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European Society of Cardiology (ESC) Annual Congress Report From Barcelona 2017

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From August 26th to 30th, the 2017 Annual Congress of the European Society of Cardiology (ESC 2017) was held in Barcelona, Spain. Despite the terrorism tradegy just before the ESC congress, the congress attracted many medical professionals from all over the world to discuss the recent topics in cardiovascular medicine in more than 500 sessions, including COMPASS (Cardiovascular OutcoMes for People using Anticoagulation StrategieS Trial), CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study), and ORION (which assessed the effect of a novel siRNA inhibitor to PCSK9 on reductions in low-density lipoprotein cholesterol). Japanese cardiologists and the Japanese Circulation Society greatly contributed to the congress. This report briefly introduces some late-breaking registry results, late-breaking clinical trials, and ESC Guidelines from the ESC 2017 Congress.

Key Words: Cardiology; European Society of Cardiology

The Annual Congress of the European Society of Cardiology 2017 (ESC 2017) was held in the beautiful city of Barcelona, Spain, from August 26th to 30th, 2017 (**Figure 1**). As the congress program committee chairperson, Professor Stephan Achenbach, mentioned in the ESC congress, this year's congress marks the 40th anniversary of the first percutaneous coronary intervention (PCI) procedure by Dr. Andreas Gruentzig in 1997, which was a focus of some sessions at the congress. Despite the awful tragedy perpetrated by terrorists just before the ESC congress, the congress attracted medical professionals from all over the world. A total of 1,147 Japanese cardiologists attended this year's congress. During the 5 days, a variety of topics were discussed in more than 500 sessions, including COMPASS, CANTOS, and ORION (which assessed the effect of a novel siRNA inhibitor to PCSK9 on reductions in low-density lipoprotein (LDL) cholesterol). This report highlights some late-breaking clinical trials, late-breaking registry results, and ESC Guidelines from the ESC 2017 congress.

Hot Line Sessions: Late-Breaking Clinical Trials

COMPASS[1]

Despite current secondary prevention strategies, recurrent cardiovascular disease (CVD) develops in the patients with a history of CVD at 5–10% per year. Aspirin produces only a 19% risk reduction, and warfarin also increases bleeding, including intracranial hemorrhage. Recently, rivaroxaban was reported to reduce deaths after acute coronary syndrome (ACS).[2] John Willian Eikelboom (Hamilton, Canada) presented the results of the COMPASS Trial (Cardiovascular OutcoMes for People using Anticoagulation StrategieS).[1] COMPASS was designed to determine whether rivaroxaban-plus-aspirin or rivaroxaban alone is more effective than aspirin alone in reducing a composite endpoint of cardiovascular death, stroke or myocardial infarction (MI), defined as a primary endpoint, in patients with stable CVD. A total of 27,395 patients were randomized to a "baby-dose" of rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily; n=9,152), rivaroxaban alone (5 mg twice daily; n=9,117), or aspirin alone (100 mg once daily; n=9,126). The primary endpoint occurred in 379 patients (4.1%) in the rivaroxaban-plus-aspirin group, 448 (4.9%) in the rivaroxaban alone group, and 496 (5.4%) in the aspirin alone group. There was a statistically significant difference in primary outcome between the rivaroxaban-plus-aspirin group and the aspirin-alone group (P<0.0001). Major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group than in the aspirin alone group (288 bleeds [3.1%] vs. 170 [1.9%], P<0.001). However, there was no significant difference in intracranial or fatal bleeding among the 3 groups. There was a highly significant net clinical benefit (primary and severe bleeding events),

