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REVIEW ARTICLE

European Society of Cardiology Congress (Paris, 2019): results of the most important clinical studies

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Summary. *The review article contains a report on the 25 most important clinical trials that were presented at the Hot Line sessions of the European Society of Cardiology (Paris, France, August 31 — September 4, 2019).*

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European Society of Cardiology (ESC) Congress together with World Congress of Cardiology, the largest annual scientific and clinical cardiovascular congress, was held in Paris, France from the August 31st to September 4th. It was attended by 32.000 health care workers from 150 countries who took part in over 500 expert sessions.

Five new ESC Clinical Guidelines were presented at ESC Congress 2019:

- Guidelines on diabetes, pre-diabetes, and cardiovascular diseases [1];
- Guidelines for the diagnosis and management of acute pulmonary embolism [2];
- Guidelines for the management of patients with supraventricular tachycardia [3];
- Guidelines for the diagnosis and management of chronic coronary syndromes [4];
- Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk [5].

Full guidelines are available on: https://www.escardio.org/guidelines/clinical-practice-guidelines.

Of particular interest were 25 randomized trials that were recently finished and presented on six Hot Line sessions.

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HOT LINE Session 1

Patients with stable coronary artery disease (CAD) and type 2 diabetes mellitus (DM) are at a high risk of cardiovascular disease (CVD) that can be explained by increased platelet aggregation. The **THEMIS** study [6] suggested that ticagrelor addition during aspirin treatment may lead to atherothrombotic events risk reduction in these patients.

Randomized double blind study involved patients over 50 years of age with stable CAD and type 2 diabetes who were administered ticagrelor (initial dose 90 mg twice daily was later decreased to 60 mg twice daily after the PEGASUS-TIMI 54 study results were received) and aspirin (n=9619) or placebo and aspirin (n=9601). Patients with previous myocardial infarction (MI) or stroke were excluded. Treatment was cancelled more frequently in patients taking ticagrelor compared with those taking placebo (34.5% versus 25.4% respectively). During a median follow-up of 39.9 months the frequency of composite primary efficacy endpoint (cardiovascular death, MI or stroke) was lower in the ticagrelor group compared with placebo group (7.7% versus 8.5% respectively; relative risk (RR) 0.9, 95% confidence interval (CI) 0.81–0.99; p=0.04). Incidence of TIMI major bleeding (primary safety endpoint) was also significantly higher in the ticagrelor group (2.2% versus 1.0% respectively, RR 2.32; 95% CI 1.82–2.94; p<0.001), as well as frequency of intracranial bleeding (0.7% versus 0.5% respectively; RR 1.71; 95% CI 1.18–2.48; p=0.005), but fatal hemorrhages were registered with similar frequency (0.2% versus 0.1% respectively; RR 1.9; 95% CI 0.87-4,15; p=0.11). There was no significant difference in the total number of 'outcomes with irreversible damage' (all-cause mortality, MI, stroke, fatal hemorrhage or intracranial hemorrhage) in the ticagrelor and placebo groups (10.1% versus 10.8% respectively; RR 0.93; 95% CI 0.86–1.02).

In patients with stable CAD and type 2 diabetes with no previous MI or stroke addition of ticagrelor to standard therapy reduces the incidence of ischemic CVD, but at the same time increases incidence of major bleeding compared with placebo. Therefore, for the majority of patients with type 2 diabetes and CAD who meet the criteria for the THEMIS study, addition of ticagrelor to aspirin therapy is not recommended.

One-half of the patients with stable CAD and type 2 diabetes who were involved in the THEMIS study (58%, n=11.154) had undergone percutaneous coronary intervention (PCI), which indicated high ischemic CVD risk. These patients are usually administered aspirin, but THEMIS substudy — THEMIS-PCI study [7] estimated probable improvement of outcomes after ticagrelor addition to standard therapy.

