Clopidogrel, P2Y12 receptor inhibitor in Polyvascular Disease
일석삼조

一石三鳥

Three birds in a throw
Contents

• Atherothrombosis and polyvascular disease
• REACH Registry “Polyvascular Disease” and Recent Update
• Clinical Trials: Clopidogrel in Polyvascular Disease
• Indication of Clopidogrel, Prasugrel, and Ticagrelor
• International Guidelines related to “Clopidogrel”
• Conclusions
Atherosclerosis leads to any number of four possible types of thrombus formation:

Atherothrombosis Manifestations: Stroke, CAD, and PAD

Prevalence of Atherothrombosis (In Millions)

- IS 5.0
- CAD 15.8
- PAD 8.0

Mortality

Patients with a history of atherothrombosis is are most likely to die of a future atherothrombotic event

PAD=Peripheral Arterial Disease.
Atherothrombosis reduces life expectancy by approximately 8-12 years in patients aged over 60 years.

Average remaining life expectancy at age 60 (men)

- Healthy: 7.4 years
- History of Cardiovascular Disease: 9.2 years
- History of MI: 12 years

Patients with previous atherothrombotic events are at increased risk of further events

### Increased risk versus general population

<table>
<thead>
<tr>
<th>Previous event</th>
<th>MI</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>2–3 X (includes angina and sudden death*)¹</td>
<td>9 X²</td>
</tr>
<tr>
<td>MI</td>
<td>5–7 X (includes death)³</td>
<td>3–4 X (includes TIA)¹</td>
</tr>
<tr>
<td>PAD</td>
<td>4 X (includes only fatal MI and other CHD death †)⁴</td>
<td>2–3 X (includes TIA)¹</td>
</tr>
</tbody>
</table>

* Sudden death defined as death documented within one hour and attributed to coronary heart disease (CHD)
† Includes only fatal MI and other CHD death; does not include non-fatal MI

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The **REduction in Atherothrombotic Events for Continued Health (REACH)** Registry:
Objectives of the REACH Registry

▪ Primary objectives
  – to generate an international data set to extend knowledge of atherothrombotic risk factors and ischemic events in the real world, outpatient setting.
  – to improve our understanding of the prevalence and clinical consequences of atherothrombosis in patients across different parts of the world.

▪ Additional aim
  – to assess use of risk management strategies and 1-, 2-, 3- and 4-year outcomes in a broad outpatient population encompassing various geographical regions and physician specialties.

REACH Registry inclusion criteria

Must include:

1. Documented cerebrovascular disease
   Ischemic stroke or TIA
2. Documented coronary disease
   Angina, MI, angioplasty/stent/bypass
3. Documented historical or current intermittent claudication associated with ABI <0.9
4. At least 3 atherothrombotic risk factors

At least 1 of four criteria

1. Male aged ≥65 years or female aged ≥70 years
2. Current smoking >15 cigarettes/day
3. Type 1 or 2 diabetes
4. Hypercholesterolemia
5. Diabetic nephropathy
6. Hypertension
7. ABI <0.9 in either leg at rest
8. Asymptomatic carotid stenosis ≥70%
9. Presence of at least one carotid plaque

Patients aged ≥45 years

Signed written informed consent

Global population coverage within REACH Registry at baseline

- 67,888 patients enrolled at 5,587 centres in 44 countries were included in the baseline analysis\(^1\)

Patient enrollment

- At the time of the announcement of the REACH Registry, the initial goal was to enroll >50,000 patients across 35 countries.

- In total, 69,005 patients were enrolled between December 2003 and December 2004 at 5,587 centres across 44 countries.

  (at the time of the baseline analyses and publication, 67,888 enrolled patients had baseline data. Baseline data and enrolment eligibility for additional patients confirmed at the time of the 1-year analyses therefore the number of patients with baseline data differs in the 1-year vs. baseline publications)

- The initial follow-up period was 2 years, but centres were later invited to participate in an extension of the study to monitor and record patient outcomes at 3 years and 4 years after enrolment.

