·临床研究·

老年冠心病患者服用替格瑞洛与氯吡格雷出血风险比较

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【摘 要】 **目的** 比较≥70 岁老年冠心病患者院外服用替格瑞洛与氯吡格雷时发生出血事件的风险。**方法** 本研究连续入选 2014 年 1 月至 2015 年 3 月期间在解放军总医院心血管内科因急性冠脉综合征(ACS)住院并行冠状动脉支架植入术的患者 597 例。根据选择的双联抗血小板方案分为两组:替格瑞洛组(同时服用替格瑞洛和阿司匹林,$n=99$)和氯吡格雷组(同时服用氯吡格雷和阿司匹林,$n=498$)。随访 1 年,比较两组患者的出血风险,并分析影响出血事件的危险因素。**结果** 替格瑞洛组患者出血事件的发生率显著高于氯吡格雷组(25.3% *vs* 14.5%),差异具有统计学意义($P=0.008$),且两组患者的Ⅰ型出血事件发生率间差异具有统计学意义($P=0.015$),而Ⅱ型出血事件发生率间差异无统计学意义($P=0.261$)。用药期间共有 263 例患者行血栓弹力图(TEG)检测,其中替格瑞洛组 77 例和氯吡格雷组 186 例。与氯吡格雷组相比,替格瑞洛组患者的二磷酸腺苷(ADP)抑制率显著增加[(80.29±20.67)% *vs* (61.65±26.81)%,$P<0.001$]、ADP 诱导的最大振幅(MA_{ADP})显著降低[(25.28±14.28) *vs* (36.41±16.20) mm,$P<0.001$]。替格瑞洛组中 $MA_{ADP}<31$ mm 的患者(68.8% *vs* 40.3%,$P<0.001$)以及此类患者中发生出血事件者(24.5% *vs* 10.7%,$P=0.037$)均显著高于氯吡格雷组。多因素 logistic 回归分析表明,低体质量指数(BMI)(OR=0.910,95% CI:0.842~0.984,$P=0.018$)和高血压病(OR=1.301,95% CI:1.036~1.635,$P=0.024$)是≥70 岁老年冠心病患者服用双联抗血小板药物期间发生出血事件的独立危险因素。**结论** 老年冠心病患者口服替格瑞洛的出血风险比氯吡格雷高,且低 BMI 与高血压病患者更易发生出血事件,因此选用双联抗血小板治疗方案时应充分考虑危险因素并行 TEG 监测,以减少出血事件的发生。

【关键词】 老年人;冠心病;氯吡格雷;替格瑞洛;出血风险
【中图分类号】 R917; R592; R541.4 【文献标识码】 A 【DOI】 10.11915/j.issn.1671-5403.2016.12.212

Comparison of ticagrelor and clopidogrel in bleeding risk among the elderly with coronary artery disease

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【Abstract】 **Objective** To compare the bleeding risk in the over-70-year-old patients with coronary artery diseases treated by ticagrelor or clopidogrel after discharge from hospital. **Methods** Consecutive 597 elderly patients who were admitted to our department due to acute coronary syndrome (ACS) and underwent percutaneous coronary intervention (PCI) from Jan. 2014 to Mar. 2015 were enrolled in this study. According to their dual antiplatelet therapy, they were divided into ticagrelor group ($n=99$, treated with ticagrelor combined aspirin) and clopidogrel group ($n=498$, treated with clopidogrel combined aspirin). After 1 year's follow-up, their bleeding risk was compared, and the risk factors of bleeding events were analyzed. **Results** The incidence of bleeding events was significantly higher in the ticagrelor group than the clopidogrel group (25.3% *vs* 14.5%, $P=0.008$), and significant difference was seen in the ratio of type Ⅰ bleeding events ($P=0.015$), but not in the type Ⅱ bleeding events ($P=0.261$) between the 2 groups. During the medication period, 263 patients underwent thrombelastography (TEG), including 77 cases from the former and 186 from the latter group. ADP-induced inhibition of platelet aggregation was significantly increased [(80.29±20.67)% *vs* (61.65±26.81)%, $P<0.001$], but ADP-induced maximum amplitude (MA_{ADP}) was significantly reduced [(25.28±14.28) *vs* (36.41±16.20) mm, $P<0.001$] in the ticagrelor group than the clopidogrel group. The ticagrelor group had significantly larger percentage of patients with $MA_{ADP}<31$ mm than the clopidogrel group (68.8% *vs* 40.3%, $P<0.001$), and these patients had obviously higher occurrence of bleeding events as well (24.5% *vs* 10.7%, $P=0.037$). Multivariate logistic regression analysis indicated that low body mass index (BMI; OR=0.910, 95% CI: 0.842–0.984, $P=0.018$) and being complicated with hypertension (OR=1.301, 95% CI: 1.036–1.635,

