·临床研究·

# 血栓弹力图指导下的替格瑞洛与氯吡格雷在急性冠脉综合征患者中的疗效比较

高 洁,耿晓雯,吕中华,程庆强,任艺虹*
(解放军总医院心内科,北京 100853)

【摘 要】 **目的** 比较急性冠脉综合征(ACS)患者服用替格瑞洛和氯吡格雷后的疗效。**方法** 收集解放军总医院心内科2014年3月至2015年5月657例服用双联抗血小板药物并进行血栓弹力图(TEG)监测的ACS患者临床资料。出院后随访12个月内再发主要不良心血管事件(MACE)情况,比较替格瑞洛和氯吡格雷的疗效,并分析再发MACE的危险因素。**结果** 替格瑞洛组患者二磷酸腺苷(ADP)抑制率明显高于氯吡格雷组($P<0.001$),且药物抵抗(ADP<30%)发生比例低($P<0.001$);Kaplan-Meier法计算替格瑞洛组与氯吡格雷组的MACE发生率分别为11.74%和9.82%,差异无统计学意义($P=0.574$);采用Cox回归分析MACE发生的危险因素:心率(B=0.040,RR=1.041,95% CI:1.018~1.064,$P=0.000$),估算的肾小球滤过率(eGFR;B=-0.010,RR=-0.990,95% CI:0.981~1.000,$P=0.048$)。替格瑞洛组无致命性出血事件发生,非活动性出血事件与eGFR(B=-0.022,OR=0.978,95% CI:0.958~0.998,$P=0.031$)相关。**结论** 替格瑞洛组的疗效并不优于氯吡格雷组,但其药物抵抗发生率低,eGFR低的患者易发生非活动性出血事件,心率快的ACS患者易再发生MACE。

【关键词】 急性冠脉综合征;替格瑞洛;氯吡格雷;药物抵抗;主要不良心血管事件
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# Efficiency of ticagrelor and clopidogrel in treatment of acute coronary syndrome: a comparative study by thromboelastography

GAO Jie, GENG Xiao-Wen, LYU Zhong-Hua, CHENG Qing-Qiang, REN Yi-Hong*
(Department of Cardiology, Chinese PLA General Hospital, Beijing 100853, China)

【**Abstract**】 **Objective** To compare the therapeutic efficiency of ticagrelor and clopidogrel in the patients with acute coronary syndrome(ACS). **Methods** Clinical data of 657 ACS patients who were treated with aspirin combined with ticagrelor or clopidogrel and monitored by thromboelastography(TEG) in our department from March 2014 to May 2015 were collected in this study. They were all followed up for 12 months after discharge for the recurrence of major adverse cardiovascular events(MACE). The efficiency of ticagrelor and clopidogrel was compared between the 2 groups, and the risk factors for recurrence of MACE were analyzed. **Results** The ticagrelor group had significantly higher inhibitory rate in adenosine diphosphate(ADP) pathway($P<0.001$), but obviously lower drug resistance(ADP<30%) than the clopidogrel group($P<0.001$). The Kaplan-Meier survival analysis showed the incidence of MACE was 11.74% and 9.82% respectively in the ticagrelor and clopidogrel groups($P=0.574$). Cox regression analysis suggested that the risk factors for MACE were heart rate(B=0.040, RR=1.041, 95% CI: 1.018-1.064, $P=0.000$) and estimated glomerular filtration rate(eGFR, B=-0.010, RR=0.990, 95% CI: 0.981-1.000, $P=0.048$). There was no fatal bleeding events in the ticagrelor group, and the risk factor of inactive bleeding events was eGFR(B=-0.022, OR=0.987, 95% CI: 0.985-0.998, $P=0.031$). **Conclusion** The therapeutic effect of ticagrelor is not superior to clopidogrel, but the former leads lower rate of drug resistance. ACS patients with lower eGFR are prone to experiencing inactive bleeding events, and those with faster heart rate are more likely to have recurrence of MACE.