The REACH Registry

5 KEY FINDINGS
Atherothrombotic status of REACH Registry patients at baseline:
- 18.2% RFO (n=12 389)
- 59.3% CAD (n=40 258)
- 27.8% CVD (n=18 843)
- 12.2% PAD (n=8273)

(Cardiovascular risk-factor profiles were consistent across patient types and across all participating regions.¹)

CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; RFO, Risk Factors Only.

• 1 in 7 patients with symptomatic disease at baseline had a major vascular event or were rehospitalized for a vascular event / intervention procedure.¹

• CV event rates increased according to number of disease beds.¹

CV, cardiovascular; MI, myocardial infarction.

¹Steg PG et al. JAMA 2007;297:1197.
Event rates at 1 and 3 years according to disease

- At enrolment, 53.7% of CVD patients had stroke only, 27.7% had a history of TIA only, 18.5% had experience both a stroke and TIA.¹
- By the 3-year follow-up, 40% of PAD patients had experienced a CV/ischemic event or been rehospitalized for another event.²

TIA, Transient Ischemic Attack.

Patients with symptomatic disease at baseline had high rates of the combined endpoint of vascular death, MI, stroke and re-hospitalisation, despite currently available medications.¹

3-Year event rates appeared to be higher in men then women, driven mostly by higher rates of vascular death.²

²Alberts MJ on behalf of the REACH Registry investigators presented at Hotline Sessions at ESC 2009.
Predicting CV event rates at 4 years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvascular disease vs risk factors only</td>
<td>1.99 (1.78–2.24)</td>
</tr>
<tr>
<td>CHF (yes/no)</td>
<td>1.71 (1.60–1.83)</td>
</tr>
<tr>
<td>Ischemic event ≤ 1 year vs no ischemic event</td>
<td>1.71 (1.57–1.85)</td>
</tr>
<tr>
<td>History of diabetes (yes/no)</td>
<td>1.44 (1.36–1.53)</td>
</tr>
<tr>
<td>Ischemic event &gt; 1 year vs no ischemic event</td>
<td>1.41 (1.32–1.51)</td>
</tr>
<tr>
<td>Single vascular disease vs risk factors only</td>
<td>1.39 (1.25–1.54)</td>
</tr>
<tr>
<td>Body mass index &lt; 20 kg/m² (yes/no)</td>
<td>1.30 (1.14–1.49)</td>
</tr>
<tr>
<td>Current smoker (current vs former vs never)</td>
<td>1.30 (1.20–1.41)</td>
</tr>
<tr>
<td>E. Europe and Middle East vs other regions</td>
<td>1.28 (1.19–1.39)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter (yes/ no)</td>
<td>1.28 (1.18–1.38)</td>
</tr>
<tr>
<td>Gender (male vs female)</td>
<td>1.14 (1.07–1.21)</td>
</tr>
<tr>
<td>Age (per 1 year)</td>
<td>1.04 (1.03–1.04)</td>
</tr>
<tr>
<td>Aspirin (yes/no)</td>
<td>0.93 (0.87–0.98)</td>
</tr>
<tr>
<td>Statins (yes/no)</td>
<td>0.73 (0.69–0.77)</td>
</tr>
<tr>
<td>Japan vs. other regions</td>
<td>0.70 (0.63–0.77)</td>
</tr>
</tbody>
</table>

*Bhatt DL on behalf of the REACH registry Investigators. Presented at Clinical Trial Update session at ESC 2010.
5 Key Findings of the the REACH Registry

- A significant proportion of the symptomatic population have **polyvascular disease**. About **25%** of patients with CAD have polyvascular disease.
- CV event rates **increased** in patients with the **number of disease beds**.
- 3-Year event rates appeared to be **higher** then 1-year.
- Patients with symptomatic disease at baseline had high rates of the combined endpoint of vascular death, MI, stroke and re-hospitalisation, despite currently available medications.
- Patients with **polyvascular disease** had much worse overall outcomes.
Long-term prognosis of patients with PAD with or without polyVD

- 2933 PAD patients were screened prior to surgery for concomitant documented CV disease and coronary artery disease.
- The number of affected vascular beds (AVB) was determined.
- One-AVB: PAD
- 2-AVB: PAD + CAD or PAD + CVD
- 3-AVB: PAD + CAD + CVD

Polyvascular disease in PAD patients is independently associated with an increased risk for all-cause and cardiovascular mortality during long-term follow-up.

