·临床研究·

老年与中年急性冠脉综合征患者不同双联抗血小板方案疗效与出血风险比较

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【摘 要】 **目的** 比较≥75岁老年急性冠脉综合征(ACS)患者与<60岁中年ACS患者"阿司匹林+替格瑞洛"与"阿司匹林+氯吡格雷"两种双联抗血小板治疗(DAPT)方案的疗效与出血风险。**方法** 连续入选2014年3月至2015年5月于解放军总医院心血管内科住院治疗的ACS患者、年龄<60岁及≥75岁,并进行血栓弹力图(TEG)检查的患者416例,分为:(1)年龄<60岁阿司匹林+氯吡格雷(<60C组),(2)年龄≥75岁阿司匹林+氯吡格雷(≥75C组),(3)年龄<60岁阿司匹林+替格瑞洛(<60T组),(4)年龄≥75岁阿司匹林+替格瑞洛(≥75T组),随访1年,比较各组主要不良心血管事件(MACE)及出血情况。**结果** 各组MACE事件发生率、TEG检测的最大振幅(MA)值、花生四烯酸抑制率(AA-IPA)差异均无统计学意义($P>0.05$);相同年龄段"阿司匹林+替格瑞洛"患者二磷酸腺苷抑制率(ADP-IPA)高于"阿司匹林+氯吡格雷"($P<0.05$),但"阿司匹林+替格瑞洛"在两个年龄段的ADP-IPA差异无统计学意义($P=0.828$),≥75C组ADP-IPA较<60C组低($P=0.011$);相同年龄段"阿司匹林+替格瑞洛"患者出血事件发生率高于"阿司匹林+氯吡格雷"患者($P<0.05$),但多为Ⅰ型非致命性出血;"阿司匹林+替格瑞洛"在不同年龄段出血事件发生率差异无统计学意义($P=0.392$)。应用Cox回归分析MACE危险因素:血糖(B=0.111,RR=1.117,95% CI:1.014~1.231,$P=0.025$),eGFR(B=-0.023,RR=0.977,95% CI:0.961~0.993,$P=0.005$),心率(B=0.040,RR=1.041,95% CI:1.013~1.070,$P=0.004$)。应用logistic回归分析出血事件危险因素:DAPT方案(B=3.527,OR=34.025,95% CI:9.560~121.101,$P<0.001$),性别(B=1.126,OR=3.085,95% CI:1.083~8.788,$P=0.035$)。**结论** 在本研究中"阿司匹林+替格瑞洛"的临床疗效不优于"阿司匹林+氯吡格雷",且Ⅰ型出血风险增高;中、老年人口服"阿司匹林+替格瑞洛"的出血风险无差异。

【关键词】 冠心病;氯吡格雷;替格瑞洛;出血风险;双联抗血小板治疗
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Comparison of bleeding risk and efficacy in elderly and middle-aged acute coronary syndrome patients treated with different dual antiplatelet therapy

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【Abstract】 **Objective** To compare the bleeding risk and curative effect in the elderly (≥75 years old) and middle-aged patients (<60 years old) suffering from acute coronary syndrome (ACS) treated with different regimens of dual antiplatelet therapy (DAPT), aspirin combined with clopidogrel or with ticagrelor. **Methods** A total of 416 consecutive ACS patients admitted in our hospital from March 2014 to May 2015 were enrolled in this study. And all of them underwent thromboelastography (TEG). According to their age and antiplatelet regimen, they were divided into 4 groups, that is, <60 years old and treated with aspirin + clopidogrel (<60C group), ≥75 years old and treated with aspirin + clopidogrel (≥75C group), <60 years old and treated with aspirin + ticagrelor (<60T group), and ≥75 years old and treated with aspirin + ticagrelor (≥75T group). All the patients were followed up for 1 year. The occurrences of major adverse cardiovascular events (MACE) and bleeding events were recorded and compared in the groups. **Results** There were no significant differences in the occurrence of MACE, maximal amplitude (MA) value obtained with TEG, and inhibitory rate of arachidonic acid (AA)-induced platelet aggregation (AA-IPA) in each group ($P>0.05$). The inhibitory rate of adenosine diphosphate-induced platelet aggregation (ADP-IPA) was obviously higher in the same-aged patients treated by aspirin combined with ticagrelor than those with clopidogrel ($P<0.05$), but no difference was found in the <60T group and ≥75T group ($P=0.828$), and the ADP-IPA rate was remarkably lower in the ≥75C group than the <60C group ($P=0.011$). The occurrence of bleeding risk was significantly higher in the same-aged patients treated with aspirin + ticagrelor than with clopidogrel