【**Key words**】 acute coronary syndrome; ticagrelor; clopidogrel; drug resistance; major adverse cardiovascular events
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*Corresponding author*: *REN Yi-Hong*, *E-mail*: *rainbowren301@163.com*

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**通信作者**:任艺虹,E-mail:rainbowren301@163.com

阿司匹林(aspirin)联合一种 $P2Y_{12}$ 受体拮抗剂双联抗血小板疗法是预防急性冠脉综合征(acute coronary syndrome, ACS)患者再缺血事件及支架内血栓发生的标准治疗方案[1-3]。氯吡格雷(clopidogrel)是一种前体药物,需经肝酶细胞色素P450系统代谢为活性代谢产物,是一种选择性不可逆的 $P2Y_{12}$ 受体抑制剂,抑制由二磷酸腺苷(adenosine diphosphate,ADP)诱导的血小板聚集;替格瑞洛(ticagrelor)是一种可逆的选择性强效 $P2Y_{12}$ 受体抑制剂,本身即为活性药物,可直接作用于 $P2Y_{12}$ 受体,从而抑制由ADP介导的血小板聚集,而且其起效时间以及停药后血小板恢复时间均较氯吡格雷短[1,2,4]。然而接受了阿司匹林及替格瑞洛或氯吡格雷双联抗血小板药物后,仍有部分患者血小板活性高,或再次出现心血管缺血事件,称为抗血小板药物抵抗[5,6]。本研究比较替格瑞洛组与氯吡格雷组主要不良心血管事件(major adverse cardiovascular events,MACE)发生情况,并分析MACE再发生的危险因素。

## 1 对象与方法

### 1.1 研究对象

收集解放军总医院心内科2014年3月至2015年5月657例服用双联抗血小板药物并进行血栓弹力图(thromboelastography, TEG)监测的ACS患者临床资料。根据 $P2Y_{12}$ 受体拮抗剂类型将其分为替格瑞洛组($n=273$)和氯吡格雷组($n=384$)。

### 1.2 方法

回顾性收集两组患者住院期间的临床资料,并进行组间比较。患者出院后进行电话随访,记录患者服用双联抗血小板药物期间再发MACE情况。若患者在12个月内因各种原因停用替格瑞洛或氯吡格雷,则随访终止。共有23例患者失访,失访率为3.5%。

### 1.3 相关概念

本研究相关概念如下。(1)MACE:再次血管血运重建(包括靶血管及非靶血管再狭窄、血栓形成)、再次心肌梗死、全因性死亡等。(2)TEG指标:最大振幅(maximal amplitude,MA),代表血小板聚集功能;血小板抑制率(%):花生四烯酸(arachidonic acid,AA)通路、ADP通路[7,8];(3)替格瑞洛或氯吡格雷药物抵抗:TEG测定的ADP诱导的血小板抑制率<30%[7,9];(4)出血事件参照出血学术研究会(Bleeding Academic Research Consortium,BARC)定义标准[10]。

### 1.4 统计学处理

所有数据采用SPSS17.0统计软件进行处理。计量资料以均数±标准差表示,比较采用方差分析(正态分布)或秩和检验(偏态分布);计数资料以百分率表示,组间比较采用 $\chi^2$ 检验;用Kaplan-Meier法描述MACE第1次发生的累计发生率;采用Cox/logistic回归分析筛选MACE的危险因素。以 $P<0.05$ 为差异具有统计学意义。

## 2 结 果

### 2.1 两组患者一般临床资料比较

氯吡格雷组患者吸烟者比例高于替格瑞洛组,差异有统计学意义($P<0.05$;表1)。

### 2.2 两组患者血小板活性比较

替格瑞洛组较氯吡格雷组ADP通路的血小板抑制率高,药物抵抗发生率低,差异有统计学意义($P<0.05$;表2)。

### 2.3 两组患者发生MACE情况比较

Kaplan-Meier法计算替格瑞洛与氯吡格雷组患者12个月MACE事件发生率分别为11.74%和9.82%,差异无统计学意义($P=0.574$;表3,图1)。

Cox回归分析得出发生MACE的危险因素有心率(B=0.040,RR=1.041,95% CI:1.018~1.064,$P=0.000$)和eGFR(B=-0.010,RR=0.990,95% CI:0.981~1.000,$P=0.048$),并未发现药物抵抗会影响MACE的发生。