Patients were stratified according to the presence of PAD, CVD, neither, or both. In-hospital management, treatment at discharge and outcomes at 6 months were recorded. (6745 patients)

- 597 (8.85%) had PAD
- 392 (5.8%) had CVD
- 131 (1.94%) had both
- 5625 (83.4%) had neither.

Patients with acute coronary syndrome and concomitant arterial disease had more extensive coronary artery disease and poorer outcomes, both in hospital and at 6 months, but frequently did not receive regularly recommended treatment.

Ferreira-González I et al., the MASCARA Study investigators. Rev Esp Cardiol 2009 Sep;62(9):1012-21.
Relative Risk of Stroke after MI

Patients (N=2,160) hospitalized for MI were followed for a median of 5.6 years*.

The risk of stroke after MI in the first month is 44x that of the general population.

The risk for stroke remained 2–3x higher than expected during the first 3 years after MI.

The unadjusted risk reduction for death was calculated to be 3.94 (3.32–4.67, P<0.001).

* Range = 0–22.2 years.
SMR=Standardized Mortality Ratio.
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Proven Efficacy of Clopidogrel

- Cerebrovascular disease (CVD)
  - Ischemic stroke, TIA
  - CAPRIE, CARESS, MATCH

- Coronary artery disease (CAD)
  - Acute coronary syndrome (ACS; unstable angina, STEMI and non-STEMI)
  - CURE, PCI-CURE, CLARITY, CREDO
  - CAPRIE

- Peripheral arterial disease (PAD)
  - Critical limb ischemia, intermittent claudication, limb loss.
  - CAPRIE, CASPAR
CAPRIE: Design

N=19,185

Patient Population
- Patients with recent MI, recent IS, or established PAD

n=9,599

Clopidogrel 75 mg

n=9,586

ASA 325 mg

Follow-up 1 to 3 years

Primary End Point
- First occurrence of IS, MI, or vascular death

384 centers
- 16 countries

CAPRIE population (vs. REACH population)

**CAPRIE population**¹ (n=19,185)

- CAD 29.9%
- PAD 19.2%
- CVD 24.6%
- Other 11.9%

**REACH population**² (n=67,888)

- CAD 44.6%
- PAD 4.7%
- CVD 16.6%
- Other 8.4%

CAPRIE: Efficacy of Clopidogrel vs Aspirin in MI, IS, or Vascular Death (N=19,185)

Median follow-up=1.91 years

- Clopidogrel: 10.6%
- ASA: 9.8%

$P=0.045^2$

$8.7\%^*$

**Overall RRR$^{1,2}$**

Study subjects had either recent MI, recent IS, or established PAD

* ITT analysis.
RRR=Relative Risk Reduction; ITT=Intent-To-Treat.
2. PLAVIX Prescribing Information, sanofi-aventis U.S. LLC.
CURE (Clopidogrel in Unstable angina to prevent Recurrent Events)  
ACS medical or PCI

- Design

n = 12,562
28 countries

Patients with acute coronary syndrome
(unstable angina or non-Q-wave myocardial infarction)

Double-blind treatment up to 12 months

Clopidogrel 75mg o.d.  
(n = 6,259)

Placebo  
1 tab o.d.  
(n = 6,303)

R = Randomization

CURE: Early and Long-term Efficacy of Clopidogrel\textsuperscript{1,2}

Cumulative events
(myocardial infarction, stroke, or cardiovascular death)

*On top of standard therapy (including acetylsalicylic acid)

2. Data on file, 2002, p73 internal CSR-EFC 3307
PCI-CURE: 31% RRR at long-term

Endpoint: MI or CV death

Placebo* (n = 1,345)

Clopidogrel* (n = 1,313)