The study involved patients over 50 years of age with type 2 diabetes, stable CAD and who met one of three additional criteria: previous PCI, coronary artery bypass grafting (CABG) or at least one artery 50% stenosis. After randomization the patients were given (received) ticagrelor (n=5558) or placebo (n=5596). During a median follow-up of 3.3 years, the incidence of complications (composite primary efficacy endpoint: cardiovascular death, MI or stroke) was lower in the ticagrelor group compared with the placebo group (7.3% versus 8.6% respectively; RR 0.85; 95% CI 0.74–0.97; p=0.013), but the risks of cardiovascular mortality (3.1% versus 3.3% respectively; p=0.68) and all-cause mortality 5.1% versus 5.8% respectively; p=0.11) were similar. TIMI major bleeding rate was higher in the ticagrelor group compared with the placebo group (2.0% versus 1.1% respectively; RR 2.03; 95% CI 1.48–2.76; p<0.0001), however, comparable rates were identified for intracranial bleeding (0.6% versus 0.6% respectively; p=0.45) and fatal hemorrhage (0.1% versus 0.1%, respectively; p=0.83). In the ticagrelor group reduction in the total number of 'outcomes with irreversible damage' (death from any reason, MI, stroke, fatal hemorrhage or intracranial hemorrhage) was achieved, which determined the 'pure clinical benefit' (9.3% versus 11.0% in placebo group; RR 0.85; 95% CI 0.75–0.95; p=0.005). There was no association with the time of PCI.

In patients with type 2 diabetes and stable CAD with previous PCI the addition of ticagrelor to aspirin reduces the total risk of cardiovascular death, MI and stroke, but increases the risk of bleeding at the same time. Nevertheless, compared with patients without previous PCI addition of ticagrelor provides 'pure clinical benefit' that indicates the feasibility of its administration in patients with high risk of ischemia and low risk of bleeding.

Angiotensin receptor blocker and sacubitril/valsartan were more effective than enalapril in reducing the risk of hospitalizations for chronic heart failure (CHF) or cardiovascular deaths in patients with CHF with reduced ejection fraction (HFrEF). In the randomized **PARAGON-HF** [8] study efficacy and safety of sacubitril/valsartan (purposed dose 97/103 mg twice daily) and valsartan (purposed dose 160 mg twice daily) were compared in 4822 NYHA functional class II–IV patients with ejection fraction 45% or higher.

During a median follow-up of 35 months composite primary endpoint event rate (hospitalization for heart failure or cardiovascular death) was similar in the sacubitril/valsartan and valsartan groups (RR 0.87; 95% CI 0.75–1.01; p=0.059), and, separately, frequencies of cardiovascular deaths (RR 0.95; 95% CI 0.79–1.16) and hospitalizations for heart failure (RR 0.85; 95% CI 0.72–1.00) were comparable. Sacubitril/valsartan was more effective in decreasing functional class of CHF and increasing the quality of life in 8 months (quality of life was assessed with the Kansas City Cardiomyopathy Questionnaire), it also less affected renal function (RR 0.5; 95% CI 0.33–0.77). In the sacubitril/valsartan group hypotension (15.8% versus 10.8% in the valsartan group) and angioneurotic edema (0.6% versus 0.2% respectively) developed more often, and hypokalemia more rarely compared with the valsartan group (13.2% versus 15.3% respectively). Analysis which was planned in advance identified that sacubitril/valsartan was superior to valsartan in patients with lower ejection fraction (57% and less) and in women.

Sacubitril/valsartan does not provide significant reduction in total number of hospitalizations for heart failure and cardiovascular deaths in patients with CHF with ejection fraction 45% or higher. However, some new findings about the benefits of sacubitril/valsartan in patients with CHF with ejection fraction 45–57%, and especially in women, were made.

In patients who had ST-segment elevation MI (STEMI) PCI of the affected artery decreases cardiovascular death and recurrent MI risks. **COMPLETE** [9] study investigated the hypothesis of additional risk reduction in patients who undergo simultaneous PCI of other stenosed coronary arteries.

Patients with MI and multivessel CAD who successfully underwent PCI of the affected artery were randomized for complete PCI revascularization of all angiographically significant lesions (at least 70% vessel diameter stenosis or 50–69% stenosis with low fractional flow reserve) (n=2016) or refusal of complete revascularization (n=2025). During a median follow-up of 3 years significantly less poor outcomes included in primary composite endpoint (cardiovascular death, MI) were observed in patients with complete revascularization compared with patients with PCI of only affected artery (7.8% versus 10.5% respectively; RR 0.74; 95% CI 0.6–0.91; p=0.004), as well as the total number of cardiovascular deaths, MI and revascularizations caused by ischemia (8.9% versus 16.7% respectively; RR 0.51; 95% CI 0.43–0.61; p<0.001). Complete revascularization proved to be beneficial if performed both during the hospitalization and after several weeks (up to 45 days) after the discharge, i.e. complications occurred after considerable time and could be successfully prevented. Considering safety and other outcomes, including stroke, stent thrombosis, major bleeding, acute kidney failure and severe CHF no significant difference between two groups was detected.

