Role of Novel Oral Anticoagulant for Patient with Atrial Fibrillation Underwent Percutaneous Coronary Intervention

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ABSTRACT

Atrial fibrillation (AF) is very common arrhythmic disorder especially in elderly population, and makes higher major adverse cardiac events (MACEs) in the patients with acute coronary syndrome (ACS) or underwent percutaneous coronary intervention (PCI). Pivotal drug for AF patients to reduce systemic embolism was warfarin, and certain duration of dual antiplatelet therapy (DAPT) is important after PCI with stent. But, best regimen of antithrombotic agent after PCI in AF is unclear especially in the clinical use of novel oral anticoagulant (NOAC). This manuscript will deal those clinical studies to indicate optimal regimen and duration of NOAC use for AF patients underwent PCI. NOAC use on DAPT significantly reduces major or minor bleeding compared to warfarin in AF patients with ACS or underwent PCI. But, the duration of NOAC use is still unclear, and there is exist clear contraindication to use it in clinical field. NOAC use reduced major or minor bleeding significantly compared to warfarin, but the incidence of MACEs was similar between warfarin and NOAC. Physician should understand the advantage or disadvantage of NOAC use, and be able to tailor the regimen and duration of antithrombotics including NOAC in this higher risk patient population.

Keywords: Atrial fibrillation; Anticoagulants; Percutaneous coronary intervention; Bleeding

INTRODUCTION

Atrial fibrillation (AF) is common arrhythmic disorder especially in elderly population. The general prevalence of AF is approximately 1.5–2%.[1] Average are of AF population is continuously increasing, and it is reach 75 to 85 years old.[1] AF is associated with 5-fold risk of stroke, a 3-fold risk of heart failure (HF), wider area of ischemia in stroke cases, and higher mortality in general or cardiovascular disease population.[1] The prevalence of AF continuously increased by 2.10-fold from 0.73% in 2006 to 1.53% in 2015 in Korea.[2] The annual AF incidence was stable with the 10-year overall incidence of 1.77/1,000 person-years (PYs), and 10-year overall incidence in men was 1.89/1,000 PYs, 1.65/1,000 PYs in women in Korea.[2] AF is significant and independent risk factor for stroke, and appropriate use of anticoagulant can reduce incidence of systemic embolism, including stroke with two-third risk reduction. Incidence and prevalence of ischemic heart disease (IHD) is also
steeply increasing in developed countries, and it is one of major public health problem even
in underdeveloped countries. This public health problem comes from diverse etiologies,
including the aging population structure, increasing prevalence of atherosclerosis risk
factors, for example, hypertension, diabetes mellitus, dyslipidemia and smoking. Even
the widespread use of antihypertensives, hypoglycemic agent, statin and antiplatelet
agent, the incidence of percutaneous coronary intervention (PCI) for IHD is continuously
increasing. Aged population structure makes one more drastic problem in IHD clinical
field. Concomitant occurrence of isocitrate dehydrogenase and AF is increasing recently.
Especially, incidence of AF in acute coronary syndrome (ACS) patients, especially in acute
myocardial infarction (AMI) is increasing. Life-long or temporal oral anticoagulation (OAC)
is needed by 5–7% of patients who underwent PCI, especially with metallic stent, and most of
them are patients with AF, and the other minors are patients with coagulopathy, cardiac valve
replacement, or venous thromboembolic disease. ARIAM registry, and the harmonizing
outcomes with revascularization and stents in AMI (HORIZONS-AMI) study clearly showed
AF was independent risk factor for major adverse cardiac event (MACE) in ACS, especially
in AMI patients. These studies have proven new-onset AF during AMI period was worse
prognostic factor for MACE compared to chronic or pre-existing AF in AMI. The Demark
Nationwide Study which included 89,703 patients with a first time AMI proved that new onset
AF was important risk factor for higher all-cause mortality, cardiovascular mortality, and
stroke. Basically, warfarin was the mainstay of drug to reduce systemic embolic event in AF
patients with 2 or higher of CHA2DS2-VASc score. But, novel oral anticoagulants (NOACs)
replaced much portion of warfarin use in AF patients. In patients with AF underwent PCI
using drug eluting stent (DES), the appropriate use of warfarin on dual antiplatelet therapy
(DAPT) was not established well, and use of warfarin for this population, especially in AMI
patients was exceptionally low and unreasonable. This evidence-practice gap originated
from the fear of increment of major bleeding in physicians, patients, and their guardians, and
lack of confirmable data to prove definitive reduction of all-cause mortality, cardiovascular
mortality or major stroke in the specific population of AF patients underwent PCI should
have been prescribed DAPT. NOACs have shown that effective reduction of major or minor
bleeding rate compared to warfarin in AF patients, some NOACs also have proved better
reduction of stroke in same population. With these studies, NOACs have replaced warfarin
use in AF. And, recently some important randomized, controlled studies of NOAC use in
patients with AF underwent PCI or suffered ACS compared to warfarin on diverse regimens
of DAPT were revealed, its delivered important clinical message for physicians to use NOAC
in AF patients underwent PCI.

