# 冠状动脉支架植入术后氯吡格雷低反应患者短期替格瑞洛强化治疗研究

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[摘 要] **目的**:探讨经皮冠状动脉支架植入术(percutaneous coronary intervention,PCI)后氯吡格雷低反应(clopidogrel low response,CLR)患者短期替格瑞洛强化抗血小板治疗的临床疗效。**方法**:连续入选PCI术后经光学血小板聚集(light transmittance aggregation,LTA)法检出的CLR患者100例,随机分为氯吡格雷组(50例)和替格瑞洛组(50例)。氯吡格雷组予氯吡格雷75 mg/d;后者予替格瑞洛90 mg,2次/d,bid,强化1个月后改为氯吡格雷75 mg/d;两组患者均联合服用阿司匹林100 mg/d。治疗1个月后检测所有患者的血小板聚集率;随访6个月,比较两组心血管不良事件的发生情况。**结果**:两组患者随机治疗前二磷酸腺苷诱导的血小板聚集率(adenosine diphosphate-induced platelet aggregation,$PL_{ADP}$)及花生四烯酸诱导的血小板聚集率(arachidonic acid-induced platelet aggregation,$PL_{AA}$)均无统计学差异($P > 0.05$);治疗1个月时,替格瑞洛组$PL_{ADP}$显著低于氯吡格雷组[(21.27 ± 12.81)% *vs*.(48.72 ± 10.92)%,$P < 0.01$],两组患者$PL_{AA}$无统计学差异($P > 0.05$);6个月时随访,替格瑞洛组心源性再入院患者显著低于氯吡格雷组(6% *vs*. 20%,$P < 0.05$),但轻微出血增加(24% *vs*. 8%,$P < 0.05$)。**结论**:替格瑞洛的抗血小板聚集作用显著优于氯吡格雷,对CLR患者PCI术后替格瑞洛强化抗血小板治疗1个月可能减少心源性住院事件。

[关键词] 替格瑞洛;氯吡格雷;血小板聚集率;经皮冠状动脉支架植入术

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## Short-term intensive treatment of ticagrelor for patients with low response to clopidogrel after percutaneous coronary intervention

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[**Abstract**] **Objective**: To investigate the clinical efficacy of short-term intensive antiplatelet treatment of ticagrelor for patients with low response to clopidogrel after percutaneous coronary intervention (PCI). **Methods**: A total of 100 cases who underwent PCI and were confirmed with low response to clopidogrel by light transmittance aggregation (LTA) were consecutively recruited and equally randomized into Clopidogrel ($n$=50) and Ticagrelor ($n$=50) groups. In Clopidogrel group, patients maintained clopidogrel 75 mg, gd in combination with aspirin 100 mg, gd; while in Ticagrelor group, patients were treated with ticagrelor 90 mg twice daily for 1 month, then switching to clopidogrel 75 mg, gd in combination with aspirin 100 mg, gd. The light transmission aggregations were determined for all patients 1 month after randomization; all participants were followed up and the adverse cardiovascular events were recorded for 6 months. **Results**: There were no significant differences between the two groups regarding both the adenosine diphosphate-induced platelet aggregation ($PL_{ADP}$) and the arachidonic acid-induced platelet aggregation ($PL_{AA}$) prior to randomization ($P > 0.05$). At 1 month after randomization, $PL_{ADP}$ in the Ticagrelor group was significantly lower than that in the Clopidogrel group [(21.27 ± 12.81)% *vs*. (48.72 ± 10.92)%] ($P < 0.01$), while $PL_{AA}$ showed no significant difference between the two groups. The incidence of cardiogenic rehospitalization was significantly lower (6% *vs*. 20%, $P < 0.05$), although minimal bleeding was significantly higher (24% *vs*. 8%, $P < 0.05$) in the Ticagrelor group compared with that in the Clopidogrel group. **Conclusion**: The antiplatelet effect of ticagrelor is significantly more potent than that of clopidogrel, and 1-month intensive treatment of ticagrelor may reduce the cardiogenic rehospitalization in patients with CLR after PCI.