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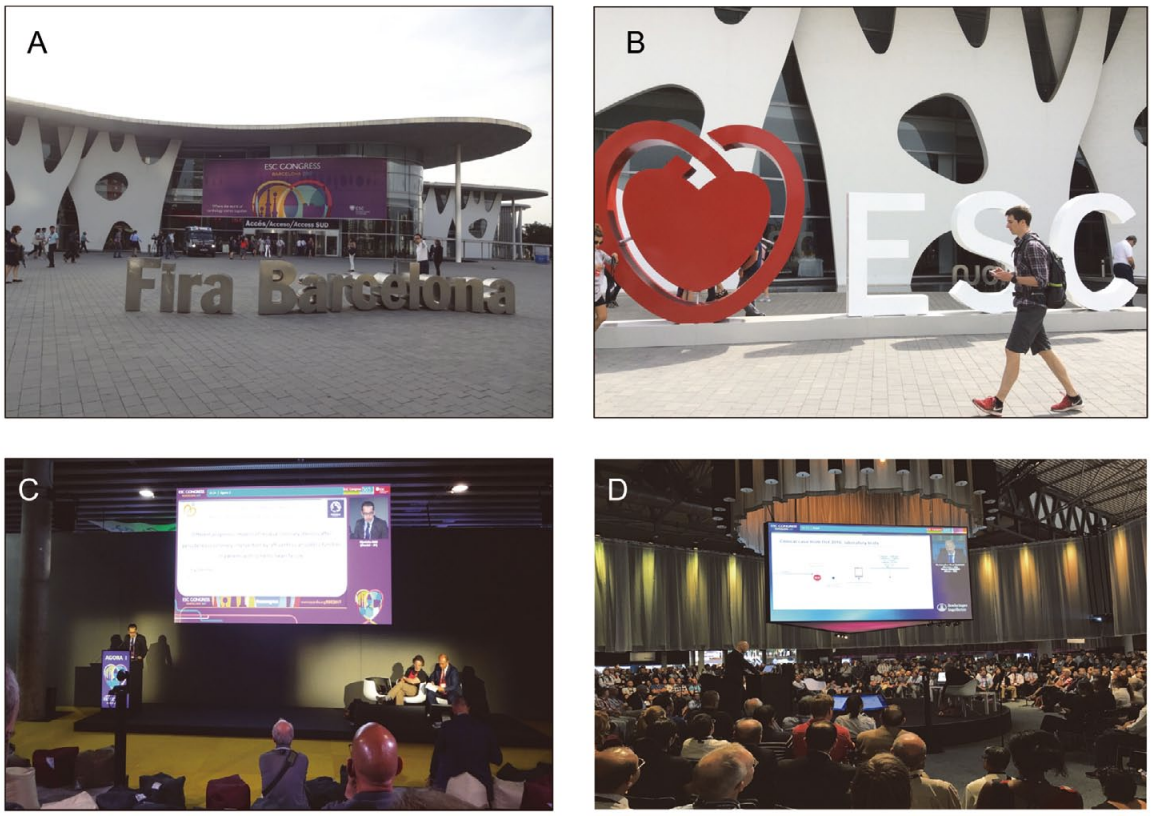

Figure 1. Snapshots of ESC 2017. (**A**,**B**) Main entrance to ESC 2017 in Barcelona. (**C**,**D**) ESC 2017 encouraged active discussion and interaction among cardiologists.

with 431 (4.7%) events in the rivaroxaban-plus-aspirin group compared with 534 (5.9%) events in the aspirin alone group (P=0.0005). Dr. Eugene Braunwald (Boston, USA) commented, "This trial was an important step in thrombo-cardiology. The COMPASS Trial is a large, rigorously conducted trial with unambiguous results which should change guidelines."

CANTOS[3]

Plasma levels of LDL cholesterol and inflammatory biomarkers, including high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6, could predict the first and/or recurrent cardiovascular event. Dr. Paul M Ridker (Boston, USA), the presenter of CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study),[3] stated, "Although statins have not only lipid-lowering but also anti-inflammatory effects, clinicians now distinguish between those with residual cholesterol risk and those with residual inflammatory risk." He and his colleagues conducted a randomized, double-blind trial of canakinumab, which is a high-affinity therapeutic monoclonal anti-human IL-1β antibody and functionally neutralizes the bioactivity of this pro-inflammatory cytokine, in 10,061 patients with stable coronary artery disease (CAD) after previous MI and persistent hsCRP level ≥2 mg/L. The trial compared 3 doses of canakinumab (50 mg: n=2,170; 150 mg: n=2,284; 300 mg: n=2,263, administered subcutaneously every 3 months) with placebo (n=3,344). Although the lipid levels were unchanged, the levels of hsCRP decreased significantly in all groups receiving canakinumab compared with the placebo group. At a median follow-up of 3.7 years, the incidence rate for the primary efficacy endpoint including nonfatal MI, nonfatal stroke, or cardiovascular death, was 4.50 events per 100 person-years in the placebo group, 4.11 in the 50-mg group, 3.86 in the 150-mg group, and 3.89 in the 300-mg group. The 150-mg group, but not the other groups, met the multiplicity adjusted threshold for statistical significance for both the primary and secondary endpoints (hazard ratio [HR] 0.83; 95% confidence interval [CI] 0.73–0.95; P=0.005). Meanwhile, the incidence of fatal infection was higher in the patients with canakinumab than in those with placebo. In conclusion, anti-inflammatory therapy with canakinumab could reduce the incidence of recurrent cardiovascular events without lipid-level lowering.