IMPACT OF AF IN PATIENTS WITH ACS OR UNDERWENT
PCI WITH METALLIC STENTS

Sutton et al. have shown that patients underwent PCI with a history of AF were older and
more likely to have comorbidities, including HF, cerebrovascular disease, chronic lung
disease, and higher rate of in-hospital mortality compared patients with normal sinus rhythm
(NSR). This study included 113,283 patients (patients with AF was 12%) underwent PCI
from 47 hospitals in United States between 2011 and 2014, patients with AF were associated
with an increased risk of post-procedural bleeding (odds ratio [OR], 1.32; 95% confidence
interval [CI], 1.15–1.52), HF (OR, 1.33; 95% CI, 1.17–1.52), cardiogenic shock (OR, 1.26; 95%
CI, 1.08–1.48), and in-hospital mortality (OR, 1.41; 95% CI, 1.18–1.68) in propensity score
matching analysis compared to patients with NSR. Choi et al. showed long-term clinical

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outcomes of AF patients received DES implantation. They have used a consecutive series of 10,027 patients who underwent DES implantation between 2003 and 2011, 7.1% of patients had AF at the time of index PCI, and they were older, higher numbers of comorbidities, and history of stroke compared to NSR. 88.4% of AF patients were prescribed DAPT without OAC, and 10.5% of them were got the prescription of OAC at discharge. In the primary outcome analysis after PCI for 6-year follow-up, patients with AF suffered significantly higher MACEs (22.1% vs. 8.0%, p<0.001). After multivariable analysis, the AF was significantly associated with a higher risk of primary outcome (hazard ratio [HR], 2.33; 95% CI, 1.95–2.79; p<0.001) and major bleeding (HR, 2.01; 95% CI, 1.32–3.06; p=0.001). Among patients with AF, adjusted risk for the primary outcome was similar between the DAPT group and the triple therapy group (HR, 1.01; 95% CI, 0.60–1.69; p=0.98), but triple therapy was associated with a significantly higher risk of hemorrhagic stroke (HR, 7.73; 95% CI, 2.14–27.91; p=0.002) and major bleeding (HR, 4.48; 95% CI, 1.81–11.08; p=0.001). Patients with AF suffered significantly higher MACE, and they had multiple comorbidities compared to NSR patients. And, warfarin prescription was exceptionally low for AF patients underwent PCI with DES, use of OAC did not make systemic embolic risk and provoked more rate of bleeding stroke. In the HORIZONS-AMI registry including ST-segment elevation myocardial infarction (STEMI) who underwent primary PCI (PPCI), patients who have shown new-onset AF after PCI suffered higher rate of net adverse clinical event (46.5% vs. 25.7%; HR, 2.12; 95% CI, 1.66–2.72), MACE (38.4% vs. 21.2%; HR, 2.05; 95% CI, 1.56–2.69), all-cause of death (11.9% vs. 6.3%; HR, 1.91; 95% CI, 1.16–3.14), ischemic stroke (5.8% vs. 1.3%; HR, 4.07; 95% CI, 1.91–8.66), and non-coronary artery bypass grafting (CABG) related major bleeding (20.9% vs. 8.2%; HR, 2.67; 95% CI, 1.83–3.89) for 3 years clinical follow-up compared to patients without now-onset AF. Importance of new-onset AF in AMI was announced again in the Denmark nation-wide AMI registry. It included 89,703 AMI patients from 1997 to 2009 in Denmark, new-onset AF patients (n=10,708) suffered higher rate of all-cause mortality 173.9 vs. 69.4 per 1,000 PYs, cardiovascular death 137.2 vs. 50.0 per 1,000 PYs, fatal/nonfatal stroke 19.6/19.9 vs. 6.2/6.6 per 1,000 PYs, fatal/nonfatal re-infarction 29.0/60.7 vs. 14.2/37.9 per 1,000 PYs. In time-dependent multiple Cox analyses, new-onset AF remained predictive of increased all-cause mortality (HR, 1.9; 95% CI, 1.8–2.0), fatal/nonfatal stroke (HR, 2.3; 95% CI, 2.1–2.6), ischemic stroke (HR, 1.7; 95% CI, 1.6–1.8), non-coronary artery bypass grafting (CABG) related major bleeding (HR, 2.2; 95% CI, 1.9–2.5), fatal/nonfatal re-infarction (HR, 1.7; 95% CI, 1.6–1.8), MI (HR, 1.8; 95% CI, 1.7–1.9). But, in the Swedish Heart registry including 155,071 hospital survivors of AMI from 2000 to 2009, AF was documented in 24,023 (15.5%) cases. The AF subtypes were new-onset AF with sinus rhythm at discharge (3.7%), new-onset AF with AF at discharge (3.9%), paroxysmal AF (4.9%), and chronic AF (3.0%). The event rate per 100 PYs for the composite cardiovascular outcome (all-cause mortality, MI, or ischemic stroke) was 90.9 in patients with any type of AF versus 45.2 in patients with sinus rhythm, adjusted HR was 1.28 with 95% CI (1.19–1.37). There were no significant differences in the composite cardiovascular outcome between AF subtypes, AF showed significantly higher incidence of all-cause mortality (HR, 1.19; 95% CI, 1.41–1.80), MI (HR, 1.14; 95% CI, 1.05–1.24), and ischemic stroke (HR, 2.29; 95% CI, 1.92–2.74). Hwang et al. had analyzed the clinical impact of AF in the patients with appropriately treated with PPCI within 12 hours after chest pain onset with Korean AMI Registry from January 2008 to September 2009. Total 2,755 patients were included, patients with documented AF in emergency room were 119 (4.3%), patients with AF were older (70.7±13.6 years vs. 65.5±12.7 years, p<0.001), lower systolic blood pressure on arrival (120.6±30.2 mmHg vs. 125.9±28.0 mmHg, p=0.05), higher N-terminal (NT)-pro hormone BNP (proBNP) level (2,465.0±5,547.1 mg/dL vs. 1,579.8±4,301.3 mg/dL, p=0.049), strong tendency of lower left ventricular ejection fraction (49.6±13.7% vs. 52.3±14.2 mmHg, p=0.057). Patients with AF showed higher all-
cause mortality (22.7% vs. 9.5%; HR, 2.51; 95% CI, 1.68–3.76), and cardiac mortality (17.7% vs. 7.5%; HR, 2.59; 95% CI, 1.59–3.90) compared to patients with NSR for 1-year follow-up. Prescription of warfarin for patients with AF on hospital discharge was only 7.6%. AF was one of independent predicting factors including lower systolic blood pressure, faster heart rate, higher creatinine, higher classes of Killip, higher level of NT-proBNP for all-cause mortality in this high risk population. And, according to the report of Rogacka et al. adding DAPT after PCI with bare metal stent (BMS) or DES on long-term use of OAC developed 4.7% of major bleeding complications for mean clinical follow-up duration of 21.0±19.8 months and 67% of major bleeding event occurred in the first month after DAPT initiation. So, AF is clear and definite risk factor for MACE including all-cause mortality even in appropriately treated with timely-fashioned proton pump inhibitor in STEMI patients, and prescription rate of OAC was unreasonably low universally. It is definitely needed appropriate use of OAC on DAPT after PCI with metallic stent in IHD with AF.