[**Key words**] ticagrelor; clopidogrel; platelet aggregation; percutaneous coronary intervention

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阿司匹林联合$P2Y_{12}$受体拮抗剂的抗血小板治疗是经皮冠状动脉支架植入(percutaneous coronary intervention,PCI)术后的Ⅰ类推荐治疗措施[1]。目前临床最普遍使用的$P2Y_{12}$受体拮抗剂包括氯吡格雷和替格瑞洛。

文献报道,约4%~30%患者在服用常规剂量氯吡格雷(75 mg/d,1次/d)的情况下,血小板功能未能被理想抑制,称为氯吡格雷低反应(clopidogrel low response,CLR)[2],CLR患者的心血管事件发生风险显著增高[3]。

替格瑞洛是新一代口服$P2Y_{12}$受体拮抗剂,相比氯吡格雷,替格瑞洛为原形药,其不经过肝脏代谢可直接产生抗血小板作用[4]。$PL_{ATO}$研究显示:替格瑞洛应用于急性冠妆动脉综合征(ACS)患者较氯吡格雷可显著减少心肌梗死和血管源性死亡,但同时亦显著增加非冠状动脉搭桥(CABG)相关的出血[5]。新近TOPIC研究显示,冠心病患者PCI术后强化替格瑞洛抗血小板治疗1个月后改用氯吡格雷治疗,较之持续替格瑞洛抗血小板治疗可显著减少出血事件,不增加血栓事件[6]。综上所述,PCI术后早期强化抗血小板治疗是必要的,但长时间强化抗血小板治疗可能带来更多出血事件。本研究探讨对于CLR患者采用替格瑞洛强化抗血小板治疗1个月的临床疗效。

## 1 对象和方法

### 1.1 对象

连续入选在南京医科大学第一附属医院心脏科接受PCI治疗并通过光学血小板聚集(light transmittance aggregation,LTA)法检出的CLR患者100例。其中男68例,女32例,平均年龄(63.75 ± 11.47)岁。入选标准:①18~80岁男性或非妊娠女性;②确诊为稳定性心绞痛(stable angina pectoris,SA)、不稳定性心绞痛(unstable angina pectoris,UA)、非ST段抬高型心肌梗死(non-ST-elevation myocardial Infarction,NSTEMI)或ST段抬高型心肌梗死(ST-elevation myocardial infarction,STEMI)并接受支架植入治疗的患者;③服用氯吡格雷75 mg/d 1次和阿司匹林100 mg/d 1次 ≥5 d;④签署知情同意书。排除标准:①已知阿司匹林,氯吡格雷或替格瑞洛过敏者;②严重肝肾功能不全者。

### 1.2 方法

#### 1.2.1 血小板聚集功能检测

在患者晨起服用二磷酸腺苷(adenosine diphosphate,ADP)受体拮抗剂(氯吡格雷或替格瑞洛)2 h后,用含3.2%的枸橼酸钠抗凝管采集肘静脉血4.5 mL,3 h内用LTA法检测血小板聚集率。具体方法如下:将采集的静脉血置室温下200 *g* 离心8 min,吸取富血小板血浆(platelet-rich plasma,PRP),用全血自动分析仪检测PRP中的血小板计数,将剩余血样经2 460 *g* 离心10 min,获取贫血小板血浆(platelet-poor plasma,PPP),如PRP中血小板计数>$250\times10^9$个/L,则用PPP稀释PRP中的血小板计数至$250\times10^9$个/L。将2.5 μL ADP和10 μL花生四烯酸(arachidonic acid,AA)分别加入2只含0.5 mL PRP的比色杯中,以PPP作为空白对照,运用LTA分别检测在5 μmol/L ADP和1 mmol/L AA诱导下持续8 min的血小板聚集率,记为$PL_{ADP}$和$PL_{AA}$[7]。本研究将$PL_{ADP}$>40%定义为CLR[8]。