DETO2X-AMI[4]

Supplemental oxygen has been routinely used in the treatment of patients with suspected acute MI (AMI) and it also has been recommended in clinical guidelines.[5] However, there is no evidence from large trials to support the efficacy of routine oxygen therapy in suspected AMI patients. Thus, DETO2X-AMI[4] was conducted to examine the clinical effect for routine oxygen therapy in normoxic patients with suspected AMI. In this nationwide Swedish registry-based randomized clinical trial, a total of 6,629 patients with suspected AMI and an oxygen saturation of

≥90% were randomly assigned to receive either supplemental oxygen (6 L/min) or ambient air. There was no significant difference between the 2 groups in terms of both the primary endpoint (one-year all-cause death; 5.0% in oxygen group vs. 5.1% in ambient air group) and the secondary endpoint including rehospitalization with MI and cardiovascular death. These results were consistent across all predefined subgroups including old age, smoking status, and diabetes. DETO2X-AMI confirmed that routine use of supplemental oxygen in patients with suspected AMI who did not have hypoxemia does not reduce 1-year all-cause death.

SPYRAL HTN-OFF MED[6]

Up to one-third of adults have hypertension and many of them remain uncontrolled. Renal denervation (RDN) therapy targets the sympathetic nervous system. However, the SYMPLICITY HTN-3 Trial failed to demonstrate a significant blood pressure-lowering effect of RDN.[7] SPYRAL HTN-OFF MED[6] was a randomized and sham-controlled trial to evaluate the effect of RDN on blood pressure, which differed from the previous trial[7] in terms of study population, RDN technique, and the presence or absence of antihypertensive medications. To be included in SPYRAL HTN-OFF MED, mild to moderate hypertensive patients had to be off any antihypertensive medication or had to be allowed discontinuation of drug therapy. In addition, they had to have an office systolic blood pressure (SBP) ≥150 mmHg and <180 mmHg, office diastolic blood pressure (DBP) ≥90 mmHg, and 24-h ambulatory SBP ≥140 mmHg and <170 mmHg at second screening. Finally, 80 patients were randomized to undergo RDN (n=38) or a sham procedure (n=42), and were followed up for 3 months. For the RDN group, the total number of ablations was 43.8±13.1 per patient, including 25.9±12.8 branch ablations. The results showed that, from baseline to 3 months, office and 24-h ambulatory BP significantly decreased in the RDN group (24-h SBP −5.5 mmHg, 24-h DBP −4.8 mmHg, office SBP −10.0 mmHg, office DBP −5.3 mmHg), but not in the sham group (24-h SBP −0.5 mmHg, 24-h DBP −0.4 mmHg, office SBP −2.3 mmHg, office DBP −0.3 mmHg). There were no major adverse events (AEs) in either group. Thus, SPYRAL HTN-OFF MED offers biological proof of principle for the BP-lowering efficacy of RDN in the absence of antihypertensive medications.

SIOVAC

Sildenafil is a vasodilator that is typically used for pulmonary arterial hypertension, and is believed to be safe and well tolerated for patients with post-capillary pulmonary hypertension. The SIOVAC Trial, which was conducted in 18 tertiary public hospitals in Spain, examined the potential of sildenafil to improve long-term outcomes of patients with successfully corrected valvular disease and residual pulmonary hypertension. A total of 200 patients were randomized to sildenafil (40 mg 3 times a day) or placebo for 6 months. The primary endpoint was the clinical composite score of all-cause death, hospital admission for heart failure, worsening exercise tolerance, and feeling worse than when starting the medication. The study results showed that clinical outcomes were worse in the sildenafil group compared with the placebo group. At 6 months, 33 patients (33%) in the sildenafil group and 14 patients (15%) in the placebo group had worse composite clinical scores than at the beginning of the study (odds ratio for improvement 0.39; 95% CI 0.22 to 0.67; P<0.01). The overall risk for hospital admission for heart failure doubled in the sildenafil group compared with the placebo group. Dr. Javier Bermejo (Madrid, Spain) concluded that long-term use of sildenafil for treating residual pulmonary hypertension in patients after successful heart valve surgery should be avoided.