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($P<0.05$), but most of them was type Ⅰ non-fetal bleeding events. There was no difference in bleeding risk between the <60T group and the ≥75T group ($P=0.392$). Cox regression analysis revealed that blood glucose level (B=0.111, RR=1.117, 95% CI: 1.014 – 1.231, $P=0.025$), estimated glomerular filtration rate (eGFR, B = –0.023, RR=0.977, 95% CI: 0.961 – 0.993, $P=0.005$), and heart rate (B=0.040, RR=1.041, 95% CI: 1.013 – 1.070, $P=0.004$) were risk factors for MACE. Logistic regression analysis showed that different strategies of DAPT (B=3.527, OR=34.025, 95% CI: 9.560 – 121.101, $P<0.001$) and sex (B=1.126, OR=3.085, 95% CI: 1.083 – 8.788, $P=0.035$) were risk factors for bleeding events. **Conclusion** The clinical efficacy of aspirin + ticagrelor is not superior to that of aspirin + clopidogrel, and the former regimen is associated with higher risk of type Ⅰ bleeding. No difference is observed in the bleeding risk in the patients treated with aspirin + ticagrelor at different age period.

【Key words】 coronary artery disease; clopidogrel; ticagrelor; bleeding risk; dual antiplatelet therapy

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双联抗血小板治疗(dual antiplatelet therapy, DAPT)已经成为急性冠脉综合征(acute coronary syndrome, ACS)和经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI)患者的标准治疗方案,目前主要为阿司匹林(aspirin)联合氯吡格雷(clopidogrel)或替格瑞洛(ticagrelor)[1,2]。替格瑞洛凭借其快速、可逆的抗血小板聚集作用,不受代谢酶影响[3-5],逐渐成为首选推荐药物。临床观察中发现即使规律应用抗血小板聚集药物,仍有部分患者再出现心血管事件及血栓弹力图(thromboelastography, TEG)检测血小板抑制率不达标情况。本研究旨在比较年龄<60岁阿司匹林+氯吡格雷组(<60C组)与年龄<60岁阿司匹林+替格瑞洛组(<60T组)、≥75岁阿司匹林+氯吡格雷组(≥75C组)与年龄≥75岁阿司匹林+替格瑞洛组(≥75T组)、<60T组与≥75T组、<60C组与≥75C组主要不良心血管事件(major adverse cardiovascular events, MACE)、出血事件发生情况,并分析相应的危险因素。

1 对象与方法

1.1 研究对象

连续收集2014年3月至2015年5月于解放军总医院心血管内科住院治疗的ACS、年龄<60岁及≥75岁、并进行TEG检查的416例患者的临床资料。根据年龄及应用$P2Y_{12}$受体拮抗剂类型分为4组:(1)年龄<60岁阿司匹林+氯吡格雷组(<60C组,$n=193$),(2)年龄≥75岁阿司匹林+氯吡格雷组(≥75C组,$n=58$),(3)年龄<60岁阿司匹林+替格瑞洛组(<60T组,$n=129$),(4)年龄≥75岁阿司匹林+替格瑞洛组(≥75T组,$n=36$)。

1.2 研究方法

临床医师根据患者病情确定治疗药物。收集4组患者的临床资料,并随访,记录患者DAPT期间MACE情况、出血情况。患者因任何原因停止DAPT,终止随访。16人失访,失访率3.85%。