**RANDOMIZED CLINICAL TRIALS USING NOACS IN PATIENTS WITH AF UNDERWENT PCI**

Clinical data about patients with AF underwent PCI prescribed OAC

Chaudhary et al. have compared rate of MACEs and bleeding between DAPT and warfarin plus DAPT after coronary stent implantation with meta-analysis based on previous 17 clinical studies for 15 months follow-up. It included 20,456 patients with AF (13,253 patients prescribed DAPT) underwent PCI, patients with DAPT have shown lower rate of major bleeding (OR, 0.62; 95% CI, 0.50–0.77), comparable rate of MI (OR, 1.27; 95% CI, 0.92–1.77) or MACEs (OR, 1.77; 95% CI, 0.99–1.39). But, stent thrombosis, stroke, and all-cause mortality was significantly higher in patients with DAPT, with OR 1.98 (95% CI, 1.03–3.81), 1.59 (95% CI, 1.09–2.34), and 1.41 (95% CI, 1.03–1.94), respectively. The admission rate for bleeding after the use of various types of antithrombotics for patients with AMI was analyzed with the Danish AMI registry. Bleeding rate was 2.6% in aspirin, 4.6% in clopidogrel, 4.3% in warfarin, 3.7% in aspirin plus clopidogrel, 5.1% in aspirin plus warfarin, 12.3% in warfarin plus clopidogrel, and 12.0% warfarin on DAPT per PY.

**Adjuvant tamoxifen longer against shorter (ATLAS) ACS 2-thrombolysis in MI (TIMI) 51 study**

ATLAS ACS 2-TIMI 51 trial was phase 3 trial including more than 15,570 patients with ACS. All patients were treated with low-dose aspirin, and stratified by a thienopyridine (clopidogrel or ticlopidine), and randomized with 1:1:1 ratio into rivaroxaban 2.5 mg bid, rivaroxaban 5 mg bid, or placebo bid, the primary efficacy end points was composite of cardiovascular death, MI or stroke, and the primary efficacy end point is TIMI major bleeding not associated with CABG. Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with respective rates of 8.9% and 10.7% (HR in the rivaroxaban group, 0.84; 95% CI, 0.74–0.96; p=0.008), with significant improvement for both the 2.5 mg bid dose (9.1% vs. 10.7%, p=0.02) and the 5 mg bid dose (8.8% vs. 10.7%, p=0.03). 2.5 mg bid of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%, p=0.002) and from any cause (2.9% vs. 4.5%, p=0.002), a survival benefit that was not seen in 5mg bid dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to CABG (2.1% vs. 0.6%, p<0.001) and intracranial hemorrhage (0.6% vs. 0.2%, p=0.009), without a significant increase in fatal bleeding (0.3% vs. 0.2%, p=0.66). The 2.5 mg bid dose resulted in fewer fatal bleeding events than
the 5 mg bid dose of rivaroxaban (0.1% vs. 0.4%, p=0.04). Additionally, rivaroxaban 5.0 mg bid and 2.5 mg bid decreased significantly Academic Research Consortium definite and probable stent thrombosis rate compared to placebo (1.9% vs. 1.5%; HR, 0.65; p=0.017 and 1.9% vs. 1.5%; HR, 0.61; p=0.089), respectively. In the STEMI subgroup, rivaroxaban 2.5 mg bid reduced all-cause of death rate compared to placebo (HR, 0.63; 95% CI, 0.45–0.89), but 5.0 mg bid did not reduce it. So, rivaroxaban 2.5 mg bid decreased effectively reduced all-cause and cardiovascular morality, predefined primary efficacy end points, but provoked significantly higher rate non-CABG related major bleeding without increment of intracranial bleeding or fatal bleeding compared to placebo.