### 2.4 两组患者不良反应发生情况

出血事件根据BARC标准,服用替格瑞洛期间仅1人出现消化道大出血并输血治疗(3a型),但最终证实为胃窦部肿瘤所致,其他出血事件均为非活动性出血(1型)。轻微非活动性出血事件有皮肤淤斑、淤点55例(20.1%)、口腔出血(包括牙龈出血)18例(6.6%)、痰中带血1例(0.4%)、鼻出血10例(3.7%)、眼底出血1例(0.4%)、耳道出血2例(0.7%)以及穿刺处长时间出血4例(1.5%)。其中有3例因皮肤多处淤斑、1例因痰中带血、1例因眼底出血停用替格瑞洛,换为氯吡格雷。采用logistic回归分析非活动性出血事件的危险因素:eGFR(B=-0.022,OR=0.978,95% CI:0.958~0.998,$P=0.031$)。服用替格瑞洛期间共有18例(6.5%)出现呼吸困难,其中7例(41.2%)因无法耐受停用替格瑞洛,其余患者呼吸困难均可耐受并逐渐缓解。

**表1 两组患者一般临床资料比较**

Table 1 Comparison of the baseline information between the two groups

| Item | Ticagrelor group($n$=273) | Clopidogrel group($n$=384) | $P$ value |
|---|---|---|---|
| Male[$n$(%)] | 65(23.81) | 98(25.52) | 0.617 |
| Age(years, $\bar{x}\pm s$) | 61.17±0.62 | 60.75±0.60 | 0.324 |
| BMI(kg/m$^2$, $\bar{x}\pm s$) | 25.90±0.19 | 25.73±0.16 | 0.586 |
| SBP(mmHg, $\bar{x}\pm s$) | 132.41±1.13 | 132.13±0.92 | 0.992 |
| DBP(mmHg, $\bar{x}\pm s$) | 75.18±0.68 | 75.04±0.56 | 0.808 |
| HR(beats/min, $\bar{x}\pm s$) | 73.42±0.77 | 73.31±0.56 | 0.595 |
| Hypertension[$n$(%)] | 172(63.00) | 249(64.84) | 0.628 |
| DM[$n$(%)] | 90(32.97) | 127(33.07) | 0.977 |
| CKD[$n$(%)] | 40(14.65) | 60(15.63) | 0.732 |
| Smoking[$n$(%)] | 123(45.05) | 207(53.91) | 0.025 |
| TC(mmol/L, $\bar{x}\pm s$) | 3.85±0.06 | 3.99±0.08 | 0.227 |
| TG(mmol/L, $\bar{x}\pm s$) | 1.60±0.07 | 1.63±0.06 | 0.914 |
| HDL-C(mmol/L, $\bar{x}\pm s$) | 1.10±0.07 | 1.05±0.02 | 0.480 |
| LDL-C(mmol/L, $\bar{x}\pm s$) | 2.33±0.05 | 2.40±0.06 | 0.460 |
| FBG(mmol/L, $\bar{x}\pm s$) | 6.91±0.18 | 6.85±0.16 | 0.579 |
| SCr(μmol/L, $\bar{x}\pm s$) | 79.40±1.65 | 87.75±4.00 | 0.488 |
| eGFR[ml/(min·1.73 m$^2$), $\bar{x}\pm s$] | 91.53±1.76 | 90.85±1.66 | 0.786 |
| SUA(μmol/L, $\bar{x}\pm s$) | 333.67±5.80 | 333.91±5.00 | 0.853 |
| Aspirin[$n$(%)] | 271(99.27) | 377(98.18) | 0.398 |
| Statins[$n$(%)] | 268(98.17) | 374(97.40) | 0.513 |
| Beta-blockers[$n$(%)] | 216(79.12) | 311(80.99) | 0.554 |
| ACEI/ARB[$n$(%)] | 112(41.03) | 158(41.15) | 0.756 |
| PPI[$n$(%)] | 49(17.95) | 51(13.28) | 0.101 |

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; DM: diabetes mellitus; CKD: chronic kidney disease; TC: total cholesterol; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; FBG: fasting blood glucose; SCr: serum creatinine; eGFR: estimated glomerular filtration rate; SUA: serum uric acid; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; PPI: proton pump inhibitor