This research is the first large randomized study that demonstrated the reduction of severe CVD risk in complete coronary revascularization compared with PCI of only one effected artery in patients with STEMI in multivessel CAD. The reduction in composite primary endpoint event frequency was determined by lower number of non-ST-segment elevation MI (non-STEMI), but not by cardiovascular disease mortality. The study had no statistical power to determine difference in mortality. The COMPLETE project confirmed that complete coronary revascularization is feasible, the statement that was already in STEMI treatment guidelines.

In patients with type 2 diabetes sodium-glucose transport protein 2 (SGLT2) inhibitors reduce the risk of first hospitalization for heart failure, apparently by mechanisms that are independent from their hypoglycemic actions. The hypothesis of the **DAPA-HF** study [10] was that the HFrEF can be effectively treated in patients with diabetes as well as in patients without diabetes.

NYHA II, III and IV patients with LV ejection fraction 40% or less were randomized and administered dapagliflozin 10 mg once daily (n=2373) or placebo (n=2371) in addition to recommended therapy. On average, after over 18.2 months of follow-up, significant reduction in total number of primary endpoint events (hospitalization for heart failure, urgent intravenous CHF therapy, cardiovascular death) in the dapagliflozin group was determined (16.3% versus 21.2% in placebo patients; RR 0.74; 95% CI 0.65–0.85; p<0.001). Both components of primary endpoint — first deterioration of CHF (10.0% versus 13.7% in placebo group; RR 0.70; 95% CI 0.59–0.83; p=0.00 001) and cardiovascular death (9.6% versus 11.5% in placebo group; RR 0.82; 95% CI 0.69–0.98; p=0.03) as well as death from any cause (11.6% versus 13.9% respectively; RR 0.83; 95% CI 0.71–0.97; p=0.022) were identified less frequently in the dapagliflozin group. Decrease in CHF symptoms (Kansas City Cardiomyopathy Questionnaire) was also noted in patients getting dapagliflozin compared with patients

getting placebo. The benefits of dapagliflozin were independent from sacubitril/valsartan therapy as these medications have different mechanisms of action. The frequency of poor outcomes in patients with and without type 2 diabetes appeared to be similar. The frequency of poor outcomes including decreased circulating volume, kidney dysfunction, severe hypoglycemia, amputation and bone fractures were also comparable between two groups.

In patients with HFrEF addition of dapagliflozin to the standard therapy reduces the risk of CHF deterioration or cardiovascular death compared with placebo, irrespective of type 2 diabetes presence. Dapagliflozin that is already successfully used for type 2 diabetes treatment and CHF prevention can also be used in patients with systolic CHF and without diabetes.

HOT LINE Session 2

In the **NZOTACS** (New Zealand Oxygen in Acute Coronary Syndromes) trial [11] ambulance acute coronary syndromes care records were analyzed in order to compare 30-day mortality in 20.304 patients with high-oxygen protocol and 20.568 patients with low-oxygen protocol. The high-oxygen protocol consisted of oxygen delivered by face mask at 6 to 8 L given to all patients with suspected acute coronary syndrome (ACS) (patients presenting with retrosternal ischemic pain or specific ECG findings), irrespective of oxygen saturation levels, with oxygen stopped when clinical evidence indicated the ischemia had resolved. The low-oxygen protocol recommended that oxygen was given only when saturation fell below 90% and stopped when saturation reached 90–94%. ACS was later confirmed in 43% of patients, and in 10% STEMI was diagnosed.

Primary outcome showed that high-oxygen administration did not reduce 30-day mortality compared with low-oxygen (3.02% in the routine-oxygen group and 3.12% in low-oxygen group; RR 0.97; 95% CI 0.86–1.08). At the same time in the group of patients with STEMI who were started on high-oxygen protocol 30-day mortality rates were much lower (8.8% versus 10.6% in low-oxygen protocol group; p=0.016). Reduction in mortality rates was also registered in high-oxygen protocol group in patients with low saturation that was recorded on ambulance arrival (10.1% versus 11.1% in low-oxygen group; RR 0.88; 95% CI 0.70–1.11).