PIONEER AF-PCI trial
PIONEER AF-PCI is an open-label, randomized, multicenter clinical study assessing the safety of 2 rivaroxaban treatment strategies and 1 warfarin treatment strategy in subjects with non-valvular AF and underwent PCI with metallic stent implantation. 2,124 patients were randomized in a 1:1:1 ratio to receive either rivaroxaban 15 mg qd plus clopidogrel 75 mg qd for 12 months (group 1, a What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary Sten Ting (WOEST) trial-like strategy), or rivaroxaban 2.5 mg bid (group 2, with stratification to a prespecified duration of DAPT for 1, 6, or 12 months, an ATLAS trial-like strategy), or dose-adjusted warfarin qd (group 3, with stratification to a prespecified duration of DAPT for 1, 6, or 12 months, traditional triple therapy). All patients underwent PCI, and 65% of PCI cases was used DES. 93% patients were used clopidogrel, prasugrel and ticagrelor was used in 2% and 5% respectively. 52% of participants were ACS. All patients will be followed up for 12 months for the primary safety composite outcome with clinically significant bleeding (a composite of major bleeding or minor bleeding according to TIMI criteria or bleeding requiring medical attention). Two regimens of rivaroxaban including group 1, 2 showed significantly lower rates of clinically significant bleeding than in the patients received warfarin (group 1:2:3=16.8%:18.0%:26.7%; HR for group 1 vs. group 3: 0.59, 95% CI: 0.47–0.76, p<0.001; HR for group 2 vs. group 3: 0.63, 95% CI: 0.50–0.80, p<0.001). MACEs occurred in 3 groups similar (group 1:2:3=6.5%:5.6%:6.0%; HR for group 1 vs. group 3: 1.08, 95% CI: 0.69–1.68, p=0.75; HR for group 2 vs. group 3: 0.93, 95% CI: 0.59–1.48, p=0.76), rate of stent thrombosis was also comparable (group 1:2:3=0.8%:0.9%:0.7%; HR for group 1 vs. group 3: 1.20, 95% CI: 0.32–4.45, p=0.79; HR for group 2 vs. group 3: 1.44, 95% CI: 0.40–5.09, p=0.57). In this PIONEER AF-PCI trial, the administration of rivaroxaban 15 mg qd plus clopidogrel 75 mg qd or rivaroxaban 2.5 mg bid plus DAPT showed significantly lower clinically relevant bleeding than dose adjusted warfarin plus DAPT in non-valvular AF patients underwent PCI with metallic coronary stent for 12 months, and MACEs and stent thrombosis rate was completely comparable among 3 groups. In the medical cost analysis for this study revealed that compared with warfarin, both rivaroxaban treatment strategies had higher medication costs, but these were more than accounted for by fewer hospitalizations.

RE-DUAL PCI study
The RE-DUAL PCI trial was a phase 3b, a prospective, randomized, open-label, blinded-endpoint trial. The main objective is to evaluate DAPT with dabigatran (110 or 150 mg bid) and a P2Y12 inhibitor (either clopidogrel or ticagrelor) compared with DAPT plus warfarin which was composed with a P2Y12 inhibitor (either clopidogrel or ticagrelor), and low-dose aspirin (for 1 or 3 months) depending on stent type in non-valvular AF patients who underwent PCI with stenting. The primary endpoint was time to first International Society of Thrombosis and Hemostasis (ISTH) major bleeding event or clinically relevant non-
major bleeding event, and the secondary endpoints were the composite of all cause death or thrombotic events (MI or stroke/systemic embolism) and unplanned revascularization; death or thrombotic events; individual outcome events; death, MI, or stroke; and unplanned revascularization.\textsuperscript{20} Mean follow-up period was 14 months. Indication of PCI was stable angina or positive stress test (48%) and ACS (52%), DES was used in 83%, staged PCI was performed in 16%.\textsuperscript{13} The incidence of the primary end point was 15.4% in the group with dabigatran 110 mg bid plus P2Y12 inhibitor as compared with 26.9% in the group with warfarin plus DAPT (HR, 0.52; 95% CI, 0.42–0.63; p<0.001 for non-inferiority; p<0.001 for superiority) and 20.2% in the group with dabigatran 150 mg bid plus P2Y12 inhibitor as compared with 25.7% in the corresponding group with warfarin plus DAPT, which did not include elderly patients outside the United States (HR, 0.72; 95% CI, 0.58–0.88; p<0.001 for non-inferiority).\textsuperscript{13} The incidence of the composite efficacy end point was 13.7% in the 2 regimen group with dabigatran and P2Y12 inhibitor combined as compared with 13.4% in the warfarin plus DAPT group (HR, 1.04; 95% CI, 0.84–1.29; p=0.005 for non-inferiority).\textsuperscript{13} The rate of composite efficacy endpoint was comparable between 110 mg bid dabigatran and matched warfarin based treatment group (15.2% vs. 13.4%, p=0.30), between 150 mg bid dabigatran and matched warfarin based treatment group (11.8% vs. 12.8%, p=0.44). Serious adverse events did not differ significantly among the 3 groups.\textsuperscript{13} In the RE-DUAL PCI trial, 240 East-Asian patients were included, the rate of ISTH major or clinically relevant non-major bleeding was comparable in both dabigatran 110 mg dual therapy group and warfarin triple therapy group (21.7% vs. 28.7%, p=0.223), and in both dabigatran 150 mg dual therapy group and warfarin triple therapy group (19.6% vs. 26.7%, p=0.337). Ischemic end point also was similar in 4 treatment regimen group.\textsuperscript{27}