REVEAL[8]

Pharmacologic inhibition of cholesteryl ester transfer protein (CETP) can produce substantial increases in high-density lipoprotein (HDL) cholesterol levels, along with reductions in levels of non-HDL cholesterol (particularly LDL cholesterol). The DEFINE Trial has previously demonstrated that treatment with anacetrapib had robust effects on LDL- and HDL-cholesterol with an acceptable side-effect profile in patients with high risk for CAD.[9] However, trials of other CETP inhibitors have shown neutral or adverse effects on cardiovascular outcomes. The phase 3 REVEAL Trial aimed to determine whether lipid modification with anacetrapib could reduce the risk of a first major coronary event in more than 30,000 patients with atherosclerotic vascular disease who were receiving intensive atorvastatin therapy and who had a mean LDL-cholesterol level of 61 mg/dL (1.58 mmol/L), a mean non-HDL-cholesterol level of 92 mg/dL (2.38 mmol/L), and a mean HDL-cholesterol level of 40 mg/dL (1.03 mmol/L).[8] The patients were assigned to receive either 100 mg of anacetrapib once daily (15,225 patients) or matching placebo (15,224 patients). The primary outcome was the first major coronary event, a composite of coronary death, MI, or coronary revascularization. During a median follow-up period of 4.1 years, the primary outcome occurred in significantly fewer patients in the anacetrapib group than in the placebo group (10.8% vs. 11.8%; rate ratio, 0.91; 95% CI, 0.85 to 0.97; P=0.004). The relative difference in risk was similar across multiple prespecified subgroups. At the trial midpoint, the mean level of HDL-cholesterol was higher by 43 mg/dL (1.12 mmol/L) in the anacetrapib group than in the placebo group (a relative difference of 104%), and the mean level of non-HDL-cholesterol was lower by 17 mg/dL (0.44 mmol/L), a relative difference of −18%. There were no significant between-group differences in the risk of death, cancer, or other serious AEs. The presenter, Dr. Martin Landray (Oxford, UK) concluded that the use of anacetrapib resulted in a lower incidence of major coronary events than the use of placebo among patients with atherosclerotic vascular disease who were receiving intensive statin therapy.

Hot Line Sessions: Late-Breaking Registry Results

Risk of Triggering AMI and Asian Dust Exposure[10]

Although several studies have demonstrated an association between Asian dust exposure and CVD, the effects of Asian dust exposure on the occurrence of AMI in patients with various AMI risk factors remain unclear. Dr. Sunao Kojima (Kumamoto, Japan) reported on the association between Asian dust exposure and AMI, using data for Asian dust events measured at the Kumamoto Local Meteorological Observatory in Kumamoto City.[10] They analyzed 3,713 consecutive AMI patients from 21 participating hospitals throughout the Kumamoto prefecture between April 2010 and March 2015, showing that the incidence of AMI was associated with the occurrence of Asian dust events on the day before the onset of AMI.

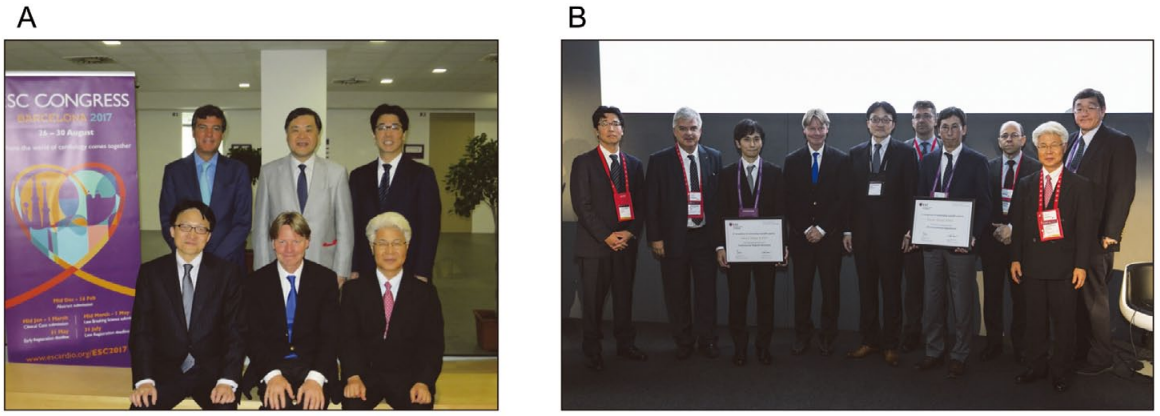

Figure 2. Contribution of the Japanese Circulation Society (JCS). (**A**) The ESC-JCS Leadership Meeting on August 26, 2017. (**B**) The leadership and congress prize winners at the ESC-JCS networking reception on August 27, 2017.