The investigators concluded that patients with suspected ACS and with normal blood oxygen level do not benefit from high-level oxygen administration. European and American clinical guidelines recommend that oxygen be given only when oxygen saturation levels are below 90% in patients with ACS.

It is known that remote ischemic conditioning with transient ischemia and reperfusion applied to the arm has been shown to reduce myocardial infarct size in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI). **CONDI-2/ERIC-PPCI** trial [12] investigated whether remote ischemic conditioning could reduce the incidence of cardiac death and hospitalization for heart failure at 12 months.

Patients with suspected STEMI and who were eligible for PPCI were randomly allocated to receive standard treatment (including a sham simulated remote ischemic conditioning intervention — control group, n=2701) or remote ischemic conditioning treatment before PPCI (n=2700). An automated cuff device was used to deliver the remote ischemic conditioning protocol, which comprised four alternating cycles of cuff inflation for 5 min and deflation for 5 min. Study team members collecting the data and assessing outcomes were masked to the treatment allocation. At 12 months post-PPCI frequencies of cardiac death or hospitalization for heart failure (the primary combined endpoint events) were similar in the control group and in the remote ischemic conditioning group (8.6 and 9.4% respectively; RR 1.10; 95% CI 0.91–1.32; p=0.32). No severe adverse side effects of remote ischemic conditioning were observed. It was concluded that remote ischemic conditioning does not improve clinical outcomes (cardiac death or hospitalization for heart failure) at 12 months follow-up in patients with STEMI undergoing PPCI.

ISAR-REACT 5 trial [13] compared efficacy and safety of ticagrelor or prasugrel therapy in patients with acute coronary syndromes for whom invasive evaluation is planned. Patients were randomized to receive standard therapy which included ticagrelor (n=2012) or prasugrel (n=2006). Loading doses were administered differently depending on the type of ACS. Patients with STEMI received the loading dose of ticagrelor (180 mg) or prasugrel (60 mg) soon after randomization. Patients with non-STEMI/unstable angina received ticagrelor after randomization, and prasugrel after randomization and angiography.

At 1 year after randomization, the incidence of the combined primary efficacy endpoint (death, MI, or stroke) was significantly higher in the ticagrelor group (9.3% versus 6.9% in the prasugrel group;

RR 1.36; 95% CI 1.09–1.7; p=0.006). Adverse events included: death from any cause (4.5% vs. 3.7%); MI (4.8% vs. 3.0%); stroke (1.1% vs. 1.0%); definite or probable stent thrombosis (1.3% vs. 1.0%); definite stent thrombosis (1.1% vs. 0.6%) in the ticagrelor and prasugrel respectively. The incidence of safety endpoint (Bleeding Academic Research Consortium type 3, 4, or 5 bleeding) was higher in the ticagrelor group compared with the prasugrel group (5.4% versus 4.8% respectively; RR =1.12; 95% CI 0.83–1.51; p=0.46).

In patients with STEMI/non-STEMI the incidence of death, MI, or stroke is significantly lower in the prasugrel group compared with ticagrelor group, and there was no significant difference in the risk of major bleeding in these patients. Current findings confirm that prasugrel is first line antithrombotic medication in patients with ACS with STEMI and non-STEMI. The open-label nature of the trial and the fact that most of the follow-up was conducted by telephone remain a limitation. The number of patients excluded from the safety analysis was 10 times higher in the prasugrel group compared with the ticagrelor group, which may have influenced the final total number of major bleedings. Previous findings suggest that antithrombotic effects of ticagrelor and prasugrel are similar. Therefore, it seems unlikely that prasugrel was indeed beneficial over ticagrelor and it is necessary to confirm the ISAR-REACT 5 trial findings in a double-blind study.

In the **HISTORIC** trial [14] involved 32.837 patients and estimated different cardiac troponin values measured by high-sensitivity cardiac troponin I (hs-cTnI) assay in order to rule out MI and safely discharge patients directly from ED without increase in poor cardiologic events frequency. After the initial troponin assessment (or after repeated troponin assessment if the symptoms started less than 2 hours before the presentation), low-risk patients (cTnI<5 ng/L) with symptoms that started more than 2 hours prior the presentation were identified. Patients who were considered to be at high risk and had cTnI level higher than the sex-specific 99th centile at presentation were admitted. Intermediate-risk patients with cTnI levels between 5 ng/L and the 99th centile were retested after 3 hours and were sent home if the cTnI was <3 ng/L; they were admitted if it was ≥3 ng/L.