**AUGUSTUS trial**

The objectives of the AUGUSTUS trial\textsuperscript{4} were to prove non-inferiority of major bleeding for 6 months use of apixaban compared to warfarin, and superiority of major bleeding rate in use OAC (NOAC or warfarin) plus P2Y12 inhibitor compared to OAC plus DAPT for 6 months.\textsuperscript{28} In detail, the AUGUSTUS study was 2 by 2 factorial design to compare the rate of ISTH defined major or clinically relevant minor bleeding between apixaban 5 mg bid and warfarin (open label), and between aspirin 100 mg qd vs. placebo (blinded) based on the use of clopidogrel 75 mg qd for all participants.\textsuperscript{28} Primary end-point was ISTH defined major or clinically relevant minor bleeding, key secondary end-point was all-cause of death, all-cause of hospitalization, and secondary end-point was death, MI, stroke, hospitalization for urgent revascularization.\textsuperscript{28} This study enrolled 4,600 patients with ACS and/or underwent PCI, composition of P2Y12 inhibitor was 93:2:5% in clopidogrel:prasugrel:ticagrelor. PCI composition was 37%:23%:38% in ACS and PCI:medically treated ACS:elective PCI.\textsuperscript{14} So, this study included certain portion of medically treated ACS patients not underwent PCI. Apixaban significantly reduced ISTH major or clinically relevant non-major bleeding compared to warfarin (10.5% vs. 14.7%; HR, 0.69; 95% CI, 0.58–0.81; p<0.001 for non-inferiority and superiority), and aspirin showed worse finding in bleeding compared to placebo (16.1% vs. 9.0%; HR, 1.89; 95% CI, 1.59–2.24; p<0.001).\textsuperscript{14} In the efficacy analysis, apixaban group showed lower incidence of death or hospitalization than warfarin group (23.5% vs. 27.4%; HR, 0.83; 95% CI, 0.74–0.93; p=0.002), and ischemic event rate was comparable in both groups. Incidence of death, hospitalization and ischemic event was similar in aspirin group and matched placebo group. According to the AUGUSTUS trial, Apixaban 5 mg bid plus clopidogrel 75 mg qd regimen showed significantly lower bleeding rate compared to warfarin plus clopidogrel 75 mg qd, and rate death or hospitalization also was lower in apixaban for the patients with ACS or underwent PCI in AF. And, adding aspirin
on OAC plus clopidogrel made significantly higher rate of bleeding than placebo on OAC plus clopidogrel, and there was no benefit to reduce ischemic event, hospitalization or death in enrolled population. So, the best regimen of this trial was apixaban 5 mg bid plus clopidogrel 75 mg qd without aspirin in the aspect of ISTH defined major bleeding or clinically relevant non-major bleeding and ischemic event including death or hospitalization for the patients with AF and ACS or underwent PCI.