Median time to PCI

Cumulative hazard rate

Days of follow-up

31% RRR

p = 0.002

*On top of standard therapy (including ASA)

1Overall (including events before and after PCI)

**CLARITY (CLopidogrel as Adjunctive Reperfusion Therapy): Study design**

Double-blind, randomized, placebo-controlled trial in patients aged 18–75 years with STEMI ≤ 12 hours

- **Clopidogrel 300 mg loading dose / 75 mg QD**

- **Study treatment until angiography (2–8 days) or hospital discharge (maximum 8 days)**

- **Clinical follow-up at 30 days**

- **Thrombolysis, heparin and ASA**

- **n = 3,491**

- **Placebo**

- **n = 1,739**

**Primary endpoint:** occluded artery (TIMI flow grade [TFG] 0/1), death/MI by time of angiography

*ASA = 150–325 mg (if no ASA within prior 24 h). Heparin if fibrin-specific thrombolytic
†All patients: ASA 75–162 mg/day plus other standard care
**CLARITY: Primary endpoint**

- Odds ratio = 0.64 (95% CI 0.53–0.76)
- 36% Odds reduction
- 21.7

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### Pivotal studies in ACS

#### Randomization (R)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Randomization</th>
<th>Diagnostic (No CA)</th>
<th>Coronary Angiography (CA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CURRENT OASIS</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>CA, R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLATO</td>
<td>R</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Initiation

- Pre Cath. Lab. (Ambul., ER)
- Cath. Lab.

#### Follow-up

- 30 days
- 1 year

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Initiation</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>R</td>
<td>CABG, PCI, Med. Treat., Non ACS</td>
</tr>
<tr>
<td>CURRENT OASIS</td>
<td>R</td>
<td>CABG, PCI, Med. Treat., Non ACS</td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
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</tr>
<tr>
<td>PLATO</td>
<td>R</td>
<td>CABG, PCI, Med. Treat., Non ACS</td>
</tr>
</tbody>
</table>

- Unknown due to non-systematic CA

#### Notes

- UA/NSTEMI
- CABG: Coronary Artery Bypass Graft
- PCI: Percutaneous Coronary Intervention
- Med. Treat.: Medical Treatment
- Non ACS: Non-Acute Coronary Syndrome
- PRASUGREL
- PLATO
- Ticagrelor
- STEMI: ST-Elevation Myocardial Infarction
- TRITON-TIMI 38
- who underwent PCI
- CA known
- treated early before CA
Proven Efficacy of Clopidogrel

- **Cerebrovascular disease (CVD)**
  - Ischemic stroke, TIA
  - CAPRIE, CARESS, MATCH

- **Coronary artery disease (CAD)**
  - Acute coronary syndrome (ACS; unstable angina, STEMI and non-STEMI)
  - CURE, PCI-CURE, CLARITY, CREDO CAPRIE

- **Peripheral arterial disease (PAD)**
  - Critical limb ischemia, intermittent claudication, limb loss.
  - CAPRIE, CASPAR
Indication coverage

- ACS
- Stroke
- PAD
- A-fib

- Clopidogrel
- Prasugrel (PCI only)
- Ticagrelor
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## Stroke - International Guidelines

