

# 순환기 질환에서 항응고 및 항혈소판 요법

정 명 호

## The Anticoagulant and Antiplatelet Therapy in Cardiovascular Patients

Myung Ho Jeong, MD, PhD

The Heart Center, Chonnam University Hospital, Kwang Ju, Korea

### 서 론

60 70 warfarin  
, 75  
가  
, 60 lone atrial  
fibrillation 가  
가 .  
warfarin, heparin, direct SPAF - III<sup>6)</sup>  
thrombin inhibitor 가  
platelet glycoprotein IIb/IIIa receptor blocker, ticlo - 가 aspirin(325 mg/  
pidine, cilostazol genetic therapy day) fixed dose warfarin(INR = 1.2 - 1.5)  
adjusted dose warfarin(INR 2 - 3)

### Warfarin

adjusted dose warfarin  
(7.9% : 1.1%, p<0.0001).  
warfarin work - up  
warfarin  
AFSAD, BAATAF, CAFA, SPAF - 1, SPINAF<sup>1-5)</sup> adjusted dose  
International normalized ratio(INR)<sup>7)</sup>  
1.8 4.2 , 25%  
70% , 1%  
160 mmHg , 75  
가  
: , 501 - 757 1 8  
: (062) 220 - 6243 : (062) 228 - 7174  
가  
가<sup>8-10)</sup>

American College of Chest Physician Guidelines (sudden cardiac death)

48

3, 4, 7, 8

heparin warfarin

heparin 4 5 (PT) 가

prothrombin time, warfarin

24%, 32% 가

17)

헤파린

11)(12)

warfarin

warfarin 가

Warfarin

SOLVE<sup>14)</sup> trial

warfarin

15)

warfarin

INR 2 3, 4

INR 1.5

가 INR 3.0

INR 1.3

INR 1.8

Vit K 1 mg

16)

histidine - rich glycoprotein, vitronectin, lipoprotein, fibronectin, fibrinogen

platelet factor 4, high - molecular - weight von Willebrand factor

acute phase reactants

가 standard unfractionated heparin

fibrin phospholipid

thrombin Factor Xa

, (low molecular weight heparin : LMWH) , <sup>25)</sup> da -  
 2,000 6,000 Dalton lteparin <sup>26)</sup>  
 .  
 , 가 가 .  
 , LMWH heparinoids 가  
 , PF4 가 , IST<sup>27)</sup>  
 . TOAST<sup>28)</sup> heparin heparinoids  
 가 .  
 , 6  
 , (adjusted dose heparin), <sup>29)</sup>  
 , <sup>18)</sup>  
 (low dose heparin) 65% APTT monitoring 가  
 , LMWH 가 .  
 warfarin , prot -  
 hrombin time Direct thrombin inhibitor  
 warfarin PT Hirudin 65  
 . LMWH 7000 . E. coli  
 가 , , thrombin 10  
 . Hirudin  
 thrombin 가 , 50  
<sup>19)20)</sup> LMWH APTT 65 . LMWH  
 monitoring fibrin thrombin  
 가 가  
 가 platelet factor IV  
 ,  
<sup>21)</sup>  
 Q dalteparin ,  
 (FRISC, FRIC)<sup>22)23)</sup> , 가  
 60% Bivalirudin  
 . Enoxaparin  
 , ,  
<sup>24)</sup> , dalteparin  
 가 , , ,

Hirulog Angioplasty Trial<sup>30)</sup>

EPILOG trial<sup>31)</sup> . ab -

1100 ciximab

PTCA HELVETICA trial<sup>32)</sup> .

hirudin , abciximab GPIIb/IIIa

hirudin , 가

hirudin . Eptifibatide,

ombin inhibitor . , direct thr - Tirofiban and Lamifiban, Xemilofiban ,

41)42)

Ticlopidine, clopidogrel, cilostazol

bivalirudin [CACHET ;

Comparison of Abciximab Complications with Hiru - Ticlopidine and clopidogrel

log(and Back - up Abciximab) Events Trial]<sup>33)</sup>가 ADP(adenosine 5 - diphosphate) , ADP

가 fibrinogen GP IIb/IIIa

Platelet glycoprotein IIb/IIIa blocker von Willebrand factor

Glycoprotein(GP) IIb/IIIa receptor me - 43 - 45)

gakaryocyte fibrin - Ticlopidine

ogen 가 가

GP IIb/IIIa receptor monoclonal antibody (warfarin or aspirin) 가

c7E3 Fab 가 46 - 53)