DISCUSSION

Related to aged population structure, increasing prevalence of diabetes mellitus, hypertension or dyslipidemia, enlarging population of smoking, the incidence of IHD is still in uphill, even in Korea. With similar reasons, incidence and prevalence of AF also is increasing. AF is one of major and independent risk factor for worse clinical outcome in patients with ACS or underwent PCI majorly based with DES. So, it is very important to establish optimal antithrombotic regimen for AF patients with ACS or underwent PCI especially using DES to reduce systemic thromboembolism, ischemic cardiovascular event, and bleeding episode at once. According to ACTIVE studies, DAPT could not replace warfarin treatment for AF patients, and DAPT showed better systemic embolic outcome than aspirin single therapy for AF patients who could not continue warfarin therapy. So, DAPT agent is not able to replace OAC for AF patients, even more AF with underwent PCI. According to WARIS-2 trial performed in 3,600 patients with MI, warfarin plus aspirin or warfarin single treatment reduced ischemic event compared to aspirin single treatment in long-term follow up, but rate of major or minor bleeding episode was significantly higher in warfarin user than aspirin user. In the ASPECT-2 trial including 999 ACS patients, aspirin and warfarin treatment provoked higher rate of minor bleeding event. It is widely accepted that the combination use of OAC and DAPT during certain period after ACS or PCI in AF patients. But, prescription rate of OAC, especially warfarin in DAPT was exceptionally low, especially in condition of AML. NOAC introduced in clinical filed for non-valvular AF patients since about year of 2,010. After that, prescription of OAC increased gradually, and NOAC prescription exceed warfarin in non-valvular AF patients. With this background, several clinical trials which confirmed bleeding episode and ischemic outcomes of the regimen including NOAC on antiplatelet agent, for example, clopidogrel single or DAPT. In the RE-DUAL PCI trial, dabigatran 110 mg or 150 mg bid plus clopidogrel 75 mg qd or ticagrelor 90 mg bid was compared with warfarin plus clopidogrel 75mg qd or ticagrelor 90 mg bid and aspirin 100 mg qd regimen. All regimens were used for 12 months. Aspirin was used for 1 month (PCI with BMS) or 3 months (PCI with DES) in classical triple antithrombotics group, and all patients was performed PCI. Two dose of dabigatran regimen reduced ISTH defined major or clinically relevant minor bleeding compared to warfarin including treatment group, ischemic event evaluation was under-powered related to paucity of enrolled patients. Recently, dabigatran use was contracted for the reason of frequent gastrointestinal discomfort related to innate acidity of dabigatran. So, penetration of dabigatran use might be limited in clinical practice. The bleeding rate and ischemic event of apixaban was analyzed in AUGUSTUS study. This study enrolled the highest number of patients, 4,600 patients of ACS or PCI performed AF patients were randomized into the 2 by 2 factorial designed this study. It examined the effect of apixaban 5 mg bid vs. warfarin and aspirin 100 mg vs. placebo on clopidogrel 75 mg qd regimen for 6 months. Ischemic events were comparable among 4 kinds of antithrombotic regimen, but, the rate of ISTH defined
Role of NOAC for Patient with AF and PCI

**CONCLUSION**

Even though several randomized clinical studies were conducted to confirm the safety and efficacy of NOAC on antiplatelet agents for AF patients with ACS or underwent PCI, the best answer is still unclear. Risk of ischemic event and bleeding episode should be evaluated carefully, and then regimen should be constructed in personal level.

**Table 1.** The comparison of study scheme and result of 3 clinical studies

|                      | PIONEER AF-PCI trial | RE-DUAL PCI trial | AUGUSTUS trial |
|----------------------|----------------------|-------------------|----------------|
| Enrolled population  | 2,100 patients, PCI (100%) | 2,175 patients with PCI | 4,600 patients with ACS and/or PCI |
| Clopidogrel:prasugrel:ticagrelor=93%:2%:5% | Clopidogrel:ticagrelor=88%:12% | Clopidogrel:prasugrel:ticagrelor=93%:1%:5% |
| DES user: 65%        | DES:BSM:mixed=83%:15%=2% | Medically treated ACS patients: 23% |
| Studied regimens     | 1. VKA+ASA+P2Y12i | 1. VKA+ASA+P2Y12i | 1. VKA+P2Y12i+ASA |
| 2. Rivaroxaban 2.5 mg bid+ASA+P2Y12i | 2. Dabigatran 110 mg bid+P2Y12i | 2. VKA+P2Y12i |
| 3. Rivaroxaban 15 mg qd+P2Y12i | 3. Dabigatran 150 mg bid+P2Y12i | 3. Apixaban 5 mg bid+P2Y12i+ASA |
| 4. Rivaroxaban 5 mg bid+P2Y12i | 4. Apixaban 5 mg bid+P2Y12i |
| Time from ACS/PCI to randomization | Within 72 hours after sheath removal | Within 120 hours post-PCI | Stabilization period of up to 14 days (mean 6.6 days) |
| Study duration       | 14 months (mean) | 14 months (mean) | 6 months |
| Bleeding end-point   | TIMI major or minor bleeding or requiring medical attention | ISTH major or clinically relevant Non-major bleeding | ISTH major or clinically relevant Non-major bleeding |
| Efficacy endpoint    | MACE (cardiac death, MI, or stroke), each components of MACE, stent thrombosis | Thromboembolic event (MI, stroke, systemic embolism), death, unplanned revascularization | The composite of death or hospitalization The composite of death or ischemic events (stroke, MI, stent thrombosis, or urgent revascularization) |
| TTR of warfarin (%)  | 65 | 64 | 59 |

ACS = acute coronary syndrome; AF = atrial fibrillation; ASA = aspirin low dose; DES = drug eluting stent; ISTH = International Society on Thrombosis and Hemostasis; MACE = major adverse cardiac event; MI = myocardial infarction; P2Y12i = P2Y12 inhibitor; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction; TTR = time in therapeutic range; VKA = vitamin K antagonist.