<table>
<thead>
<tr>
<th>Class/Level of Evidence</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemic Stroke 또는 TIA</strong></td>
<td>• 혈청성 뇌졸중 또는 TIA가 있었던 extracranial carotid or vertebral atherosclerosis 환자에게 이스피린 단독 75-325mg/d, 플리박스 단독 75mg/d 또는 이스피린/디퍼리디올 서방형 복합제 (25mg+200mg, 1일 2회)를 권장</td>
</tr>
<tr>
<td><strong>Secondary Stroke Prevention</strong></td>
<td>• 아스피린과 플리박스의 뇌졸중 약물에 의한 증상은 유사한 출혈 위험에 있어, 출혈 위험 때문에 피판 사용이 금지(hemorrhagic contraindication)인 환자에게 권장되지 않음</td>
</tr>
<tr>
<td><strong>Ischemic Stroke (Secondary prevention)</strong></td>
<td>• 아스피린과 플리박스의 뇌졸중 약물에 의한 출혈 위험에 있어, 출혈 위험 때문에 피판 사용이 금지(hemorrhagic contraindication)인 환자에게 권장되지 않음</td>
</tr>
<tr>
<td><strong>2008 ESO Guidelines for Management of Ischemic Stroke and TIA</strong></td>
<td>• 혈응고요법이 필요하지 않은 환자에게 플리박스 단독 투여 권장</td>
</tr>
<tr>
<td><strong>2008 ACCP - Antithrombotic and Thrombolytic Therapy for Ischemic Stroke</strong></td>
<td>• 비만성 뇌졸중 또는 TIA 환자에게 초기요법으로 플리박스 75mg 투여 권장</td>
</tr>
<tr>
<td>• 비만성 뇌졸중 또는 TIA 환자에게 아스피린보다 플리박스 투여 권장</td>
<td></td>
</tr>
<tr>
<td>• 아스피린에 알러지가 있는 환자에게 플리박스 투여 권장</td>
<td></td>
</tr>
</tbody>
</table>
# ACS - International Guidelines

<table>
<thead>
<tr>
<th>환자별</th>
<th>Class/ Level of Evidence</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With UA/NSTEMI**¹ | IB | • 아스피린을 투여 할 수 없는 환자*에게 플러리바스 부하용량 투여 후 유지용량 투여  
• 과민성 또는 주요혈관경화가 있는 경우 |
| | IA | • PCI 시술 예정인 환자에게 PCI 시술 전 또는 시술 시 최대한 빠리 플러리바스 부하용량 300mg 에서 600mg 까지 투여 권장  
• PCI 시술 받은 환자에게 플러리바스 75mg을 적어도 12개월 투여 권장 |
| | IB | • 초기 침습적 치료를 받는 중등도/고위험군 환자에게 이중항혈소판요법이 권장되며, 아스피린에 추가되는 두 번째 항혈전제로서  
- PCI 시술 전, 플러리바스 투약  
- PCI 시술 중, PCI 시술 전에 플러리바스 투어가 안 되었다면, 플러리바스 투어 권장 |
| **UA/NSTEMI** (initial invasive strategy) | IB | • 항응고요법과 아스피린에 가능한 빠리 플러리바스(부하용량 투여 후 유지용량)를 추가해야 하며 적어도 1개월에서 가급적 1년까지 투여할 것을 권장 |
| | IA | • 출혈 위험과 같은 투여 급기 사유를 제외하고 P2Y12 receptor 억제제는 아스피린에 가능한 빠리 추가되어야 하며 12개월 동안 유지 |
| | IB | • 플러리바스를 포함한 초기치료요법에 상관 없이, 혈혈성 사건의 중증-고위험군 환자에게 티아그레必然会 부하용량 180mg, 유지용량 90mg 일 2회)가 권장 (플라임 투여 중단 후 티아그레必然会 투여 시작) |
| | IB | • coronary anatomy가 확인되고, PCI 시술 예정인 P2Y12 receptor 억제제를 처음 사용하는 환자(특히 난노환자)에게 생명을 위험하는 출혈이나 투여 급기 사유가 없다면 프리니그릴  
(부하용량 60mg, 유지용량 10mg)가 권장 |
| NSTEAMI | IA | • 티아그레必然会 티아그레必然会 투여할 수 없는 환자에게 플러리바스 부하용량 300mg, 유지용량  
75mg/d 투여 권장 |
| | IB | • 티아그레必然会 또는 프리니그릴 투여가 가능한 환자에게 티아그레必然会 (부하용량 600mg 또는 300mg 부하용량 투여 후 PCI 시 300mg 추가) 투여 권장 |
| IIaB | • 출혈의 위험이 증가하지 않는 PCI 시술 환자에게 적어도 첫 7일 동안 플러리바스 유지용량 150mg 투여가 고려되어야 함 |

¹ 2011 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation²
# ACS - International Guidelines