**表2 两组患者血小板活性指标比较**

Table 2 Comparison of the platelet activity indices between the two groups

| Index | Ticagrelor group($n$=273) | Clopidogrel group($n$=384) | $P$ value |
|---|---|---|---|
| MA(mm, $\bar{x}\pm s$) | 66.99±0.36 | 66.46±0.31 | 0.225 |
| Inhibition rate in AA pathway(%, $\bar{x}\pm s$) | 89.79±1.14 | 91.96±2.63 | 0.073 |
| Inhibition rate in ADP pathway(%, $\bar{x}\pm s$) | 81.62±1.29 | 65.50±1.42 | 0.000 |
| ADP hyporesponsiveness[$n$(%)] | 8(2.93) | 50(13.02) | 0.000 |

MA: maximal amplitude; AA: arachidonic acid; ADP: adenosine diphosphate

**表3 Kaplan-Meier 法计算12个月 MACE 发生率**

Table 3 Incidence of 12-month MACE estimated by Kaplan-Meier [$n$(%)]

| Event | Ticagrelor group($n$=273) | Clopidogrel group($n$=384) | $P$ value |
|---|---|---|---|
| MACE | 16(11.74) | 33(9.82) | 0.574 |
| PCI | 10(7.52) | 23(6.84) | 0.820 |
| MI | – | 1(2.60) | – |
| Death from any cause | 5(3.76) | 10(2.92) | 0.738 |

MACE: major adverse cardiovascular events; PCI: percutaneous coronary intervention; MI: myocardial infarction

服用氯吡格雷患者,随访期间出现便血1例、上消化道出血1例、月经量过多1例(3a型),均暂停氯吡格雷并输血治疗,非活动性出血事件包括鼻出血1例、淤斑1例,服药期间未出现呼吸困难症状。

## 3 讨 论

血小板活化是心血管缺血事件发生的病理学关键因素[11]。阿司匹林联合氯吡格雷双联抗血小板

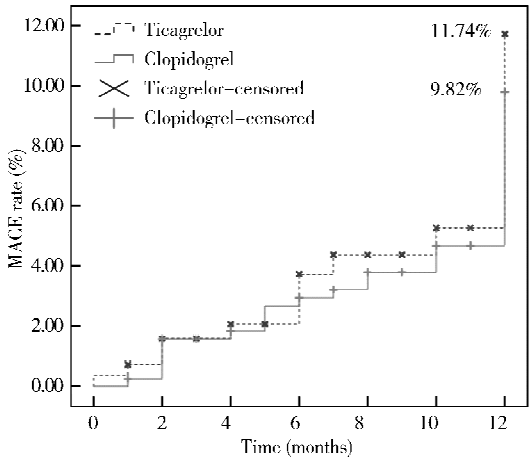



**图1 Kaplan-Meier法计算两组患者的MACE发生率**

Figure 1 Incidence of 12-month MACE estimated by Kaplan-Meier

MACE: major adverse cardiovascular events

疗法是指南推荐的ACS和经皮冠状动脉介入(percutaneous coronary intervention, PCI)术后的标准治疗方案[1-3]。替格瑞洛是一种可逆的选择性$P2Y_{12}$受体拮抗剂,其抗血小板作用较氯吡格雷起效快、作用强,可进一步降低MACE的再发生及总病死率,并已被指南推荐(Ⅰb)[1,2,4]。两组患者在随访期间均有MACE事件发生,然而采用Kaplan-Meier法计算替格瑞洛组与氯吡格雷组之间MACE事件发生率,差异并无统计学意义,与文献报道并不一致,可能与本研究单中心、样本量小、随访时间短有关。