0.25 mg/kg bolus 10 μ

g/minute , 30

GP , 4

6 50% , , , , ,

1980 abciximab

가 elective

PTCA elective stent , 2 3

(30 ) nonfatal MI 50% , ticlopidine 500 mg clo -

EPIC, IMPACT - II, RESTORE, pidogrel 75 mg , 4 7

CAPTURE, EPILOG, EPISTENT 가

34 - 38) , 7 10

nonfatal MI 가

39)40) ,

가 , 가 가

3.5% . 가  
3 2 ,<sup>58)</sup> 6  
59 - 61)  
Cilostazol  
Thrombotic thrombocytopenic purpura(TTP) 가  
60 가  
33% . stazol 가<sup>62)</sup> Cilo -  
Clopidogrel ,  
0.1% aspirin .  
20% Genetic therapy  
Clopidogrel ticlopidine carboxymethyl , 가  
side group FDA . Prostacyclin synthetic pathway,  
nitric oxide synthase, thrombin inhibitor, hirudin, th -  
rombomodulin, plasminogen activator<sup>64 - 67)</sup>  
Ticlopidine clopidogrel encoding .  
GP IIb/IIIa, Bival - 가 in vitro  
irudin . 가 in vivo  
Cilostazol  
Cilostazol in vitro<sup>54)</sup> 가 .  
, dipyridamole ticlopidine  
가 , in vivo  
<sup>55)</sup> Cilostazol cyclic AMP  
(adenosine monophosphate) phosphodiesterase III . PTCA Stent , byp -  
, c - AMP 가 ass graft  
가 .  
, Cilos -  
tazol c - AMP 가  
Cilostazol .  
가  
<sup>56)</sup><sup>57)</sup> .  
t - PA, urokinase, hirudin, cyclooxygenase  
in vivo<sup>68 - 70)</sup>  
ticlopidine .