<table>
<thead>
<tr>
<th>2011 AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease[^3]</th>
</tr>
</thead>
</table>
| **CAD** | IA | • 아스피린에 투여 금기 사유가 있는 환자를 제외한 CAD 환자에게 아스피린 75-162mg/d를 권장  
  • 아스피린에 과민증 또는 주요위장장애가 있는 환자에게 플라비كس 75mg/d가 대체요법으로 권장 |
| ACS 환자 또는 스텝트 시술한 PCI 환자 | IA | • ACS 환자 또는 스텝트 시술한 PCI 환자에게 아스피린과 P2Y12 receptor 억제제 병용요법을 권장  
  • BMS 또는 DES PCI를 시술한 환자에게 플라비كس 75mg/d, 프리수그릴 10mg/d 또는  
    티코글리리 90mg(1일 2회)을 적어도 12개월 투여 권장 |
| **CABG** | IIaC | • 아스피린 75-162mg/d와 플라비كس 75mg/d의 병용요법이 고려 |
| Stable CAD | IIbB | • Stable CAD 환자에게 아스피린 1일 용량 75~162mg과 플라비كس 1일 용량 75mg의 병용요법이 고려 |
| **축성동맥경화증** | IIbA | • 축성동맥경화증 환자의 치료를 위해 항응고요법(아스피린 또는 비타민 K 긁항제)보다는 항혈소판제제를 권장  
  • 아스피린 (and/or 플라비كس)과 외피판의 병용투여는 출혈의 위험이 있고 면밀히 관찰 권장 |


| Primary/non-primary PCI 예정인 STEMI 환자 | IC | • PCI 시술 전 또는 시술 시에 적어도 플라비كس 부하용량 300mg에서 600mg까지 투여 |
| Non-primary PCI 예정인 STEMI 환자 | IC | • 혈전응해제와 플라비كس를 모두 투여 받은 환자에게, 플라비كس 투여를 계속 권장  
  • Thienopyridine계열 약물투여 없이 혈전응해제만 투여 받은 환자에게 플라비كس 부하용량  
    300mg에서 600mg까지 투여 권장 |
| PCI (BMS 또는 DES) 시술 받는 ACS 환자 | IB | • 플라비كس 75mg을 적어도 12개월까지 투여 권장  
  • DES-PCI 시술받는 ACS 환자에게 플라비كس 15개월 이상 투여 고려 가능 |
| UA/NSTEMI | IB | • 침습적 치료를 받는 환자에게 이상 항혈소판요법을 투여할 것을 권장  
  • 아스피린은 바로 투여하고, PCI 시술 전 또는 시술 시에 플라비كس가 두 번째 항혈전제로로 권장 |

[^3]: International Guidelines
[^4]: International Guidelines
## A-Fib / PAD - International Guidelines

### A-Fib

<table>
<thead>
<tr>
<th>환자별</th>
<th>Class/ Level of Evidence</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation</strong>&lt;sup&gt;10&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>IIbB</td>
<td>• 환자의 선호도 혹은 OAC를 안전하게 지속할 수 있는지에 대한 의사의 평가를 근거로 OAC(Warfarin) 투여가 적합하지 않은 심방세동 환자에서 뇌졸중을 포함한 주요 혈관질환 사망의 위험을 낮추기 위해 아스피린에 플러바스코를 추가하는 것을 고려</td>
</tr>
</tbody>
</table>

### PAD

<table>
<thead>
<tr>
<th>환자별</th>
<th>Class/ Level of Evidence</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2011 AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>IA</td>
<td>• 증상이 있는 혈관질환성 하지 PAD 환자에게 아스피린 75–325mg/d 또는 플러바스코 75mg/d 을 권장</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>환자별</th>
<th>Class/ Level of Evidence</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease</strong>&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>B</td>
<td>• 축상혈관성 하지 PAD 환자*에게 심근경색, 뇌졸중 또는 혈관관사망의 위험을 감소시키는데 아스피린을 대체할 수 있는 항혈소판요법으로 플러바스코 권장</td>
</tr>
<tr>
<td>* Including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>환자별</th>
<th>Class/ Level of Evidence</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TASC II guideline 2007 Inter-Society Consensus for the Management of PAD Recommendation. Antiplatelet therapy in PAD</strong>&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>B</td>
<td>• Symptomatic PAD를 가진 환자에게 심혈관 사망의 감소에 플러바스코가 효과적</td>
</tr>
</tbody>
</table>
Take home messages