#### 1.2.2 分组及服药

采用随机数字法将100例CLR患者随机分为氯吡格雷组和替格瑞洛组,各组50例。氯吡格雷组患者随机后继续服用氯吡格雷75 mg/d,1次/d至随访终点;替格瑞洛组患者随机后停服氯吡格雷、改服替格瑞洛90 mg/d,2次/d,1个月后再恢复服用氯吡格雷75 mg/d,1次/d至随访终点;两组均联合服用阿司匹林100 mg/d,1次/d。

#### 1.2.3 随访

入组后1个月行门诊随访,复查血小板聚集率;继续门诊或电话随访6个月,记录以下不良事件:①心源性死亡、非致死性心肌梗死、缺血性脑卒中、心源性再入院、支架内血栓、靶血管重建;②出血事件:TIMI(thrombolysis in myocardial infarction)定义的大出血,小出血及轻微出血[9]。

### 1.3 统计学方法

采用SPSS19.0统计软件进行资料分析,符合正态分布的计量资料以均数±标准差($\bar{x} \pm s$)表示,组间比较采用$t$检验;不符合正态分布的计量资料以中位数(四分位间距)[$M(P_{25},P_{75})$]表示,组间比较采用秩和检验;计数资料以百分率表示,组间比较采用卡方检验或Fisher's精确检验。$P \leqslant 0.05$为差异有统计学意义。

## 2 结 果

### 2.1 患者基本资料

两组患者间的基本资料、诊断、既往史及合并用药均无统计学差异(表1)。

### 2.2 血小板聚集功能检测结果及心血管不良事件发生情况

随机治疗前替格瑞洛组与氯吡格雷组$PL_{ADP}$及

**表1　患者基本临床资料**

**Table 1　Clinical characteristics of the patients**

[$n$(%)，$\bar{x} \pm s$]

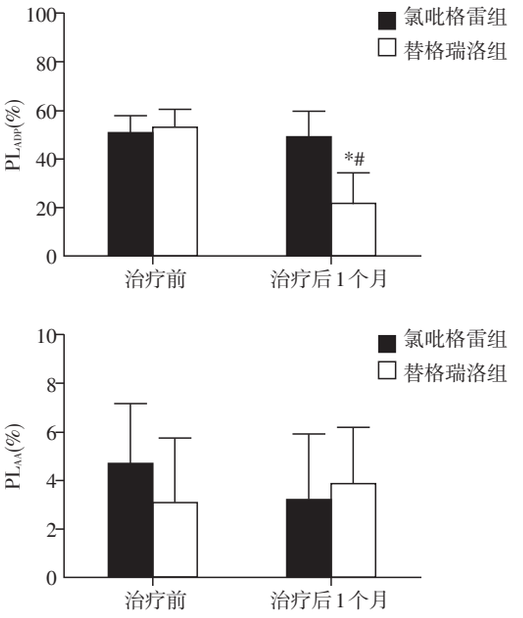
| 项目 | 氯吡格雷组($n$=50) | 替格瑞洛组($n$=50) | $P$值 |
|---|---|---|---|
| 性别(男/女) | 33(66)/17(34) | 35(70)/15(30) | 0.67 |
| 年龄(岁) | 62.31 ± 12.58 | 64.18 ± 11.49 | 0.45 |
| BMI(kg/m$^2$) | 24.81 ± 2.47 | 25.16 ± 3.08 | 0.51 |
| 高血压 | 32(64) | 33(66) | 0.83 |
| 糖尿病 | 14(28) | 16(32) | 0.66 |
| 高脂血症 | 13(26) | 11(22) | 0.64 |
| 吸烟 | 18(36) | 23(46) | 0.31 |
| 临床诊断 | | | |
| SA | 9(18) | 6(12) | 0.40 |
| UA | 22(44) | 26(52) | 0.42 |
| STEMI | 10(20) | 13(26) | 0.48 |
| NSTEMI | 9(18) | 5(10) | 0.25 |
| 合并用药 | | | |
| 他汀类 | 49(98) | 48(96) | 1.00 |
| ACEI/ARB | 35(70) | 29(58) | 0.36 |
| β受体阻滞剂 | 38(76) | 32(64) | 0.19 |
| 钙离子拮抗剂 | 11(22) | 10(20) | 0.81 |
| 硝酸酯类 | 35(70) | 33(66) | 0.17 |
| 质子泵抑制剂 | 4(8) | 8(16) | 0.22 |
| 利尿剂 | 3(6) | 5(10) | 0.71 |
| 曲美他嗪 | 18(36) | 21(42) | 0.54 |