## 결론

가

가

## REFERENCES

- 1) Stroke Prevention in Atrial Fibrillation Investigators. *Stroke prevention in atrial fibrillation study: Final results.* *Circulation* 1991;84:527-39.
- 2) Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. *Placebo controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAD study.* *Lancet* 1989;1:175-9.
- 3) Boston Area Anticoagulation Trial For Atrial Fibrillation Investigators. *The effect of low-dose warfarin on the risk of stroke in patients with non-rheumatic atrial fibrillation.* *N Engl J Med* 1990;323:1505-11.
- 4) Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. *Canadian Atrial Fibrillation Anticoagulation (CAFA) Study.* *J Am Coll Cardiol* 1991;18:349-55.
- 5) Ezedowitz MD, Bridgers SL, James KE, Carlineer NH, Colling CL, Gornick CC, et al. *Warfarin in the prevention of stroke associated with non-valvular atrial fibrillation (SPINA).* *N Engl J Med* 1992;32:1406-12.
- 6) Stroke prevention of Atrial Fibrillation Investigators. *Adjusted dose warfarin versus low-intensity, fixed dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomized clinical trial.* *Lancet* 1996;348:633-8.
- 7) Feinberg WM. *Anticoagulation for prevention of stroke.* *Neurology* 1998;51 (S):S20-22.
- 8) Kannel W, Abbott RD, Savage DD, McNamara PM. *Epidemiological features of chronic atrial fibrillation: The Framingham Study.* *N Eng J Med* 1982;306:1018-22.
- 9) Benifamin EJ, D Agostino RB, Belanger AJ, Wolf PA, Levy D. *Left atrial size and the risk of stroke and death: The Framingham Heart Study.* *Circulation* 1995;92:835-41.
- 10) Giardina EV. *Atrial fibrillation and stroke: Elucidating a newly discovered risk factor.* *Am J Cardiol* 1997;80(4C): D11-8.
- 11) Vaitkus PT, Barnathan ES. *Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: A meta analysis.* *J Am Coll Cardiol* 1993;22:1004-9.
- 12) Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. *Placebo controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: The Copenhagen AFASAD study.* *Lancet* 1989;1:175-9.
- 13) Loh E, Sutton MS, Wun CC, et al. *Ventricular dysfunction predicts stroke following myocardial infarction.* *N Engl J Med* 1997;336:251-7.
- 14) Dries DL, Rosenberg Y, Waclawiw M, Domanski M. *Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: Evidence for gender differences in the studies of left ventricular dysfunction trials.* *J Am Coll Cardiol* 1997;29:1074-80.
- 15) Koniaris LS, Goldhaber SZ. *Anticoagulation in dilated cardiomyopathy.* *J Am Coll Cardiol* 1998;31:745-8.
- 16) Kearon C, Hirsh J. *Management of anticoagulation before and after elective surgery.* *N Engl J Med* 1997;May 22: 1506-11.
- 17) Dries DL, Domanski MJ, Waclawiw MA, Gersh BJ. *Effect of Antithrombotic Therapy on Risk of Sudden Coronary Death in Patients With Congestive Heart Failure.* *Am J Cardiol* 1997;79:909-13.
- 18) Siragusa S, Cosmi B, Piovella F, Hirsh J, Ginsberg JS. *Low-molecular weight heparin and unfractionated heparin in the treatment of patients with acute venous thromboembolism: Results of a meta analysis.* *Am J Med* 1996;100: 269-77.
- 19) Prandoni P, Lensing AW, Buller HR, Carta M, Cogo A, Vigo M, et al. *Comparison of subcutaneous low molecular weight heparin with intravenous standard heparin in proximal deep vein thrombosis.* *Lancet* 1992;339:441-5.
- 20) Hull RD, Raskob GE, Pineo GF. *Subcutaneous low molecular weight heparin compared with continuous intravenous heparin in the treatment of proximal vein thrombosis.* *N Eng J Med* 1992;326:975-82.
- 21) Gurfinkel EP, Manos EF, Mejail RI, Cerda MA, Duronoto EA, Garcia CN, et al. *Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia.* *J Am Coll Cardiol* 1995; 26:313-8.
- 22) FRISC Study Group. *Low molecular weight heparin during instability in coronary artery disease.* *Lancet* 1996; 347:561-8.
- 23) Klein W, Buchwald A, Hillis SE, Monrad S, Sanz G, Turpie AGG, et al. *for the FRIC Investigators. Comparison of low molecular weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease.* *Circulation* 1997;96:61-8.
- 24) Cohen M, Demers C, Gurfinkel MD, Trupie AGG, Fromell GJ, Goodman S, Lnager A, et al. *for the ESSENCE study group. A comparison of low molecular weight heparin with unfractionated heparin for unstable coronary artery disease.* *N Engl J Med* 1997.
- 25) Kontny F, Dale J, Abildgaard U, Pedersen TR. *Randomized Trial of Low Molecular Weight Heparin in Prevention of Left Ventricular Thrombus Formation and Arterial Embolism After Acute Anterior Myocardial Infarction: The Fragmin in Acute Myocardial Infarction (FRAMI) Study.* *J Am Coll Cardiol* 1997;30:962-9.
- 26) Park WS, Jeong MH, Cho JH, Kim JW, Kim SH, Kim NH, Ahn UK, Cho JG, Park JC, Kang JC. *The effects of low molecular weight heparin in patients with intracoro-*