1. Patients with CAD or CVD or PAD have high risk for the development of another event or other diseases.
2. CV event rates increased in patients with the number of disease beds.
   → Comprehensive prevention of atherothrombotic polyvascular disease as a systemic vascular disease is important for improving clinical prognosis.
3. Only clopidogrel has both evidence and a broad indication for polyvascular disease.
CRUSADE registry: Prior polyVD, risk factor for adverse ischemic outcomes in ACS

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>$\chi^2$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.26</td>
<td>1.24, 1.28</td>
<td>605</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (per 10 mm Hg)</td>
<td>0.94</td>
<td>0.93, 0.94</td>
<td>295</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Signs of CHF</td>
<td>2.32</td>
<td>2.06, 2.61</td>
<td>195</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1.31</td>
<td>1.25, 1.37</td>
<td>119</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive cardiac marker</td>
<td>1.94</td>
<td>1.69, 2.24</td>
<td>84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (per 10 b.p.m.)</td>
<td>1.04</td>
<td>1.04, 1.05</td>
<td>83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST-depression *</td>
<td>1.32</td>
<td>1.25, 1.38</td>
<td>68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transient ST-elevation</td>
<td>1.31</td>
<td>1.19, 1.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1.49</td>
<td>1.24, 1.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.16</td>
<td>1.11, 1.20</td>
<td>48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Polyanlsed disease *&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td></td>
<td>43</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>One vascular bed</td>
<td>1.07</td>
<td>1.02, 1.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two vascular beds</td>
<td>1.26</td>
<td>1.19, 1.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three vascular beds</td>
<td>1.31</td>
<td>1.17, 1.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.88</td>
<td>0.85, 0.92</td>
<td>39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior CHF</td>
<td>1.23</td>
<td>1.15, 1.32</td>
<td>33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.91</td>
<td>0.87, 0.94</td>
<td>25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiologist</td>
<td>0.86</td>
<td>0.81, 0.92</td>
<td>19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.08</td>
<td>1.03, 1.12</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Patients were categorized as having prior 0, 1, 2, or 3 affected arterial beds. (95749 patient)
- Factors associated with the composite outcome of in-hospital death, MI, stroke, or congestive heart failure

Identification of polyvascular patients in clinical trial and real world populations may provide an opportunity to reduce their excess risk with intensive secondary prevention efforts.

## CAPRIE: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin (325 mg/day)</th>
<th>Clopidogrel (75 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage(^1)</td>
<td>0.49</td>
<td>0.35</td>
</tr>
<tr>
<td>Gastrointestinal bleeding(^1)</td>
<td>2.66(^*)</td>
<td>1.99</td>
</tr>
<tr>
<td>Gastrointestinal ulcers(^2)</td>
<td>1.15(^*)</td>
<td>0.68</td>
</tr>
<tr>
<td>Indigestion/nausea/vomiting(^1)</td>
<td>17.59(^*)</td>
<td>15.01</td>
</tr>
<tr>
<td>Diarrhea(^1)</td>
<td>3.36</td>
<td>4.46(^*)</td>
</tr>
<tr>
<td>Rash(^1)</td>
<td>4.61</td>
<td>6.02(^*)</td>
</tr>
<tr>
<td>Neutropenia(^1)</td>
<td>0.17</td>
<td>0.10</td>
</tr>
</tbody>
</table>

\(^1\)CAPRIE Steering Committee. Lancet 1996;348:1329-1339.