Importantly, this association remained significant even after adjustment for temperature, humidity, each air pollutant, and influenza epidemics. In addition, more risk for this association was noted in patients older than 75 years, males, those with hypertension or diabetes mellitus, never-smoking status, and especially in patients with chronic kidney disease (CKD). Finally, they developed a scoring system based on several AMI risk factors and found that AMI after Asian dust events was more likely to occur in patients with a high-risk score. They concluded that Asian dust events may lead to AMI and have a great effect on its occurrence in patients with CKD.

Leaflet Thrombosis Following Transcatheter Aortic Valve Replacement[11]

Leaflet thrombosis is a recently recognized and important mechanism of transcatheter heart valve failure.[12] However, it remains unknown whether leaflet thrombosis after transcatheter aortic valve replacement (TAVR) has serious clinical consequences. Dr. Ankur Kalra presented data on clinical or symptomatic leaflet thrombosis following TAVR from the U.S. FDA MAUDE Database, where a total of 5,691 TAVR-related AEs have been reported.[11] Of these, structural valve dysfunction (SVD) caused by leaflet thrombosis was reported in 30 cases. Most cases (60.0%) occurred in the first year following TAVR. SVD manifested as aortic stenosis (53.3%), or regurgitation (23.3%), or both (13.3%). Interventions to address leaflet thrombosis included escalation of antiplatelet or anticoagulant therapy (30.0%), valve-in-valve TAVR (16.7%), surgery (46.7%), or their combination. Outcomes following leaflet thrombosis included stroke/TIA (10.0%), cardiogenic shock (6.7%), and death (30.0%). They concluded that clinically manifest leaflet thrombosis was associated with serious clinical manifestations that included stroke, cardiogenic shock, and death.

New Practice Guidelines

In 2017, the ESC released 4 new ESC Clinical Practice Guidelines on AMI-STEMI, dual antiplatelet therapy (DAPT), peripheral arterial diseases (PAD), and valvular heart disease.

AMI-STEMI[13]

New guidelines dedicated a chapter to MINOCA (Myocardial Infarction with Non-obstructive Coronary Arteries).[14] A sizeable proportion of STEMI patients do not present significant coronary artery stenosis on emergency angiography. It is important to perform additional diagnostic tests in these patients to identify the etiology and tailor appropriate therapy. Strategy selection and time delays were updated. New guidelines, in which STEMI diagnosis is time zero in the reperfusion strategy clock, recommend that STEMI patients should undergo a primary PCI strategy unless the anticipated absolute time from STEMI diagnosis to PCI-mediated reperfusion is >120 min, when fibrinolysis should be initiated immediately (i.e., within 10 min of STEMI diagnosis). Therefore, the term "door to balloon" was completely eliminated from the new guidelines.

Dual Antiplatelet Therapy[15]

New guidelines emphasize that DAPT in CAD is a treatment for not only patients with stent placement but also for those with more extensive acute and chronic CAD. Decisions on DAPT use (indication, time of initiation, drug choice, interruptions, and duration) may be complex, and several factors should be taken into account, including clinical setting, treatment modality for CAD, devices, bleeding risk, and concomitant therapies. In stable CAD patients treated with PCI, clopidogrel remains the default $P2Y_{12}$ inhibitor, whereas ticagrelor or prasugrel is recommended in ACS patients unless drug-specific contraindications exist. Irrespective of the type of metallic stent implanted, the duration of DAPT is 1–6 month(s) depending on the bleeding risk. A prolonged DAPT regimen (>6 months) may be considered in patients with ischemic risk over bleeding risk. In patients with ACS, the default DAPT duration is 12 months. In patients with indication for oral anticoagulation undergoing PCI, triple therapy (aspirin, clopidogrel, and oral anticoagulation) should be limited up to a maximum of 6 months and discontinuation of antiplatelet agents should be considered at 12 months. It is recommended to reassess the type, dose, and duration of

DAPT in patients with actionable bleeding complications while on treatment.