收稿日期: 2016-07-14; **修回日期**: 2016-08-08
基金项目: 国家自然科学基金面上项目(81270309)
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$P = 0.024$) were the independent risk factors of bleeding events in the ≥70-year-old patients with coronary artery disease in treatment of dual antiplatelet therapy. **Conclusion** The risk of bleeding events is higher when taking ticagrelor than clopidogrel in the elderly patients with coronary artery disease. And those with low BMI and hypertension are prone to bleeding events. Therefore, full consideration should be given to the risk factors of bleeding, and TEG monitoring should be carried out in the treatment of dual antiplatelet therapy in order to reduce the incidence of bleeding events.

【Key words】 aged; coronary artery diseases; clopidogrel; ticagrelor; bleeding risk

This work was supported by the General Program of National Natural Science Foundation of China (81270309).

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在冠心病治疗过程中,抗血小板聚集十分关键。根据美国心脏病学会/美国心脏联合会(American College of Cardiology/American Heart Association, ACC/AHA)指南[1,2]推荐,双联抗血小板药物是急性冠脉综合征(acute coronary syndrome, ACS)或经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI)术后患者的基础用药,这些药物能够预防冠状动脉支架内血栓和减少缺血性心血管不良事件的发生。目前临床上常用的双联抗血小板治疗方案主要为阿司匹林(aspirin)联合一种血小板 P2Y12 受体抑制剂,如氯吡格雷(clopidogrel)、替格瑞洛(ticagrelor)等。但双联抗血小板同时也增加了出血风险[3]。特别是替格瑞洛,虽然在预防支架内血栓和缺血性心血管事件方面优于氯吡格雷,但出血的风险也相对更高[4]。另外,高龄也是增加出血风险的因素之一[5]。目前关于我国≥70 岁老年冠心病患者院外服用替格瑞洛与氯吡格雷出血风险比较的临床报道尚少。因此,本研究旨在比较≥70 岁老年冠心病患者院外长期服用替格瑞洛与氯吡咯雷的出血风险。

1 对象与方法

1.1 研究对象

本研究连续入选 2014 年 1 月至 2015 年 3 月期间在解放军总医院心血管内科因 ACS 住院并行冠状动脉支架植入术的患者 597 例。纳入标准:(1)年龄≥70 岁;(2)规律服用双联抗血小板药物≥6 个月。排除标准:(1)严重的血液系统疾病;(2)晚期恶性肿瘤;(3)因口服华法林等药物影响凝血机制;(4)严重肝、肾功能不全、严重感染;(5)院外 6 个月内自行停服双联抗血小板药物或服用药物剂量不符。根据选择的双联抗血小板方案分为两组:替格瑞洛组(同时服用替格瑞洛和阿司匹林,$n = 99$)和氯吡格雷组(同时服用氯吡格雷和阿司匹林,$n = 498$)。

1.2 方法

1.2.1 服用方法 阿司匹林片(拜耳医药保健有限公司)100 mg,1 次/d;替格瑞洛片(阿斯利康制药有限公司)90 mg,2 次/d;氯吡格雷片(赛诺菲安万特制药有限公司)75 mg,1 次/d。

1.2.2 观察指标 分析两组患者的性别、年龄、吸烟、体质量指数(body mass index, BMI)、既往病史、血小板计数、血脂、凝血功能、血清肌酐、估算肾小球滤过率(estimated glomerular filtration rate, eGFR)等指标及主要用药情况。