\(^*\)\(p<0.05\)
n = 2,658 CURE patients undergoing PCI

Pretreatment

Placebo + ASA*

PCI

30 days Post-PCI

Clopidogrel + ASA*

Open-label thienopyridine

Placebo + ASA*

End of follow-up Up to 12 months after randomization

R

n = 1,345

n = 1,313

*In addition to other standard therapies
PCI-CURE: 30-day results CV death, MI, or urgent revascularization

- Placebo: 30% RRR $\rho = 0.03$, $n = 2,658$
- Clopidogrel

CV death, MI, RI → urgent revasc.

Placebo

Clopidogrel

20% RRR

Percentage with endpoint (%)

Days

Odds ratio = 0.80
(95% CI 0.65–0.97)

p = 0.03

**CREDO (Clopidogrel for Reduction of Events During Observation) PCI short vs long term DAPT**

**Design**

Objective: evaluate efficacy and safety of clopidogrel 1 year vs 1 month in patients undergoing urgent or elective PCI; determine the benefit of a 300 mg LD 3–24 h prior to PCI

99 sites, US, Canada

2,116 patients urgent or elective PCI

*On top of standard therapy including ASA (325 mg)
†On top of standard therapy including ASA (81–325 mg)

Steinhubl SR *et al.* JAMA 2002;288:2411–2420
CREDO: Long-term efficacy of clopidogrel

1-year results (Stroke, MI or death)

<table>
<thead>
<tr>
<th>Months from randomization</th>
<th>Placebo (+ ASA)†</th>
<th>Clopidogrel (+ ASA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11.5%</td>
<td>8.5%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 2,116

27% RRR
p = 0.02

†All patients received clopidogrel post-PCI up to Day 28
Steinhubl SR et al. JAMA 2002;288:2411–2420
CASPAR: Study Design

Clopidogrel 75 mg/day

ASA 75–100 mg/day

Double-blind treatment up to 193 events (event-driven trial)

ASA 75–100 mg/day

Placebo 1 tab/day

Follow-up: min 6 months – max 24 months

2 to 4 days

Bypass surgery

R=Randomization stratified by type of graft (venous/prosthetic).
K-M Curves of Time to Primary Outcome Event: Each Type Of Graft (ITT)

Venous grafts Hazard ratio = 1.25 [95% CI 0.94–1.67], P=NS

Prosthetic grafts Hazard ratio= 0.65 [95% CI 0.45–0.95], P=0.025

Treatment by type-of-graft interaction

P=0.008

Time to Event (Days)

Proportion event-free
CARESS: Study Design

- Randomized, double-blind, placebo-controlled, parallel groups (n~100)

D-1  D1  D2  D7 ± 1

Clopidogrel 300 mg

Clopidogrel 75 mg o.d.

ASA 75 mg o.d. to all patients from D1 to D7 ± 1

Placebo

Placebo o.d.

Screening

MES detection

MES detection

MES detection
Clopidogrel Significantly Reduces the Incidence of MES in Patients with Recent Symptomatic Carotid Stenosis

Primary Endpoint Results: Number of MES+ Patients at D7**

- **Placebo**: 100% 100%
- **Clopidogrel**: RRR 25.2% 2%
  - *p* = 0.078
- **Placebo**: 100%
- **Clopidogrel**: RRR 37.3% 3%
  - *p* = 0.011

*On a background of ASA 75 mg qd

**Offline analysis
The MATCH Trial: Study Objectives and Design

The MATCH Trial is designed to determine the efficacy and safety of ASA compared to placebo in high-risk cerebrovascular patients receiving clopidogrel 75 mg and other standard therapies.

*All patients received clopidogrel and other standard therapies

Part 3

Adding ASA to Clopidogrel Shows a Non-Significant Trend for the Reduction of Major Vascular Events in High-Risk Cerebrovascular Patients

Primary Endpoint (ITT)

IS, MI, VD, rehospitalization for acute ischemic event

<table>
<thead>
<tr>
<th>Group</th>
<th>IS, MI, VD, rehospitalization rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA*</td>
<td>0.12</td>
</tr>
<tr>
<td>Placebo*</td>
<td>0.16</td>
</tr>
</tbody>
</table>

RRR: 6.4% (p=0.244)

Part 3

*All patients received clopidogrel and other standard therapies