Peripheral Arterial Diseases[16]

The ESC 2017 guidelines for PAD were issued in collaboration with the European Society of Vascular Surgery (ESVS). This is the first time that ESC recommendations on PAD have been developed as a collaborative effort between cardiologists and vascular surgeons. These new guidelines dedicated new chapters to the use of antithrombotic drugs and the management of other cardiac conditions frequently encountered in patients with PAD, such as heart failure, atrial fibrillation, and valvular heart disease. With regard to revascularization therapies, revascularization of asymptomatic carotid stenosis is recommended to be limited only in patients with high risk of stroke. Furthermore, routine revascularization is not recommended in renal artery stenosis secondary to atherosclerosis. In lower extremity artery disease, the importance of the new WIfI classification that has been introduced for risk stratification of patients with chronic limb threatening ischemia is emphasized. The system takes into account the 3 main factors that contribute to the risk of limb amputation: wound (W), ischemia (I), and foot infection (fI).

Valvular Heart Diseases[17]

The ESC 2017 guidelines for valvular heart diseases were published in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Recently, a new line of evidence has accumulated, particularly in the field of catheter interventional treatment of valvular heart diseases. Regarding the decision between surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) for symptomatic aortic stenosis, the guidelines emphasize that it should be made by a heart team with surgeons and cardiologists. A new recommendation is that both procedures should be performed in a heart valve center that has departments for cardiac surgery and cardiology providing structured collaboration on site, conducts structured training, records data on performance and patient outcomes, and participates in registries. Meanwhile, aortic valve repair, using re-implantation or remodeling with aortic annuloplasty technique, is recommended in young patients with aortic root dilation and tricuspid aortic valves, when performed by experienced surgeons.

Contribution of the JCS to ESC 2017

The contribution of the Japanese Circulation Society (JCS) to the ESC is increasing year by year. During the Congress, the ESC-JCS Leadership Meeting was held at the ESC headquarters on August 27, 2017. Professors Issei Komuro (Tokyo, Japan), Takashi Akasaka (Wakayama, Japan), Hiroaki Shimokawa (Sendai, Japan), and Yasushi Sakata (Osaka, Japan) discussed with ESC President Professor Jerson Bax (Leiden, The Netherlands) the importance of a closer relationship between these 2 leading cardiovascular societies (**Figure 2**). Each year, Japanese healthcare professionals contribute to the success of the ESC Congress. In 2017, the ESC received more abstracts from Japan than from any other country. Of 1,482 submitted abstracts, 590 were accepted. Among them, in a Hot Line session, Hiroshi Itoh (Tokyo, Japan) presented the data from the EMPATHY Trial. In this trial, they examined whether intensive lipid-lowering therapy is superior to standard therapy in reducing the incidence of cardiovascular events in patients with hyperlipidemia and diabetic retinopathy, but without a history of CAD. Patients who had elevated LDL-cholesterol and diabetic retinopathy without a history of CAD were randomly assigned in a 1:1 ratio to receive intensive or standard therapy. Patients were being treated with monotherapy with statin for a maximum of 5.5 years to achieve the following LDL-cholesterol targets: <70 mg/dL for the intensive therapy group and ≥100 and <120 mg/dL for the standard therapy group. The primary endpoint was a composite of incidence of CVD and death from CVD. Finally, 5,144 were assigned to the study treatment (2,571 and 2,573 in the intensive and standard therapy groups, respectively). During a mean follow-up period of 37 months, the primary outcome did not significantly occur in the intensive therapy group compared with the standard therapy group (5.1% vs. 6.1%; HR, 0.84; 95% CI, 0.67 to 1.07; P=0.15). However, in their post-hoc analysis, intensive lipid-lowering therapy significantly reduced cardiovascular events in patients who reached their LDL-cholesterol target range. The EMPATHY Trial suggested that achieving LDL-cholesterol <70 mg/dL in a treat-to-target strategy in high-risk patients with hypercholesterolemia and diabetic retinopathy may have benefit.

Closing Remarks

The ESC presents the world's leading congress, which provides the newest findings, relevant information, and updated guidelines. ESC 2018 will be held in Munich next year. We look forward to attending and discussing many hot topics in the field of CVD.

Addendum

During the Editorial Board meeting of the *European Heart Journal* held in Barcelona, on which Hiroaki Shimokawa serves as an international associate editor, Dr. Thomas Luscher, Editor-in-Chief of the Journal, announced the corrected impact factor (IF), from 19.651 to 20.213, by Clarivate Analytics, formerly Thomson Reuters. This new IF makes the *European Heart Journal* the top journal in the field of Cardiac and Cardiovascular Systems as compared with the *Journal of the American College of Cardiology* (19.896) and *Circulation* (19.309).

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