BMI：体重指数；ACEI：血管紧张素转换酶抑制剂；ARB：血管紧张素受体拮抗剂。

$PL_{AA}$均无统计学差异[$PL_{ADP}$：(52.88 ± 7.10)% *vs.* (51.26 ± 7.18)%，$P$ > 0.05；$PL_{AA}$：(3.17 ± 2.56)% *vs.* (4.66 ± 2.45)%，$P$ > 0.05]；随机治疗1个月后，替格瑞洛组$PL_{ADP}$较随机前显著下降[(21.27 ± 12.81)% *vs.* (52.88 ± 7.10)%，$P$ < 0.01]；且显著低于氯吡格雷组[(21.27 ± 12.81)% *vs.* 48.72 ± 10.92)%，$P$ < 0.01]。随机1个月时$PL_{AA}$在两组间无统计学差异[(3.84 ± 2.32)% *vs.*(3.72 ± 2.69)%，$P$ > 0.05，图1]。

两组患者6个月内不良事件的发生情况：在心源性再入院方面，氯吡格雷组显著高于替格瑞洛组(20% *vs.* 6%，$P$ < 0.05)；氯吡格雷组支架内血栓发生1例(2% *vs.* 0%)，组间无统计学差异($P$ > 0.05)；两组间心源性死亡、非致死性心肌梗死、缺血性脑卒中及其他原因再入院事件发生率均无统计学差异($P$均 > 0.05，表2)。

两组患者6个月内的大出血和小出血事件发生率均无统计学差异($P$ > 0.05)；而在轻微出血方面，




替格瑞洛组随机治疗前后比较，*$P$ < 0.01；随机治疗后两组间比较，#$P$ < 0.01。

**图1　血小板聚集率**

**Figure 1　Platelet aggregations**

**表2　不良事件发生率**

**Table 2　The incidences of adverse events**　[$n$(%)]

| 项目 | 氯吡格雷组($n$=50) | 替格瑞洛组($n$=50) | $P$值 |
|---|---|---|---|
| 心源性死亡 | 2(4) | 0(0) | 0.48 |
| 非致死性心肌梗死 | 0(0) | 1(2) | 1.00 |
| 缺血性脑卒中 | 1(2) | 1(2) | 1.00 |
| 支架内血栓 | 1(2) | 0(0) | 1.00 |
| 心源性再入院 | 10(20) | 3(6) | 0.04 |
| MI | 2(4) | 1(2) | 1.00 |
| UA | 5(10) | 2(4) | 0.43 |
| SA | 2(4) | 0(0) | 0.48 |
| 心功能不全 | 1(2) | 0(0) | 1.00 |
| 心律失常 | 0(0) | 0(0) | 1.00 |
| 因其他原因入院 | 5(10) | 3(6) | 0.71 |

氯吡格雷组显著低于替格瑞洛组(8% *vs.* 24%，$P$ < 0.05)，且多发生于1个月内(6% *vs.* 20%，$P$ < 0.05，表3)。

**表3　出血事件发生率**

**Table 3　The incidences of bleeding events**　[$n$(%)]

| 项目 | 氯吡格雷组($n$=50) | 替格瑞洛组($n$=50) | $P$值 |
|---|---|---|---|
| 大出血 | 0(0) | 0(0) | 1.00 |
| 小出血 | 0(0) | 1(2) | 1.00 |
| 轻微出血 | 4(8) | 12(24) | 0.03 |