1.3 相关概念

(1)TEG指标:最大振幅(maximal amplitude, MA)反映血小板功能;检测过程中分别加入血小板激活剂花生四烯酸(arachidonic acid, AA)、二磷酸腺苷(adenosine diphosphate, ADP),可测得相应的MA,即:MA-AA、MA-ADP;血小板抑制率(%)分为AA诱发性血小板聚集(AA-induced platelet aggregation, AA-IPA)和ADP-IPA通路[6,7]。(2)MACE:再次血运重建、再次心肌梗死及全因死亡等。(3)出血事件按照出血学术研究协议(Bleeding Academic Research Consortium, BARC)标准定义;Ⅰ型:患者无需因此就医的非活动性出血;Ⅱ型:明显活动性出血,需要就医干预,未达到以下Ⅲ~Ⅴ型标准;Ⅲ型,分为3个亚型:3a型,血红蛋白降低3~5 g/dl;3b型:血红蛋白降低≥5 g/dl,需要外科干预的出血;3c型:颅内出血,损害视力的眼内出血;Ⅳ型:冠状动脉旁路移植术(coronary artery bypass grafting, CABG)相关出血;Ⅴ型:致死性出血。

1.4 统计学处理

数据应用SPSS17.0软件进行分析。计量资料以均数±标准差表示,组间比较采用方差分析(正态分布)或秩和检验(非正态分布)。计数资料以百分率表示,组间比较采用χ^2检验。应用Cox回归分析MACE危险因素,logistic回归分析出血事件危险因素。以$P<0.05$为差异具有统计学意义。

2 结 果

2.1 各组基线资料比较

表1结果表明,<60C组与<60T组比较,各指标差异均无统计学意义($P>0.05$);≥75C组与≥75T组比较,≥75C组年龄较大($P<0.001$),其余指标差异均无统计学意义($P>0.05$);与≥75T组比

较，<60T 组吸烟比例较高（$P=0.001$），高血压患病率较低（$P=0.012$），其余指标差异均无统计学意义（$P>0.05$）；<60C 组与≥75C 组比较，<60C 组男性比例、体质量指数（body mass index，BMI）、吸烟比例均较高（$P<0.001$），eGFR 亦较高（$P=0.001$），其余指标差异均无统计学意义（$P>0.05$）。

2.2 TEG 指标比较

表 2 结果表明，<60C 组与 <60T 组比较，<60T组 ADP 途径抑制率较高（$P<0.001$），MA-ADP 较低（$P<0.001$），其余各项指标差异均无统计学意义（$P>0.05$）；≥75C组与≥75T 组比较，≥75T 组 ADP 途径抑制率较高（$P<0.001$），MA-ADP较低（$P<0.001$），其余各项指标差异均无统计学意义（$P>0.05$）。

表 3 结果表明，<60T 组与≥75T 组比较，各项指标差异均无统计学意义（$P>0.05$）；<60C 组与≥75C组比较，≥75C组 ADP 途径抑制率较低（$P=0.011$），MA-ADP 较高（$P=0.001$），MA-AA 较低（$P=0.005$）。

2.3 MACE 及出血事件比较

4 组患者 MACE 发生率差异无统计学意义（$P>0.05$；表 4，表 5）。应用 Cox 回归分析总体 MACE 危险因素：将心率、性别、年龄、BMI、吸烟、饮酒、血糖、MA 值、AA-IPA、ADP-IPA、MA-ADP、MA-AA、eGFR、高血压、口服血管紧张素转换酶抑制剂/血管紧张素受体拮抗剂情况、口服 β－阻滞剂情况、DAPT 方案带入分析，得出 MACE 相关因素：血糖（B=0.111，RR=1.117，95% CI：1.014～1.231，