Implementing the early rule-out pathway reduced the time the patients spent in the ED compared with standard rule-out (6.8 versus 10.1 hours respectively; p<0.001). It also increased the proportion of patients sent home without being admitted (74% versus 53% respectively; RR 1.57; 95% CI 1.34–1.83; p<0.001). Frequency of cardiac death and MI (primary safety endpoint) was 1.8% in the early-rule-out pathway group and 2.5% in the standard care group at 1 year (corrected RR 1.02; 95% CI 0.74–1.4). Compared with the patients with cTnI levels between 5 ng/L and the 99th centile patients with cTnI levels below 5 ng/L were at a significantly lower risk of MI or cardiac death at 1 year (5.3% versus 0.7% respectively; corrected RR 0.23; 95% CI 0.19–0.28). Patients with cTnI levels below 3 ng/L were also at a lower risk of MI or cardiac death at 1 year (5.3% versus 0.3% respectively; corrected RR 0.20; 95% CI 0.14–0.29).

The early rule-out pathway implementation may prove useful for both patients and healthcare. A single cTnI test will provide an evaluation that can aid in making a safe decision about the need of hospital admission, which will also lead to cost reduction.

HOT LINE Session 3

UK Biobank study [15] assessed the effect of lower low-density lipoprotein cholesterol (LDL–C) and lower systolic blood pressure (SBP) on the lifetime risk of cardiovascular disease. The study included 438.952 participants who were enrolled in the UK Biobank between 2006 and 2010 and were under observation through 2018. The investigators used LDL–C and SBP scores as instruments to divide participants into groups with lifetime exposure to lower LDL–C, lower SBP, or both. Differences in plasma LDL–C, SBP, and cardiovascular event rates between the groups were compared in order to estimate associations with lifetime risk of cardiovascular disease.

During the observation period 24.980 patients experienced a first major coronary event (coronary death, nonfatal MI, or coronary revascularization). Participants with LDL–C genetic scores 14.7-mg/dL lower than the median levels had lower lifetime risk of major coronary events (OR 0.73; 95% CI 0.70–0.75; p<0.001). Participants with SBP genetic scores 2.9-mm Hg lower than the median also were at a lower risk of major coronary events (OR 0.82 95% CI 0.79–0.85; p<0.001). Participants in the group with both genetic scores lower than the median (13.9-mg/dL lower LDL–C, 3.1-mm Hg lower SBP) were at an even lower risk of major coronary events (OR 0.61; 95% CI 0.59–0.64; p<0.001). In a meta-regression analysis, combined effect of 38.67-mg/dL lower LDL–C and 10-mm Hg lower SBP was associated with a significantly lower lifetime risk of major coro-

nary events (OR 0.22; 95% CI, 0.17–0.26; p<0.001), and cardiovascular death (OR 0.32; 95% CI 0.25–0.40; p <0.001).

Lifelong genetic exposure to lower levels of LDL–C cholesterol and lower SBP is associated with lower cardiovascular risk. However, it cannot be assumed that these findings represent the magnitude of possible benefit from the management of these risk factors.

At 1 year after revascularization patients with stable CAD and atrial fibrillation or those who do not need revascularization are recommended to start oral anticoagulants. However, there are limited data from randomized controlled trials that evaluate this treatment. Moreover, in clinical practice most patients in these situations continue to be treated with combination antiplatelet therapy for more than a year.

An open-label **AFIRE** trial [16] carried out in Japan involved 2236 patients with atrial fibrillation who had undergone PCI (70% of cases) or CABG more than 1 year earlier or who had angiographically confirmed CAD not requiring revascularization. Patients were randomly assigned to receive monotherapy with rivaroxaban (10–15 mg once daily) or combination therapy with rivaroxaban and single antiplatelet agent (70% aspirin, 25% clopidogrel or prasugrel). The trial was stopped early because of high mortality in the combination therapy group. During a median follow-up of 2 years the total number of primary efficacy endpoint events (stroke, systemic embolism, MI, unstable angina requiring revascularization or death from any cause) was not lower in the rivaroxaban monotherapy group compared with the combination therapy group (4.14% versus 5.75% events per patient-year respectively; OR 0.72; 95% CI 0.55–0.95; p<0.001 for non-inferiority). Rivaroxaban monotherapy was superior to combination therapy for the primary safety end point (major bleeding according to the criteria of the International Society on Thrombosis and Hemostasis) with event rates of 1.62% and 2.76% per patient-year, respectively (OR 0.59; 95% CI 0.39–0.89, p=0.01 for superiority).