- nary thrombus. *Korean Circulation J* 1999 (Submitted).
- 27) Internatioal Stroke Trial Collaborative Group. *The International Stroke Trial (IST): A randomized trial of aspirin, subcutaneous heparin, both or neither among 19435 patients with acute ischaemic stroke.* *Lancet* 1997;349:1569-81.
  - 28) The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) investigators. *Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke. A randomized controlled trial.* *JAMA* 1998;279:1265-72.
  - 29) Kay R. *Low molecular weight heparin for the treatment of acute ischemic stroke.* *N Eng J Med* 1995;333:1588-93.
  - 30) Bittle JA, Strony J, Brinker JA, Ahmed WH, Meckel CR, Chaitman BR, Maraganore J, Deutsch E, Adelman B, For the Hirulog Angioplasty Trial Investigators. *Treatment with bivalirudin (hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina.* *N Eng J Med* 1995;333:764-9.
  - 31) The EPILOG Investigators. *Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization.* *N Eng J Med* 1997;336:1689-96.
  - 32) Serruys PW, Herrman J-PR, Simon R, Rutsch W, Bode C, Laarman G-J, et al. for the HELVETICA Investigators. *A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty.* *N Eng J Med* 1995;333:757-63.
  - 33) Topol EJ. *Evolution of Improved Antithrombotic and Antiplatelet Agents: Genesis of the Comparison of Abciximab Complications with Hirulog (and Back-up Abciximab) events Trial (CACHET).* *Am J Cardiol* 1998;82:63-8.
  - 34) The CAPTURE investigators. *Randomized placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: The CAPTURE study.* *Lancet* 1997;349:956-61.
  - 35) The EPIC Investigators. *Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty.* *N Eng J Med* 1994;330:956-61.
  - 36) The IMPACT-II Investigators. *Randomized placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention IMPACT-II.* *Lancet* 1997;349:1422-8.
  - 37) The RESTORE investigators. *Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty.* *Circulation* 1997;96:1445-53.
  - 38) The EPISTENT Investigators. *Randomized placebo-controlled and balloon angioplasty controlled trial to assess safety of coronary stenting with use of platelet glycoprotein IIb/IIIa blockade.* *Lancet* 1998;352:87-92.
  - 39) Topol EJ, Ferguson JJ, Weisman HF, Tchong JE, Ellis SG, Kleiman NS, Ivanhoe RJ, Wang AL, Miller DP, Anderson KM, Califf RM, For the EPIC Investigator Group. *Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta blockade with percutaneous coronary intervention.* *JAMA* 1997;278:479-84.
  - 40) Topol EJ, Califf RM, Weisman HF, Ellis SG, Tchong JE, et al. *on behalf of the EPIC Investigators. Randomized trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six month.* *Lancet* 1994;343:881-6.
  - 41) The PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin therapy) Trial Investigators. *Inhibition of the platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes without persistent ST-segment elevation.* *N Eng J Med* 1998;339:436-43.
  - 42) The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study investigators. *Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non Q wave myocardial infarction.* *N Engl J Med* 1998;338:1488-97.
  - 43) Gachet C, Stierle A, Cazenave JP, Ohlmann P, Lanza F, Bouloux C, et al. *The thienopyridine PCR 4099 selectively inhibits ADP-induced platelet aggregation and fibrinogen binding without modifying the membrane glycoprotein IIb/IIIa complex in rat and in man.* *Biochem Pharmacol.* 1990;40:229-38.
  - 44) Ki Minno G, Cerbone AM, Mattioli PL, Turco S, Iovine C, Mancini M. *Functionally thrombasthenic state in normal platelets following the administration of ticlopidine.* *J Clin Invest* 1985;75:328-38.
  - 45) Meyer D, Pietu G, Fressinadu E, Girma JP. von Willebrand factor: *Structure of ticlopidine.* *J Clin Invest* 1985;75:328-38.
  - 46) Schomig A, Neumann FJ, Kastrati A, Schuhlen . et al. *A randomized comparison of antiplatelet and anticoagulation therapy after the placement of coronary artery stents.* *N Eng Med* 1996;334:1084-9.
  - 47) Hall P, Nakamura S, Maiello L, Itoh A, Blenginson S, Martini G, et al. *A randomized comparison of combined ticlopidine and aspirin therapy versus aspirin therapy alone after successful intravascular ultrasound-guided stent implantation.* *Circulation.* 1996;93:215-22.
  - 48) Chevigne M, David JL, Rigo P, Limet R. *Effect of ticlopidine on saphenous vein bypass patency rates: A double-blind study.* *Ann Thorac Surg* 1984;37:371-8.
  - 49) Karrison GJ, Morice MC, Benveniste E, Bunouf P, Aubry P, Cattani S, et al. *Intracoronary stent implantation without ultrasound guidance and with replacement of conventional anticoagulation by antiplatelet therapy. 30-day clinical outcome of the French Multicenter Registry.* *Circulation* 1996;94:1519-27.
  - 50) Colombo A, Hall P, Nakamura S, Almagor Y, et al. *Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance.* *Circulation* 1995;91:6876-88.
  - 51) Goods CM, Al-Shaibi KF, Liu MW, UYadav JS, et al. *Comparison of aspirin alone versus aspirin and ticlopidine after coronary artery stenting.* *Am J Cardiol* 1996;78:1042-4.
  - 52) Barragan P, Sainsous J, Simeoni FB, et al. *Coronary artery stenting without anticoagulation, aspirin, ultrasound guidance, or high balloon pressure: Prospective study of 1051 consecutive patients.* *Cathet Cardiovasc Diagn* 1997;42:367-73.
  - 53) Sharis PJ, Cannon CP, Loscalzo J. *The antiplatelet effects of ticlopidine and clopidogrel.* *Ann Intern Med* 1998;129:

- 394-405.
- 54) Kimura Y, Tani T, Kanbe T, Watanabe K. *Effect of cilostazol on platelet aggregation and experimental thrombosis. Arzneimittelforschung/Drug Res* 1985;35:1144-9.
  - 55) Saito S, Saito T, Otake A, Owada T, Mitsugi M, Hashimoto H, et al. *Cilostazol, a novel cyclic AMP phosphodiesterase inhibitor, prevents reocclusion after coronary arterial thrombolysis with recombinant tissue-type plasminogen activator. Arterioscler Thromb Vac Biol* 1993;13:563-70.
  - 56) Kubata Y, Kichikawa K, Uchida H, Maeda M, Nishimine K, Makitani S, et al. *Pharmacologic treatment of intimal hyperplasia after metallic stent placement in the peripheral arteries. Invest Radiol* 1995;30:532-7.
  - 57) Mizutani M, Okuda Y, Yamashita K. *Effect of cilostazol on the production of platelet-derived growth factor in cultured human vascular endothelial cells. Biochem Molecular Med* 1996;57:156-8.
  - 58) Ochiai M, Isshiki T, Takeshita S, Eto K, Toyozumi H, Sato T, Miyashita H. *Use of Cilostazol, a novel antiplatelet Agent, in a post-Palmaz-Schatz stenting regimen. Am J Cardiol* 1997;79:1471-4.
  - 59) Tsuchikane E, Katoh O, Sumitsuji S, Fukuhara A, Funamoto M, Otsuji S, et al. *Impact of cilostazol on intimal proliferation after directional coronary atherectomy. Am Heart J* 1998;135:495-502.
  - 60) Take S, Matsutani M, Ueda H, Hamaguchi H, Konish H, Baba Y, et al. *Effects of cilostazol in preventing restenosis after percutaneous transluminal coronary angioplasty. Am J Cardiol* 1997;79:1097-99.
  - 61) Sekiya M, Funada J, Watanabe K, Miyagawa M, Akutsu H. *Effect of probucol and cilostazol alone and in combination on frequency of poststenting restenosis. Am J Cardiol* 1998;82:144-7.
  - 62) Bae Y, Jeong MH, Kim NH, Park HW, Kang KT, Lee SH, Park WS, Cho JH, Kim SH, Kim JW, Ahn UK, Cho JG, Park JC, Kang JC. *The effects of anti-platelet agents in preventing coronary stent restenosis. Korean Circulation J* 1999 (Submitted).
  - 63) Dawson DL, Cutler BS, Meissner MH, Standness E. *Cilostazol has beneficial effects in treatment of intermittent claudication. Circulation* 1998;98:678-86.
  - 64) Esmon CT. *Thrombomodulin as model of molecular mechanism that modulate protease specificity and function at the vessel surface. FASEB J* 1995;9:946-55.
  - 65) Fisher R, Waller E, Grossi G, Thompson D, Tizard R, Schleuning W. *Isolation and characterization of the human tissue-type plasminogen activator structural gene including its 5 flanking region. J Biol Chem* 1985;260:11223-30.
  - 66) Verde P, Stopelli M, Galeffi P, Di Nocera P, Blasi F. *Identification and primary sequence of an unspliced human urokinase poly A RNA. Rroc Natl Acad Sci SA* 1984;81:4727-31.
  - 67) Flaherty D, Zengxuan N, Van Pelt N, Zoldhelyi P, Gerard RD, Collen D. *Overexpression of human constitutive nitric oxide synthase gene reduces neointima formation in balloon-injured rat carotid arteries. Circulation* 1996;94 (Suppl.):I-590.
  - 68) Dichek DA, Anderson J, Kelly AB, Hanson SR, Harker LA. *Enhanced in vivo antithrombotic effects of endothelial cells expressing recombinant plasminogen activators transduced with retroviral vectors. Circulation* 1996;93:301-9.
  - 69) Rade JJ, Schulick AH, Virmani R, Dichek DA. *Local adenoviral mediated expression of recombinant hirudin reduces neointimal formation after arterial injury. Nature Med* 1996;2:293-8.
  - 70) Zoldhelyi P, McNatt J, Xu X-M, et al. *Prevention of arterial thrombosis by adenovirus-mediated transfer of cyclooxygenase gene. Circulation* 1996;93:10-7.
  - 71) Giuseppe Vassalli, David A. Dichek. *Gene therapy for arterial thrombosis Cardiovasc Res* 1997;35:459-69.