表 1 患者基线资料比较

Table 1 Comparison of the baseline information among the four groups

Item	<60C group ($n=193$)	≥75C group ($n=58$)	<60T group ($n=129$)	≥75T group ($n=36$)
Male[n(%)]	159(82.38)$^{\#\#}$	34(58.62)	111(86.05)	26(72.22)
Age(years, $\bar{x}\pm s$)	51.33±0.42	80.38±0.53**	51.84±0.50	77.42±0.49
BMI(kg/m^2, $\bar{x}\pm s$)	30.00±3.64$^{\#\#}$	24.01±0.37	26.28±0.25	25.61±0.60
HR(beats/min, $\bar{x}\pm s$)	73.33±0.79	73.40±1.38	74.22±1.07	71.89±1.93
Smoking[n(%)]	121(62.69)$^{\#\#}$	21(36.21)	75(58.14)**	9(25.00)
Hypertension[n(%)]	120(62.18)	36(62.07)	69(53.49)**	28(77.78)
DM[n(%)]	62(32.12)	22(37.93)	37(28.68)	11(30.56)
Blood glucose(mmol/L, $\bar{x}\pm s$)	6.76±0.23	6.83±0.39	6.69±0.25	5.99±0.37
TC(mmol/L, $\bar{x}\pm s$)	4.00±0.08	3.88±0.24	3.89±0.11	3.76±0.16
HDL-C(mmol/L, $\bar{x}\pm s$)	0.99±0.02	1.12±0.04	0.98±0.02	1.11±0.06
LDL-C(mmol/L, $\bar{x}\pm s$)	2.43±0.07	2.17±0.11	2.37±0.09	2.23±0.14
APTT(s, $\bar{x}\pm s$)	38.36±0.60	36.97±0.67	37.91±0.35	35.99±1.44
eGFR[ml/(min/1.73 m^2), $\bar{x}\pm s$]	107.52±2.15$^{\#\#}$	55.20±2.24	106.36±2.39	62.77±3.67
ACEI/ARB[n(%)]	82(42.49)	27(46.55)	48(37.21)	19(52.78)
β-blockers[n(%)]	162(83.94)	47(81.03)	100(77.52)	29(80.56)

<60C group: <60 years old patients treated with aspirin combined clopidogrel; ≥75C group: ≥75 years old patients treated with aspirin combined clopidogrel; <60T group: <60 years old patients treated with aspirin combined ticagrelor; ≥75T group: ≥75 years old patients treated with aspirin combined ticagrelor; BMI: body mass index; HR: heart rate; DM: diabetes mellitus; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; APTT: activated partial thromboplastin time; eGFR: estimated glomerular filtration rate; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker. Compared with ≥75T group, $^{**}P<0.01$; compared with ≥75C group, $^{\#\#}P<0.01$

表 2 相同年龄段不同 $P2Y_{12}$ 拮抗剂 TEG 指标比较

Table 2 Comparison of TEG indices between the same age with different $P2Y_{12}$ antagonist ($\bar{x}\pm s$)

Index	<60 years ($n=322$)		P value	≥75 years ($n=94$)		P value
	<60C ($n=193$)	<60T ($n=129$)		≥75C ($n=58$)	≥75T ($n=36$)	
MA(mm)	65.82±0.37	66.23±0.51	0.40	66.58±1.06	67.31±0.87	0.069
AA-IPA(%)	91.03±1.52	90.15±1.49	0.51	87.05±3.44	90.36±3.59	0.823
ADP-IPA(%)	67.60±1.89	77.88±2.22	<0.001	57.46±3.71	84.28±2.99	<0.001
MA-ADP(mm)	30.11±1.08	24.19±1.38	<0.001	38.31±2.08	23.58±2.07	<0.001
MA-AA(mm)	23.55±6.95	18.11±1.26	0.364	21.02±2.07	17.21±1.66	0.419

