; 2例球囊扩张后血流恢复, 择期又接受冠状动脉旁路移植术(coronary artery bypass grafting, CABG)治疗; 其余43例患者再次置入支架。2例患者仅行冠状动脉造影, 其中1例为外院静脉溶栓治疗后造影, 另1例择期造影复查显示原血栓消失, 药物治疗。在再次置入支架的43例患者中, 有2例置入BMS, 11例置入涂层可降解SES, 1例置入涂层可降解SES + 带膜支架(Abbot), 4例置入无载体PES, 9例置入ZES, 3例置入EES。其余13例患者则置入第1代DES(7例永久涂层SES, 6例永久涂层PES)。造影及血管重建资料见表2。

2.3 随访及分组情况

住院期间, 1例患者术后4d脑出血死亡。存活出院的61例患者完成32.1 $\pm$ 19.1(中位数: 44, 5~88)个月的随访。末次随访时, 有38例患者持续服用DAPT, 纳入持续DAPT组。其余24例患者纳入对照组, 其中2例CABG患者术后仅接受阿司匹林治疗; 1例患者因合并左室血栓, 同时合用阿司匹林和华法林; 其余21例患者在接受DAPT治疗1年后停用氯吡格雷, 仅服用阿司匹林。

表2 患者造影及介入治疗资料
Table 2 Angiographic and interventional characteristics of the patients

Item	Continuous DAPT group (n = 38)	Control group (n = 24)	P
Emergency procedure during 1st PCI[n(%)]	12 (31.6)	9 (37.5)	0.784
1st generation DES implanted during 1st PCI[n(%)]	34 (89.5)	22 (91.7)	1.000
Target vessel (LAD)[n(%)]	27 (71.1)	20 (83.3)	0.366
Non-infarct related artery with stenosis > 50%[n(%)]	30 (78.9)	22 (91.7)	0.291
With LM disease[n(%)]	4 (10.5)	1 (4.2)	0.640
Self-recanalization of IRA (TIMI class 2-3)[n(%)]	7 (18.4)	2 (8.3)	0.462
Collateral circulation (Rentrop class 2-3)[n(%)]	9 (23.7)	5 (20.8)	1.000
Thrombosis aspiration[n(%)]	10 (26.3)	2 (8.3)	0.106
Additional stent implantation[n(%)]	25 (65.8)	18 (75.0)	0.574
Re-implantation of 1st generation DES[n(%)]	3 (7.9)	10 (41.7)	0.003
Number of stents (n = 43, $\bar{x} \pm s$)	1.52 $\pm$ 0.65	1.50 $\pm$ 0.79	0.930
Additional stent diameter (n = 43, mm, $\bar{x} \pm s$)	3.14 $\pm$ 0.36	2.98 $\pm$ 0.28	0.096
Additional stent total length (n = 43, mm, $\bar{x} \pm s$)	29.8 $\pm$ 17.8	32.4 $\pm$ 13.5	0.589
Max inflation pressure (n = 43, atm, $\bar{x} \pm s$)	18.6 $\pm$ 3.85	18.1 $\pm$ 2.11	0.627

DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention; DES: drug-eluting stent; LAD: left anterior descending artery; LM: left main artery; IRA: infarct related artery; TIMI: Thrombolysis In Myocardial Infarction. 1atm=101.325kPa

与对照组比较, 持续DAPT组2007年前发生VLST的比比较低(5.3% vs 25.0%, $P = 0.047$)。持续DAPT组术后左室射血分数较高[(58.3 $\pm$ 13.0)% vs (51.9 $\pm$ 9.1)%, $P = 0.040$; 表1]。两组患者基础造影情况无显著差异, 再次置入支架比率亦无显著差异。但是, 持续DAPT组再次置入第1代DES的比率明显低于对照组(7.9% vs 41.7%, $P = 0.003$; 表2)。

随访期间, 又有17例患者再次出现MACE。7例再发VLST, 其中5例再次接受急诊PCI治疗, 3例再次置入支架(BMS1例, 新1代DES 2例), 其余2例仅行球囊扩张; 1例行CABG术; 另1例行光学相干

断层显像检查后药物治疗。在接受再次支架置入的患者中,有1例在第2次VLST后19个月第3次发生VLST,最终接受CABG治疗。3例患者因支架内再狭窄,再次行PCI干预,4例发生非靶血管相关的MI,另外有3例患者死亡。总的MACE发生率为29.0%,Kaplan-Meier分析提示无MACE生存率为45.1%。与对照组比较,持续DAPT组MACE发生率为13.2%,明显低于对照组(54.2%, $P = 0.001$)。其中,主要是对照组再ST发生率明显增高(表3)。

表3 两组心血管事件比较
Table 3 Comparison of clinical events during follow-up [n(%)]

Item	Continuous DAPT group (n = 38)	Control group (n = 24)	P
Myocardial infarction	3 (7.9)	1 (4.2)	1.000
Stent thrombosis	0 (0.0)	7 (29.2)	0.001
TVR	1 (2.6)	2 (8.3)	0.554
Death	1 (2.6)	3 (12.5)	0.289
MACE	5 (13.2)	13 (54.2)	0.001