Rivaroxaban monotherapy was not inferior to combination therapy with rivaroxaban and antiaggregant medication in decreasing the number of ischemic complications and was superior in safety (major bleeding risk). These findings confirm European and American recommendations that anticoagulant monotherapy (e.g. rivaroxaban) should be used in patients with stable CAD and atrial fibrillation.

The **GALACTIC** trial [17] evaluated the hypothesis that early intensive and sustained use of a complex of vasodilators including renin-angiotensin system (RAS) inhibitors improve outcomes compared with the standard therapy due to improve of lung congestion and organ perfusion.

Patients hospitalized for acute heart failure (AHF), NYHA III/IV functional class symptom severity with increased plasma concentrations of natriuretic peptides, and systolic blood pressure of at least 100 mm Hg were randomly assigned to standard care (n=402) or a strategy of early intensive and sustained vasodilation (n=386). In the early intensive and sustained vasodilation group included high doses of common vasodilators, including sublingual and transdermal nitrates from the 1st day, oral hydralazine during first 48 hours to avoid nitrate tolerance, and rapid up-titration of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). Other treatment options (aldosterone antagonists, beta-blockers, loop diuretics) were used according to the physician's decision and guidelines in both groups.

Rehospitalization for AHF or all-cause mortality at 180 days was comparable in both groups (30.6% in the intervention group and 27.8% in the standard care group; corrected OR 1.07; 95% CI 0.83–1.39; p=0.592. At 6 days the decrease in shortness of breath was identified in both groups. Frequency of adverse events was higher in the early intensive and sustained vasodilation group compared with the standard care group (82% versus 75% respectively). Headache and systolic arterial hypotension were identified more frequently in the intervention group as well (8% versus 2% in the standard care group).

Among patients with AHF, a strategy of early intensive and sustained vasodilation individualized doses of nitrates, hydralazine, ACEi, ARBs or sacubitril/valsartan did not significantly improve a composite outcome of all-cause mortality and AHF rehospitalization compared with usual care. Pulmonary congestion, despite being the sign of AHF, is not an ideal target for therapies. Therefore, it is necessary to focus on the means of prevention, early diagnosis and treatment of heart failure in order to avoid its progression into AHF.

J.J. Miranda presented a trial, conducted in Peru, that investigated **the effect of salt substitution in lowering the blood pressure** [18]. For 3 years households, grocery shops, bakeries, and restaurants in the rural area were provided with free potassium chloride to substitute 25% of sodium chloride in food. The

study involved 91.2% of 2605 adult residents of this area, and people with chronic kidney disease, cardiac disease or those who took digoxin were excluded to avoid hyperkalemia. Blood pressure was evaluated every 5 months for a total of 7 measurements and systolic blood pressure reduced by an average of 1.23 mmHg and diastolic blood pressure by an average of 0.72 mmHg compared with baseline 113.1/72 mmHg (p=0.04 and p=0.022 respectively). Blood pressure reductions were even greater (18%) in individuals with hypertension at baseline and in patients over 60 years (average reductions in systolic and diastolic blood pressures were 1.92 mmHg and 2.17 mmHg, respectively). No adverse effects were observed. Cumulative probability of arterial hypertension development (BP>14/90 mmHg) reduced by 55% compared with baseline (p<0.001) at 3-year follow-up.

The study demonstrates that population-wide substitution of sodium chloride with potassium chloride is effective and feasible. Although there was no significant mean blood pressure reduction, even 2 mmHg reduction is expected to reduce stroke mortality by 10% and CAD by 7%.