Major or clinically relevant non-major bleeding was lowest in the group of apixaban 5mg bid plus clopidogrel 75 mg qd without aspirin. Clinicians should take into account study duration was 6 months, not 12 months, and 23% of enrolled patients was not performed PCI. Rivaroxaban was examined in the PIONEER AF-PCI study. Regimens were not simple in this study. The first regimen was rivaroxaban 15 mg qd plus clopidogrel 75 mg qd for 12 months (WOEST trial like strategy), and the second one was rivaroxaban 2.5 mg bid plus DAPT (aspirin 100 mg qd plus clopidogrel 75 mg qd) for 1, 6, 12 months (ATLAS trial like strategy), and then regimen was changed into rivaroxaban 15 mg qd plus aspirin 100 mg qd after the pre-defined period, and the third regimen was warfarin plus DAPT for 1, 6, 12 months (traditional triple therapy), and then regimen was changed into warfarin plus aspirin 100 mg qd after predefined period. The first and second rivaroxaban regimens were better bleeding outcome compared to traditional triple therapy, and ischemic event rates were similar in 3 regimens. We should consider that dose of rivaroxaban was not consistent with previous study of rivaroxaban for non-valvular AF population, and 2.5 mg dose of rivaroxaban should be used in bid schedule, it can be 1 obstacle to use longer term. The comparison among 3 clinical studies is summarized in Table 1.
REFERENCES

1. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines-CPG; Document Reviewers. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. Europace 2012;14:i385-413.

2. Joung B, Lee JM, Lee KH, Kim TH, Choi EK, Lim WH, Kang KW, Shim J, Lim HE, Park J, Lee SR, Lee YS, Kim JB; KHR5 Atrial Fibrillation Guideline Working Group. 2018 Korean guideline of atrial fibrillation management. Korean Circ J 2018;48:1033-80.

3. King SB 3rd, Smith SC Jr, Jacobs AK, Morrison DA, Williams DO; 2005 WRITING COMMITTEE MEMBERS, Feldman TE, Kern MJ, O’Neill WW, Schaff HV, Whitlow PL, Adams CD, Anderson JL, Buller CE, Creager MA, Ettenger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association task force on practice guidelines: 2007 writing group to review new evidence and update the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention, writing on behalf of the 2005 Writing Group. Circulation 2008;117:261-95.

4. Hwang KK, Eom SY, Lee SY, Kim SM, Cho MC, Kim YJ, Seung KB, Jeong MH, Bae JW; The other Korea Acute Myocardial Infarction Registry Investigators. Atrial fibrillation on admission is related with higher mortality in ST-segment elevation myocardial infarction patients. Int Heart J 2017;58:486-94.

5. Almendro-Delia M, Valle-Caballero MJ, Garcia-Rubira JC, Muñoz-Calero B, García-Alcantara A, Reina-Toral J, Benítez-Parejo J, Hidalgo-Urbano R; ARIAM Andalucia Study Group. Prognostic impact of atrial fibrillation in acute coronary syndromes: results from the ARIAM registry. Eur Heart J Acute Cardiovasc Care 2014;3:141-8.

6. Rene AG, Généreux P, Ezekowitz M, Kirtane AJ, Xu K, Mehran R, Brener SJ, Snow GW. Impact of atrial fibrillation in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention (from the HORIZONS-AMI [harmonizing outcomes with revascularization and stents in acute myocardial infarction] trial). Am J Cardiol 2014;113:236-42.

7. Bang CN, Gislason GH, Greve AM, Bang CA, Lilja A, Torp-Pedersen C, Andersen PK, Køber L, Devereux RB, Wachtell K. New-onset atrial fibrillation is associated with cardiovascular events leading to death in a first time myocardial infarction population of 89,703 patients with long-term follow-up: a nationwide study. J Am Heart Assoc 2014;3:e000382.

8. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.

9. Granger CB, Alexander IH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golia D, Goto S, Hohosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.

10. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GI, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.

11. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinale J, Ruzyllo W, Ruda M, Kordesuey Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Conmeci M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104.
12. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Janus J, Burton P, van Eickels M, Korjjan S, Daaboul Y, Lip GY, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375:2423-34. 

13. Cannon CP, Bhatt DL, Oldgren J, Lip GY, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, Nordaby M, Kleine E, Harper R, Manassie J, Januzzi JL, Ten Berg JM, Steg PG, Hohnloser SH; RE-DUAL PCI Steering Committee and Investigators. Dual antiplatelet therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377:1513-24. 

14. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB, Alexander JH; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019;380:1509-24. 

15. Sutton NR, Seth M, Ruwende C, Gurm HS. Outcomes of patients with atrial fibrillation undergoing percutaneous coronary intervention. J Am Coll Cardiol 2016;68:895-904. 

16. Choi HI, Ahn JM, Kang SH, Lee PH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park DW, Park SJ. Prevalence, management, and long-term (6-year) outcomes of atrial fibrillation among patients receiving drug-eluting coronary stents. JACC Cardiovasc Interv 2017;10:1075-85. 

17. Batra G, Svennblad B, Held C, Fernberg T, Johanson P, Wallentin L, Oldgren J. All types of atrial fibrillation in the setting of myocardial infarction are associated with impaired outcome. Heart 2016;102:926-33. 