替格瑞洛组患者ADP抑制率明显高于氯吡格雷组,但替格瑞洛组仍有2.9%的患者ADP通路抑制率<30%,存在明显的替格瑞洛低反应性,而氯吡格雷组有13.0%的患者存在药物抵抗,明显高于替格瑞洛组。但目前为止对于低反应性并无明确定义,一般将其分为临床抵抗和实验室抵抗[5]。研究表明多种因素会影响血小板活性导致抗血小板药物低反应性。氯吡格雷是一种前体药物,需经肝酶代谢为活性代谢产物,研究表明氯吡格雷的代谢和药物疗效受ABCB1、CYP2C19基因多态性的影响,携带低代谢基因的患者MACE发生率高[12,13]。由于替格瑞洛为非前体药物,无需经过肝脏代谢活化,在PLATO亚组研究中表明替格瑞洛疗效优于氯吡格雷,与ABCB1、CYP2C19基因多态性无关[14],其他研究也表明替格瑞洛药效不受ABCB1、CYP2C19基因型影响[15,16]。替格瑞洛和氯吡格雷均是$P2Y_{12}$受体抑制剂,其抗血小板作用是否受$P2Y_{12}$基因多态性影响,目前并无统一结论[15,17]。本研究中未涉及基因多态性方面研究,有待设计实验为临床提供依据。

对于抗血小板药物低反应性主要通过监测血小板功能来实现。目前TEG已被广泛应用于冠心病抗血小板治疗后评估血小板活性及药物疗效[18]。越来越多的证据表明剩余血小板活性高,再缺血事件发生风险高。CREST注册研究表明,抗血小板药物低反应性与再缺血事件及支架内血栓发生有密切联系,而TEG可以作为一种监测血小板功能的手段来指导个体化抗血小板治疗[9]。同时也有其他研究证明,通过TEG测定的ADP诱导的血小板抑制率与支架内再狭窄(in stent restenosis, ISR)程度呈负相关,可以作为ISR的预测因素[8]。然而在回归分析中并未发现ADP诱导的血小板抑制率与MACE发生之间有关系。

多项研究表明,心率快与MACE的发生和预后密切相关,减慢心率有利于心血管病的治疗[19]。一些研究也表明,在其他心血管危险因素得到控制的情况下,静息心率高是冠心病、心肌梗死和卒中发生的独立危险因素[20]。心率快可增加心肌耗氧量,损伤血管内皮,进而导致动脉粥样硬化或斑块破裂[21]。因此,应尽量控制静息心率,避免不良事件的发生。本研究得出心率越快的ACS患者,MACE的发生率越高。

另外,本研究中替格瑞洛组并未记录到由抗血小板药物引起的致命性的大出血事件,轻微出血事件以皮肤淤斑、牙龈出血或鼻出血多见,且eGFR越低,非活动性轻微出血事件越易发生。部分患者在服用替格瑞洛开始阶段出现呼吸困难不良反应,可能的机制是由于替格瑞洛通过对腺苷脱氨酶的抑制导致血液中腺苷浓度升高,除了增加额外的抗血小板作用外,也导致了呼吸困难的发生,但研究表明,这种呼吸困难并没有导致肺功能损害[22]。多数患者呼吸困难程度较轻,无需换药即可缓解,但仍有少数患者不能耐受从而导致了替格瑞洛停药率的增加,氯吡格雷组患者并没有观察到此种现象。氯吡格雷组有3例需输血治疗的活动性出血患者,但非活动性出血事件明显较替格瑞洛组少。总之,替格瑞洛较氯吡格雷并没有增加致命性出血风险,与文献报道一致[4],但出血事件与eGFR的相关性需进一步研究证实。

综上所述,在心血管主要危险因素控制下观察替格瑞洛组和氯吡格雷组患者MACE事件发生情

况,并没有发现二者之间有差异。同时采用TEG监测血小板活性,替格瑞洛组较氯吡格雷组血小板活性低,药物抵抗发生率低,但并没有发现其与MACE事件之间有相关性。而替格瑞洛组较氯吡格雷组轻微出血事件多,但并没有增加致命性出血风险。分析原因可能如下:本研究为单中心研究,样本量小;除出血事件及呼吸困难等药物不良反应停药外,部分患者由于其他原因停用替格瑞洛,并未服用到指南推荐的12个月,导致用药期间随访时间并不一致,从而导致收集到的再发MACE情况存在较大偏倚。因此替格瑞洛与氯吡格雷药物疗效的差异性以及药物抵抗与MACE发生风险之间的关系需要多中心、大样本队列研究进一步证实。

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