<60C group: <60 years old patients treated with aspirin combined clopidogrel; ≥75C group: ≥75 years old patients treated with aspirin combined clopidogrel; <60T group: <60 years old patients treated with aspirin combined ticagrelor; ≥75T group: ≥75 years old patients treated with aspirin combined ticagrelor; MA: maximal amplitude; AA-IPA: inhibitory rate of arachidonic acid (AA)-induced platelet aggregation; ADP-IPA: inhibitory rate of adenosine diphosphate (ADP)-induced platelet aggregation; MA-ADP: ADP induced maximum amplitude; MA-AA: AA induced maximum amplitude

$P=0.025$），eGFR（B = −0.023，RR = 0.977，95% CI：0.961 ~ 0.993，$P=0.005$），心率（B = 0.040，RR = 1.041，95% CI：1.013 ~ 1.070，$P=0.004$）。

“替格瑞洛”患者出血事件发生率较“氯吡格雷”患者升高（$P<0.05$；表 4）。<60C 组出血 1 例（0.52%）表现为月经过多；≥75C 组出血 2 例（3.45%）：血尿 1 例、便血 1 例；<60T 组出血 36 例（27.91%）：淤斑 20 例、牙龈出血 10 例、鼻出血 6 例；≥75T 组出血 6 例（16.67%）：淤斑 3 例、牙龈出血 1 例、鼻出血 1 例、眼底出血 1 例。出血事件多为不需要临床干预的Ⅰ型出血。应用 logistic 回归分析出血事件危险因素：（1）总体：DAPT 方案（B = 3.527，OR = 34.025，95% CI：9.560 ~ 121.101，$P<0.001$），性别（B = 1.126，OR = 3.085，95% CI：1.083 ~ 8.788，$P=0.035$）；（2）分别对 <60C 与 <60T，≥75C 与≥75T 进行 logistic 回归分析，均提示 DAPT 方案为出血事件危险因素。

3 讨 论

DAPT 已经成为 ACS、PCI 患者抗血小板的标准方案，那么如何选择同为 $P2Y_{12}$ 受体拮抗剂的氯吡格雷与替格瑞洛，则成为临床医师面临的问题。氯吡格雷作为经典的 $P2Y_{12}$ 受体拮抗剂，仍是目前国内的一线用药，但存在着如下问题：为前体药物，需要经肝酶代谢后形成活性产物；代谢受 ABCB1、CYP2C19 基因的影响[8,9]，在慢代谢患者体内活性代谢物的血药浓度降低，抗血小板作用降低。替格瑞洛为新型 $P2Y_{12}$ 受体拮抗剂，已成为首选推荐药物[10]；半衰期短，不受代谢酶及 ABCB1、CYP2C19 基因的影响[3-5,11]。多项研究认为替格瑞洛能够更快速、强效地抑制血小板[12,13]。对氯吡格雷低反应性患者应用替格瑞洛可得到良好疗效[14]。有研究显示中国人群中替格瑞洛低反应性的比例明显低于氯吡格雷[15]，且在中国人群中有良好的疗效及安全

表 3 相同 $P2Y_{12}$ 拮抗剂不同年龄段 TEG 指标比较

Table 3 Comparison of TEG indices between the same $P2Y_{12}$ antagonist at different age （$\bar{x} \pm s$）

Index	Clopidogrel（$n=251$）		P value	Ticagrelor（$n=165$）		P value
	<60C（$n=193$）	≥75C（$n=58$）		<60T（$n=129$）	≥75T（$n=36$）	
MA（mm）	65.82 ± 0.37	66.58 ± 1.06	0.165	66.23 ± 0.51	67.31 ± 0.87	0.348
AA-IPA（%）	91.03 ± 1.52	87.05 ± 3.44	0.928	90.15 ± 1.49	90.36 ± 3.59	0.25
ADP-IPA（%）	67.60 ± 1.89	57.46 ± 3.71	0.011	77.88 ± 2.22	84.28 ± 2.99	0.368
MA-ADP（mm）	30.11 ± 1.08	38.31 ± 2.08	0.001	24.19 ± 1.38	23.58 ± 2.07	0.828
MA-AA（mm）	23.55 ± 6.95	21.02 ± 2.07	0.005	18.11 ± 1.26	17.21 ± 1.66	0.529