1.2.3 随访 通过门诊或电话随访 1 年,1 次/3 个月。内容包括:(1)是否遵医嘱坚持服用双联抗血小板药物;(2)有无出血情况,出血类型及部位;(3)是否存活,是否再次住院及死亡或住院原因;(4)对于随访中行血栓弹力图(thrombelastograghy, TEG; Haemoscope公司,美国)检测的患者,分析二磷酸腺苷(adenosine diphosphate, ADP)抑制率和 ADP 诱导的最大振幅(ADP induced maximum amplitude, MA_{ADP})。

1.3 相关定义

1.3.1 出血定义 根据出血部位不同,将出血分为鼻出血、牙龈出血、皮肤淤斑、消化道出血(呕血、便血或大便潜血阳性)、眼底出血、颅内出血、尿道出血、呼吸道出血等。

1.3.2 出血类型 根据出血学术研究会(Bleeding Academic Research Consortium, BARC)出血标准[6]将出血分为 5 种类型。(1)Ⅰ型:患者无需因此就医或住院的非活动性出血,如皮肤淤斑、血肿、牙龈出血、鼻出血、痔疮出血、少量血尿或镜下血尿、黑便等。(2)Ⅱ型:有明显活动性出血,需要内科干预,但尚未达到以下Ⅲ~Ⅴ型标准。(3)Ⅲ型:① 3a 型,明显出血致血红蛋白水平降低 < 30 ~ 50 g/L;②3b 型,明显出血致血红蛋白水平降低≥50 g/L,心脏压塞,需要外科手术干预或控制的出血(除外牙齿、鼻部、皮肤和痔疮);③3c 型,颅内出血(不包括脑微量出血和出血性转化,包括椎管内出血),损害视力的眼内出血。(4)Ⅳ型:冠状动脉旁路移植术(coronary artery bypass graft, CABG)相关出血。(5)Ⅴ型:致死性出血。本研究只搜集Ⅰ型和Ⅱ型两种出血类型。

1.3.3 MA_{ADP}治疗窗 MA_{ADP}检测在31～47 mm之间,双抗药物发挥最大的疗效和安全性;MA_{ADP} <31 mm时易发生出血事件;MA_{ADP} >47 mm时易发生血栓事件[7]。

1.4 统计学处理

采用SPSS17.0软件进行数据处理。计量资料以均数±标准差($\bar{x} \pm s$)表示,组间比较采用t检验。计数资料以百分率表示,组间比较采用χ^2检验,当理论值<5时,采用Fisher精确概率法。采用logistic回归分析发生出血事件的危险因素。以$P < 0.05$为差异具有统计学意义。

2 结 果

2.1 一般资料比较

替格瑞洛组患者的年龄显著低于氯吡格雷组,而BMI则显著增高,差异均具有统计学意义(P<0.05;表1)。

2.2 两组患者随访及预后的比较

随访时间为9～14(11.6±2.3)个月。替格瑞洛组和氯吡格雷组因缺血再入院者分别为2例(2.0%)和16例(3.2%),非出血死亡者分别为3例(3.0%)和12例(2.4%),发生出血事件者分别为25例(25.3%)和72例(14.5%)。两组患者间再入院发生率(P = 0.751)和非出血死亡发生率(P=0.719)差异无统计学意义,但是替格瑞洛组患者出血事件的发生率显著高于氯吡格雷组,差异具有统计学意义(P=0.008),且替格瑞洛组和氯吡格雷组中Ⅰ型出血分别为23例(23.3%)和68例(13.7%),差异有统计学意义(P=0.015),而Ⅱ型出血分别为2例(2.0%)和4例(0.8%),差异无统计学意义(P=0.261)。