## 3 讨 论

本研究发现PCI术后CLR患者予替格瑞洛强化抗血小板治疗1个月后血小板抑制率显著改善;6个月随访时替格瑞洛显著减少心源性再入院事件,不增加TIMI大出血和小出血事件。

文献报道,约4%~30%患者在服用常规剂量氯吡格雷(75 mg/d)的情况下出现CLR[2],CLR患者较反应正常患者PCI术后心血管不良事件的发生率增加4倍以上[3]。OPTIMUS研究发现双倍剂量氯吡格雷可降低2型糖尿病伴CLR患者的残余血小板聚集率,但此类患者中仍有60%在服用双倍剂量氯吡格雷后存在血小板高反应性[10];GRAVITAS研究显示,对VerifyNow检出的CLR患者行6个月双倍剂量氯吡格雷强化抗血小板治疗,与常规剂量氯吡格雷治疗相比并未降低心源性死亡、非致死性心肌梗死及支架内血栓的发生率,出血风险却显著增加[11]。

替格瑞洛是新一代$P2Y_{12}$受体拮抗剂,其不需经肝脏代谢即可与$P2Y_{12}$受体可逆性结合、发挥抗血小板聚集作用[4]。本课题组前期研究显示替格瑞洛的抗血小板作用显著优于氯吡格雷[12],PLATO研究也证实对于ACS患者替格瑞洛较氯吡格雷降低了心血管死亡风险21%[5]。因此,对于CLR患者采用替格瑞洛强化治疗无疑是一理想的选择,但PLATO研究同时发现替格瑞洛组治疗1年期间的非CABG相关大出血有显著增加;同时,PLATO及TRITON TIMI38等研究结果均显示ACS患者缺血性事件主要发生在冠状动脉支架植入术后的早期阶段[5,13],ADAPT-DES研究显示,CLR患者早期支架内血栓风险较正常反应者增加3倍[14],现已知支架内皮化多发生在PCI术后1个月内[15],GRAVITAS及RESPOND等研究提示早期强化抗血小板治疗可以改善患者的血小板反应性[11,16],CURRENT-OASIS 7研究同样说明早期强化抗血小板1周可以显著降低患者1个月缺血性事件的发生率[17],因此,本研究方案对CLR患者采用替格瑞洛强化治疗1个月,旨在减少支架植入术后早期的血栓性事件,同时避免形如PLATO、GRAVITAS研究方案中长时间强化抗血小板治疗带来的出血风险。

新近TOPIC研究显示对于ACS患者,在支架植入1个月后将替格瑞洛替换为氯吡格雷治疗,与替格瑞洛持续性抗血小板治疗相比,调整后的方案可显著减少1年随访时的出血事件发生率,但不增加血栓性事件的发生[6]。本研究与TOPIC研究相似之处是:均采用了PCI术后替格瑞洛强化抗血小板治疗1个月、再更换为氯吡格雷的治疗方案;与之不同的是:①本研究入选了CLR患者;②本研究与氯吡格雷持续抗血小板治疗对照,而TOPIC研究与替格瑞洛持续抗血小板治疗对照。结果显示,与氯吡格雷持续抗血小板治疗对照,替格瑞洛短期强化治疗方案减少了6个月随访时CLR患者心源性再入院事件,未增加TIMI大出血或小出血事件。

在研究中发现,替格瑞洛组有3例患者出现呼吸困难,但患者均能耐受,1个月后改用氯吡格雷治疗,上述症状均好转。此外,1例患者服用替格瑞洛1个月后血小板聚集率仍大于40%,提示少数患者可能存在替格瑞洛抵抗。

本研究存在以下不足之处:入选病例相对较少,对于临床终点差异比较的把握度较低。但后期分析结果显示,目前样本量检出血小板聚集率差异的把握度大于99%,本研究采用LTA法进行血小板功能检测,此方法被证实对临床终点事件有预测价值[18]。因此,推测研究中血小板聚集率的改善可能转变为临床血栓性事件的减少。

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