18. Rogacka R, Chieffo A, Michev I, Airoldi F, Latib A, Cosgrave J, Montorfano M, Carlino M, Sangiorgi GM, Castelli A, Godino C, Magni V, Aranzulla TC, Romagnoli E, Colombo A. Dual antiplatelet therapy after percutaneous coronary intervention with stent implantation in patients taking chronic oral anticoagulation. JACC Cardiovasc Interv 2008;1:56-61. 

19. Chaudhary N, Bundhun PK, Yan H. Comparing the clinical outcomes in patients with atrial fibrillation receiving dual antiplatelet therapy and patients receiving an addition of an anticoagulant after coronary stent implantation: a systematic review and meta-analysis of observational studies. Medicine (Baltimore) 2016;95:e5581. 

20. Sørensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jørgensen C, Madsen JK, Hansen FR, Kober L, Torp-Pedersen C, Gislason GH. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009;374:1967-74. 

21. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM; ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9-19. 

22. Gibson CM, Mega JL, Burton P, Goto S, Verheugt F, Bode C, Plotnikov A, Sun X, Cook-Bruns N, Braunwald E. Rationale and design of the anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome-thrombolysis in myocardial infarction 51 (ATLAS-ACS 2 TIMI 51) trial: a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of rivaroxaban in subjects with acute coronary syndrome. Am Heart J 2011;161:815-821.e6. 

23. Gibson CM, Chakrabarti AK, Mega J, Bode C, Bassand JP, Verheugt FW, Bhatt DL, Goto S, Cohen M, Mohanavelu S, Burton P, Stone G, Braunwald E; ATLAS-ACS 2 TIMI 51 Investigators. Reduction of stent thrombosis in patients with acute coronary syndromes treated with rivaroxaban in ATLAS-ACS 2 TIMI 51. J Am Coll Cardiol 2013;62:286-90. 

24. Mega JL, Braunwald E, Murphy SA, Plotnikov AN, Burton P, Kiss RG, Parkhomenko A, Tendera M, Widimsky P, Gibson CM. Rivaroxaban in patients stabilized after a ST-segment elevation myocardial infarction: results from the ATLAS ACS-2-TIMI-51 trial (anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome-thrombolysis in myocardial infarction-51). J Am Coll Cardiol 2013;61:1853-9.
25. Korjian S, Daaboul Y, Laliberté F, Zhao Q, Mehran R, Bode C, Halperin J, Verheugt FW, Lip GY, Cohen M, Peterson ED, Fox KA, Gibson CM, Pinto DS; PIONEER AF-PCI Investigators. Cost implications of anticoagulation strategies after percutaneous coronary intervention among patients with atrial fibrillation (a PIONEER-AF PCI analysis). Am J Cardiol 2019;123:355-60.

26. Cannon CP, Gropper S, Bhatt DL, Ellis SG, Kimura T, Lip GY, Steg PG, Ten Berg JM, Manassie J, Kreuzer J, Blatchford J, Massaro JM, Bruceckmann M, Ferreiros Ripoll E, Oldgren J, Hohnloser SH; RE-DUAL PCI Steering Committee and Investigators. Design and rationale of the RE-DUAL PCI trial: a prospective, randomized, phase 3b study comparing the safety and efficacy of dual antithrombotic therapy with dabigatran etexilate versus warfarin triple therapy in patients with non-valvular atrial fibrillation who have undergone percutaneous coronary intervention with stenting. Clin Cardiol 2016;39:555-64.

27. Ako J, Okumura K, Nakao K, Kozuma K, Morino Y, Okazaki K, Fukaya T, Kimura T; RE-DUAL PCI Trial Investigators. Dual anti-thrombotic therapy with dabigatran after percutaneous coronary intervention in atrial fibrillation-Japanese and East-Asian subgroup analysis of the RE-DUAL PCI trial. Circ J 2019;83:327-33.

28. Kim JH, Choi W, Kim KC, Nam CW, Hong BK, Kim JH, Jeon DS, Bae JW, Kim SH, Moon KW, Cho BR, Kim DJ, Jang JS. The current status of intervention for intermediate coronary stenosis in the Korean percutaneous coronary intervention (K-PCI) registry. Korean Circ J 2019 Jun 5 [E-pub ahead of print]. https://doi.org/10.4070/kcj.2019.0074.

29. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE W): a randomised controlled trial. Lancet 2006;367:1903-12.

30. ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360:2066-78.

31. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969-74.

32. van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE; Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360:109-13.

33. Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, Ghei AK, Turakhia MP, Marcus GM. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: insights from the NCDR PINNACLE registry. JAMA Cardiol 2016;1:55-62.

34. Lee SR, Choi EK, Han KD, Cha MJ, Oh S, Lip GY. Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: a nationwide population-based study. PLoS One 2017;12:e0189495.

35. Ellis CR, Kaiser DW. The clinical efficacy of dabigatran etesilate for preventing stroke in atrial fibrillation patients. Vasc Health Risk Manag 2013;9:341-52.