2.3 两组患者TEG结果比较

用药期间共有263例患者行TEG检测,其中替格瑞洛组77例(出血21例和未出血56例),氯吡格雷组186例(出血30例和未出血156例)。与氯吡格雷组相比,替格瑞洛组患者的ADP抑制率显著增加[(80.29 ± 20.67)% *vs* (61.65 ± 26.81)%, P<0.001]、MA_{ADP}显著降低[(25.28 ± 14.28) *vs* (36.41 ± 16.20) mm, P < 0.001]。替格瑞洛组中MA_{ADP} <31 mm的患者(68.8% *vs* 40.3%, P<0.001)以及此类患者中发生出血事件者(24.5% *vs* 10.7%, P=0.037)均显著多于氯吡格雷组。

表1 基线资料比较

Table 1 Comparison of baseline data between two groups ($\bar{x} \pm s$)

Item	Ticagrelor group(n=99)	Clopidogrel group(n=498)	P value
Female[n(%)]	38(38.4)	200(40.2)	0.742
Age(years,$\bar{x} \pm s$)	74.40±3.83	75.64±4.42	0.012
Smoker[n(%)]	28(28.3)	161(32.3)	0.429
BMI(kg/m^2,$\bar{x} \pm s$)	25.75±3.45	24.73±3.31	0.008
DM[n(%)]	29(29.3)	181(36.3)	0.180
Hypertension[n(%)]	68(68.7)	357(71.7)	0.547
TC(mmol/L,$\bar{x} \pm s$)	3.72±0.86	3.81±1.06	0.775
TG(mmol/L,$\bar{x} \pm s$)	1.40±0.61	1.36±0.69	0.238
HDL-C(mmol/L,$\bar{x} \pm s$)	1.17±0.41	1.13±0.32	0.574
LDL-C(mmol/L,$\bar{x} \pm s$)	2.31±0.79	2.26±0.81	0.515
Platelet($\times 10^9$/L,$\bar{x} \pm s$)	205.79±55.45	201.43±55.18	0.445
PT(s,$\bar{x} \pm s$)	16.65±2.57	17.05±3.50	0.565
APTT(s,$\bar{x} \pm s$)	37.81±6.56	37.28±6.29	0.577
D-dimer(μg/ml,$\bar{x} \pm s$)	0.69±0.74	0.67±0.75	0.960
SCr(μmol/l,$\bar{x} \pm s$)	76.85±16.72	74.76±17.49	0.231
eGFR[ml/(min·1.73m^2),$\bar{x} \pm s$]	69.56±17.65	68.70±18.26	0.545
Combined medication[n(%)]			
Beta-bolckers	71(71.7)	344(69.1)	0.602
ACEI	49(49.5)	284(57.0)	0.168
CCB	42(42.4)	231(46.4)	0.470
Statins	94(94.9)	479(96.2)	0.568
PPI	28(28.3)	132(26.5)	0.715

BMI: body mass index; DM: diabetes mellitus; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; PT: prothrombin time; APTT: activated partial thromboplastin time; SCr: serum creatinine; eGFR: estimated glomerular filtration rate; ACEI: angiotensin converting enzyme inhibitor; CCB: calcium channel blocker; PPI: proton pump inhibitor

2.4 出血事件独立危险因素分析

将性别、年龄、BMI 等因素纳入 logistic 回归模型分析，结果表明低 BMI 和高血压病是≥70 岁老年冠心病患者发生出血风险的独立危险因素（表 2）。

表 2 出血事件的多因素 logistic 回归分析

Figure 2 Multivariate logistic regression analysis of bleeding events

Factor	OR	95% CI	*P* value
Gender	1.109	0.677 – 1.816	0.680
Age	0.979	0.924 – 1.038	0.475
BMI	0.910	0.842 – 0.984	0.018
DM	0.893	0.631 – 1.264	0.524
Hypertension	1.301	1.036 – 1.635	0.024
Platelet	1.000	0.996 – 1.004	0.920
eGFR	0.993	0.977 – 1.009	0.396

OR: odds ratio; CI: confidence interval; BMI: body mass index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate

3 讨 论

随着我国人口老龄化的到来，发生 ACS 和行 PCI 的老年患者越来越多。ACC/AHA 建议[1,2]，为预防支架内血栓形成和缺血性心血管事件的发生，PCI 术后应常规口服 12 个月的双联抗血小板药物。目前，临床上对氯吡格雷和替格瑞洛的应用较为广泛，但氯吡格雷需要经肝脏转换成活性代谢产物，起效较慢，且与血小板 P2Y12 受体结合具有不可逆性[8]，再加上老年患者药物代谢能力下降，抗血小板反应性随之降低[9]。替格瑞洛及其主要代谢产物能够可逆地、直接与血小板 P2Y12 受体结合，更快、更强效地抑制血小板聚集，从而更有效地减少老年冠心病患者缺血性不良事件的发生[10]。

然而有研究发现[3]，双联抗血小板治疗增加了出血风险，且会持续整个治疗期间。CHARISMA 研究指出[11]，双联抗血小板治疗期间的第 1 年出血风险增加最大，主要出血事件与死亡率密切相关。冯雪等[12]对 2004 例服用双联抗血小板聚集药物的患者进行回顾性研究发现，消化道出血率高达 7.1%。PLATO 研究[4]证明口服替格瑞洛比氯吡格雷的出血发生率更高，以发生非活动性出血为主，并未增加如颅内出血等致死性出血和主要出血不良事件的发生率。但这些研究均以报道主要出血或次要出血事件（如消化道出血等）为主，未报道轻微的表浅出血（如皮下淤斑、手术切口出血等）发生情况。而 Ben-Dor 等[13]指出双联抗血小板治疗期间，轻微出血发生率高达 28.9%。BARC 将这些非活动性出血纳入Ⅰ型出血类型[6]。本研究中，替格瑞洛组和氯吡格雷组出血事件均以Ⅰ型出血为主，前者出血事件发生率明显高于后者，而两者 BARC Ⅱ型出血事件发生率无明显差异。Waksman 等[14]指出这些轻微出血事件虽然与远期死亡率无明显相关，但会导致患者提早结束双联抗血小板治疗，从而增加发生支架内血栓的危险。因此应对这些出血事件予以充分关注。

TEG 是临床上检测 PCI 术后缺血性和出血性事件的重要手段，可根据其结果调整药物种类或用药剂量，能够明显减少血栓和出血事件的发生率和死亡率[15]。氯吡格雷和替格瑞洛作为 ADP 受体阻滞剂，观察指标主要为 MA_{ADP} 和 ADP 诱导的血小板抑制率。多项研究[10,16,17]证实，口服替格瑞洛患者 TEG 检测的 ADP 抑制率明显高于口服氯吡格雷患者。Gurbel 等[7]专家提出 MA_{ADP} 治疗窗为 31 ~ 47 mm，在此治疗窗内，双联抗血小板药物发挥最大的疗效和安全性；MA_{ADP} > 47 mm 时易发生血栓事件；MA_{ADP} < 31 mm时易发生出血事件。本研究显示，与氯吡格雷组相比，替格瑞洛组患者的 ADP 抑制率显著增加。替格瑞洛组中 MA_{ADP} < 31 mm 的患者以及此类患者中发生出血事件者均显著高于氯吡格雷组。提示临床医师可根据 TEG 结果调整双联抗血小板药物剂量或方案，从而减少出血事件的发生。

在本研究中，多因素 logistic 回归分析提示双联抗血小板治疗时，低 BMI 和高血压病是老年冠心病患者发生出血事件的独立危险因素。Mak 等[18]研究发现低 BMI 增加了出血风险，且与发生主要心血管事件相关。Kelly 等[19]研究提示，超重或者肥胖患者服用抗血小板药物时不能充分达到血小板抵抗作用。冠心病合并高血压病的患者，因高血流动力学状态可增加内皮结构和功能损伤，在此基础上联用抗血小板药物会进一步增加出血风险[14]。因此对于 BMI 较低或患有高血压病的老年患者选择双联抗血小板治疗方案时应谨慎选择替格瑞洛。

总之，对于老年冠心病患者，服用替格瑞洛比服用氯吡格雷的出血事件发生率高，因此选用双联抗血小板治疗方案时应充分考虑出血危险因素及个体化，并行 TEG 监测，以避免或减少出血事件的发生。本研究属于单中心小样本研究，尚需进一步的多中心大样本研究加以佐证。

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(编辑: 吕青远)