DAPT: dual antiplatelet therapy; TVR: target vessel revascularization; MACE: major adverse cardiovascular events

2.4 远期预后预测因素分析

根据是否发生MACE,将患者分为事件组和无事件组。行Cox单因素分析发现再次置入第1代DES (HR: 2.69, $P = 0.04$) 和持续DAPT (HR: 0.25, $P = 0.01$) 与发生MACE相关。将这两项因素纳入Cox多因素分析,结果提示只有持续的DAPT是随访中无再发MACE的唯一预测因素 (HR: 0.30, $P = 0.04$; 表4)。

表4 再发MACE预测因素的COX分析结果
Table 4 Cox regression analysis of the predictors for the MACE

Factor	HR	95% CI	P
Univariable Cox regression analysis			
Continuous DAPT	0.25	0.09–0.71	0.01
Implantation of additional 1st generation DES	2.69	1.05–6.86	0.04
Multivariable Cox regression analysis			
Continuous DAPT	0.30	0.09–0.97	0.04
Implantation of additional 1st generation DES	1.45	0.50–4.22	0.50

MACE: major adverse cardiac events; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; HR: hazard ratio; CI: confidence interval

3 讨论

目前DES术后VLST患者的远期预后情况并不明确。以往有关ST的研究多包括BMS支架血栓和急性、亚急性及晚期血栓,专门针对DES术后VLST远期预

后情况的研究少见,而且入选例数较少。Almalla等^[12]入选116例造影证实的ST患者,其中有13例(12.2%)为VLST患者。而在van Werkun等^[13]的研究中,总共入选了431例ST患者,其中DES术后VLST患者仅为23例。在Kim等^[14]的研究中,虽然专门入选DES术后的VLST患者,但仅有19例。同时,尚未见专门针对该类患者长期DAPT时间的研究。

与对照组比较,持续DAPT组再次置入第1代DES的比率明显低于对照组(7.9% vs 41.7%, $P = 0.003$)。这可能与临床对DES术后VLST的认识逐渐深入有关,在持续DAPT组中,2007年前发生VLST的比率低于对照组。在2006年欧洲心脏病大会上,DES的远期安全问题首次被报道,之后DES的VLST问题才开始受到临床医师的广泛关注。目前有关VLST患者的最佳治疗策略尚有待确定。Kim等的观察发现,所有的MACE都发生在单纯球囊扩张组,作者认为对这样的患者可能应考虑再次置入支架。而在van Werkun等的大规模样本分析则得出了相反的结论,其研究结果显示,事件组再次置入支架的比例较高(HR: 1.73)。但是,该研究入选的DES术后VLST比例较小,仅占该研究所有人群的5.3%^[13],因此该研究结果可能并不完全适合DES术后VLST。而在本研究中,单因素Cox分析发现再次置入第1代DES与发生MACE相关。可以提示,对于这样的患者,如需再次置入支架,可能应避免再次置入永久涂层的第1代DES,可考虑置入新一代DES。这与晚近有关新一代支架的研究结果也是相符合的^[10,11,15]。此外,持续DAPT组术后LVEF较高[(58.3 ± 13.0)% vs (51.9 ± 9.1)%, $P = 0.040$],持续DAPT组再发MACE率较低可能也与这有关。

本研究中,多因素分析结果则提示,坚持DAPT治疗是远期无事件的唯一预测因素。在发生VLST时,存在不同程度停用抗血小板药物的情况。在Kim等研究中,53%的患者仅使用阿司匹林。本研究中,发生VLST时,仅应用阿司匹林的患者41例,停用所有抗血小板治疗15例。多项大规模临床试验提示,延长DAPT时间并不能减少DES术后血栓事件的发生,而出血事件可能增加^[16,17]。因此,目前指南亦推荐对于置入DES的患者,服用DAPT ≥ 1年(I类指征),但不建议 > 1年(IIb)^[3]。但是,上述研究并未覆盖DES术后VLST的患者,研究结果可能并不适于这类患者,对于该类患者DAPT时限尚无定论。在Kubo等^[18]的研究方案中,建议所有ST患者应该服用DAPT > 1年。本研究结果则显示,在VLST发生后,坚持DAPT治疗的患者远期事件发生率,其中主要是再发ST发生率明显低于对照组。提示对于DES术后发生VLST

的患者,尤其是再次置入支架的患者,可能需要延长DAPT治疗时间。

本研究的局限性在于:(1)由于医保问题,仅有极少部分患者接受血管内超声和光学相干断层显像检查,不利于对ST形态、内皮覆盖和增生情况、新发动脉粥样硬化以及血管重构等作详细观察^[19,20];(2)由于系单中心研究,样本量较小,预测因素的力度较低,有必要组织1项多中心的注册研究;(3)本研究为观察性研究,有必要采用多中心、前瞻性随机研究,进一步探讨不同抗血小板治疗方案对DES术后VLST患者远期预后的影响。

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