The Currently Widely Used Antiplatelet Regimens For CAS Patients Are Not The Right Ones: How Should They Be Changed

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Introduction

• CAS has been proposed as a safe alternative to CEA
• Intimal reaction to procedure can cause platelet activation, in-stent thrombosis, restenosis (ISR) and ischemic events
• Routine dual antiplatelet regimen (aspirin + clopidogrel) has been incorporated in guidelines for CAS since 2009

Immediate and Delayed Procedural Stroke or Death in Stenting Versus Endarterectomy for Symptomatic Carotid Stenosis

4597 patients with symptomatic carotid stenosis underwent CAS (n=2326) or CEA (n=2271) in 4 randomized trials. Compared with CEA, patients treated with CAS were at greater risk for immediate procedural events (4.7% versus 1.9%, OR 2.6) but not for delayed procedural events (2.5% versus 2.0%, OR 1.3).

Aspirin and clopidogrel resistance, thromboembolic complications and neurovascular stenting

Aspirin and clopidogrel resistance is often associated with an increased risk of thromboembolic complications. Loss-of-function (LOF) polymorphism in cytochrome P450 2C19 (CYP2C19) has been associated with clopidogrel resistance

Objective

• Dual antiplatelet regimen (aspirin + ticagrelor, a P2Y12 inhibitor) is an established approach for ACS or PTCA patients and was tested for PAD
• Lack of evidence on use of ticagrelor in CAS
• Comparative evaluation of ASA plus clopidogrel vs ASA plus ticagrelor on carotid ISR and thrombosis in a rabbit PTA±CAS model
Animal Model: 54 NZ ♂ White Rabbits 8wks old
Diet: High Cholesterol (1%) diet for 4 wks →
Aspirin: 30mg/kg/day starting 7d prior injury →

Power Analysis
Expected restenosis degree after injury 30±6%
Target diff detection between groups 25% (EffSize)
Significance level p<0.05 (α=0.05) Power (1-beta) 90%

<table>
<thead>
<tr>
<th>INJURY</th>
<th>CLINDOFOREL 10mg/kg/day</th>
<th>TICAGRELOR 25mg/kg/day</th>
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</thead>
<tbody>
<tr>
<td>PTA</td>
<td>A1=12</td>
<td>A2=12</td>
</tr>
<tr>
<td>PTA+STENT</td>
<td>B1=12</td>
<td>B2=12</td>
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Injury Technique
Anesthesia: Ketamine (25mg/kg)/Midazolame → Isoflurane 2%
RCCA cutdown → 5Fr Micropuncture set → 0.014 Coro Wire → DSA

PTA 2.25x10mm 10atm 30s
BMS 2.25x10mm Integrity Medtronic

Laboratory Investigation
- Platelet aggregation
- Lipid profile (K2EDTA)

Methods
Injury Technique – CAS example
RCA DSA → Balloon injury → BMS deployed → RCA post BMS DSA

Methods
Harvesting DSA
OCT: DragonFly Duo, St. Jude Medical
Methods

Histology

10% formaldehyde overnight → paraffin blocked → 3 non-consecutive slices (5μm) per slide at equal intervals centered on the injury site

![Images of tissue samples labeled RCA PTA CLOPIDOGREL and LCA CLOPIDOGREL.]

Results 1

Technical success

Lipid profile

Platelet aggregation

Weight

NO DIFFERENCE BETWEEN GROUPS

CLOPIDOGREL TICAGRELOR

Results 2

Balloon Injury – OCT Analysis

![Graph showing OCT analysis results for Balloon Injury with bars for CLOPIDOGREL and TICAGRELOR.]

Results 3

Injury + Stent – OCT Analysis

![Graph showing OCT analysis results for Injury + Stent with bars for CLOPIDOGREL and TICAGRELOR.]

Results 4

Injury + Stent – OCT Analysis

![Graph showing OCT analysis results for Mid-Stent with bars for CLOPIDOGREL and TICAGRELOR.]

Results 5

Histology

- Intima/(media + intima)(%) in RCA
  - PTA CLOP A1 = (68.48±12.31%)
  - PTA TIC A2 = (64.22±13.22%)
  - p=0.812

- LCA atherosclerotic lesions did not differ between groups (p>0.1)
Results 5

Thrombotic occlusions

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<td>PTA</td>
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</tr>
<tr>
<td>PTA+STENT</td>
<td>B1=3/12</td>
<td>B2=0</td>
</tr>
</tbody>
</table>

p=ns

Conclusions I

• In atherosclerotic rabbits undergoing carotid artery balloon injury, with or without stent implantation, clopidogrel and ticagrelor did not show any differential effects on the degree of neointimal formation and ISR.

Conclusions II

• When compared to clopidogrel treatment, Ticagrelor prevented thrombotic stent occlusions (NS).

• Clinical implementation of rapid CYP2C19 genotyping to guide antiplatelet therapy after CAS is probably needed.

Thank you