<60C group：<60 years old patients treated with aspirin combined clopidogrel；≥75C group：≥75 years old patients treated with aspirin combined clopidogrel；<60T group：<60 years old patients treated with aspirin combined ticagrelor；≥75T group：≥75 years old patients treated with aspirin combined ticagrelor；MA：maximal amplitude；AA-IPA：inhibitory rate of arachidonic acid（AA）-induced platelet aggregation；ADP-IPA：inhibitory rate of adenosine diphosphate（ADP）-induced platelet aggregation；MA-ADP：ADP induced maximum amplitude；MA-AA：AA induced maximum amplitude

表 4 相同年龄段不同 $P2Y_{12}$ 拮抗剂 MACE、出血事件比较

Table 4 Comparison of MACE and bleeding events between the same age with different $P2Y_{12}$ antagonist [n(%)]

Item	<60 years（$n=322$）		P value	≥75 years（$n=94$）		P value
	<60C（$n=193$）	<60T（$n=129$）		≥75C（$n=58$）	≥75T（$n=36$）	
MACE	11(5.70)	9(6.98)	0.645	8(13.79)	1(2.78)	0.146
Bleeding	1(0.52)	36(27.91)	<0.001	2(3.45)	6(16.67)	0.025

<60C group：<60 years old patients treated with aspirin combined clopidogrel；≥75C group：≥75 years old patients treated with aspirin combined clopidogrel；<60T group：<60 years old patients treated with aspirin combined ticagrelor；≥75T group：≥75 years old patients treated with aspirin combined ticagrelor；MACE：major adverse cardiovascular events

表 5 相同 $P2Y_{12}$ 拮抗剂不同年龄段 MACE、出血事件比较

Table 5 Comparison of MACE and bleeding events between the same $P2Y_{12}$ antagonist at different age [n(%)]

Item	Clopidogrel（$n=251$）		P value	Ticagrelor（$n=165$）		P value
	<60C（$n=193$）	≥75C（$n=58$）		<60T（$n=129$）	≥75T（$n=36$）	
MACE	11(5.70)	8(13.79)	0.050	9(6.98)	1(2.78)	0.692
bleeding	1(0.52)	2(3.45)	0.134	36(27.91)	6(16.67)	0.392

<60C group：<60 years old patients treated with aspirin combined clopidogrel；≥75C group：≥75 years old patients treated with aspirin combined clopidogrel；<60T group：<60 years old patients treated with aspirin combined ticagrelor；≥75T group：≥75 years old patients treated with aspirin combined ticagrelor；MACE：major adverse cardiovascular events

性[16,17]，但也有研究显示其出血风险较氯吡格雷增高，且替格瑞洛有呼吸困难等不良反应，因不良反应停药的患者中约55.6%源于呼吸困难[18]。

TEG目前常用来检测血小板活性、判断DAPT的疗效。有研究认为TEG检测的ADP-IPA可作为预测支架内再狭窄的检验指标之一[7]。TEG检测发现替格瑞洛的ADP-IPA高于氯吡格雷、MA-ADP低于氯吡格雷，但MACE发生率无明显差异。这与替格瑞洛可降低MACE[1,2]不符，考虑与此研究为小样本、单中心有关。

综上所述，本研究显示替格瑞洛Ⅰ型出血发生率高于氯吡格雷，但未增加致命性出血风险与文献报道相符[3]，出血发生率在<60T组与≥75T组无明显差异。

本研究属于单中心、小样本量研究，特别是≥75T组样本量偏小、口服氯吡格雷的两组患者仅有3例发生出血事件，因此需进一步行多中心、大样本量的随机对照研究以明确中国人群不同DAPT方案的优缺点，同时明确MACE及出血事件的相关因素，以利于临床医师在充分评估出血风险及血栓风险的基础上制定个体化的DAPT方案。

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