Arterial hypertension is the leading cause of cardiovascular disease globally, however, hypertension control in insufficient. The authors of an open randomized controlled trial, **HOPE 4** [19], hypothesized that the efficacy of hypertension control can be improved by an active involvement of primary care physicians and family members, and provision of effective medications to patients with poorly controlled or recently diagnosed hypertension. The study involved 1371 patients from 30 communities in Colombia and Malaysia who were randomly assigned to receive standard care (control group, n=727) or free antihypertensive and statin medications, support from a family member or friend (treatment supporter) in order to improve adherence to medications and healthy lifestyle (the intervention group, n=644).

The primary endpoint was the change in 10-year cardiovascular disease risk estimated by the Framingham Risk Score at 12 months between the participants from the intervention and control groups. All patients completed 12-minth follow-up and the reduction in risk estimate was –6.4% in the control group and –11.17% in the intervention group, with a difference of –4.78% (95% CI -7.11to –2.44; p<0.0001). There was an absolute 11.45 mm Hg reduction in SBP (95% CI –14.94 to –7.97) and a 0.41 mmol/L reduction in LDL (95% CI -0.60 to 0.23) in the intervention group (both p,0.0001). A blood pressure goal of <140 mm Hg was registered in 69% of patients in the intervention group versus 30% in the control group (p<0.0001).

A complex model of care, involving primary care physicians and family members that are familiar with the local context, significantly improved hypertension control. Implementation of this strategy can potentially improve the cardiovascular risk compared with current strategies that are mainly physician focused.

HOT LINE Session 4

Patients with severe renal failure are usually excluded from randomized studies that makes it hard to found optimal CHF therapy for individuals with renal dysfunction.

BB-meta-HF study [20] estimated the influence of beta-blockers on the outcomes in CHF patients with reduced LV ejection fraction and renal function impairment using the data from 10 double-blind placebo-controlled randomized studies (n=16.740). Renal dysfunction was the key marker of CHF patients' mortality, with a 12% increase in the mortality for every 10 ml/min lower eGFR (p<0.001). Positive prognostic effect of beta-blockers (death from all causes absolute risk reduction was 4.7% per year) was most prominent in patients with moderate chronic kidney disease (eGFR 30–44 ml/min/1.73 m^2). No deterioration in renal function in patients taking beta-blockers was observed. Patients with systolic CHF and concomitant atrial fibrillation lacked benefit from beta-blockers regardless of eGFR.

Beta-blockers reduce mortality in patients with CHF with reduced ejection fraction and sinus rhythm, even with moderate kidney dysfunction at baseline. Beta-blockers do not decrease renal function and therefore patients with systolic CHF should receive beta-blocker therapy even with moderate or moderately severe renal dysfunction.

The SYNTAX study compared PCI using first-generation paclitaxel-eluting Taxus stents with CABG in patients with de-novo three-vessel and left main coronary artery disease and reported results up to 5 years. The SYNTAX Extended Survival (**SYNTAXES**) study [21] evaluated 10-year all-cause mortality from these two types of interventions according to the intention-to-treat principle. From 2005 to 2007 1800 patients were randomly assigned to the PCI group (n=903) or to the CABG group (n=897). At 10 years the primary endpoint (death from all causes) was identified in 27% of PCI patients and in 24% of CABG patients

(hazard ration (HR) 1.17; 95% CI 0.97–1.41; p=0.092). Among the patients with three-vessel CAD, 28% had died after PCI versus 21% after CABG (HR 1.41; 95% CI 1.10–1.80); among the patients with left main artery disease — 26% after PCI versus 28% after CABG (HR 0.9; 95% CI 0.68–1.20). These findings were not affected by diabetes.

At 10 years, there was no significant difference in death from all causes between PCI using first-generation paclitaxel-eluting stents and CABG. Of note, CABG provided a significant survival benefit in patients with three-vessel disease, but not in patients with left main coronary artery disease.

The **MITRA-FR** trial [22] involved patients with mitral regurgitation and symptomatic heart failure treated using guideline-directed medical treatment who were hospitalized at least once in the last 12 months. The patients were randomly assigned to the percutaneous mitral valve repair with the MitraClip device group (the intervention group, n=152) or the medical treatment group (the control group, n=152). At 24 months death from any cause or unplanned hospitalization for heart failure (combined primary endpoint) occurred in 63.8% of patients in the intervention group and in 67.1% of patients in the control group (HR 1.01; 95% CI 0.77–1.34). Death from any cause occurred in 34.9% versus 34.2% respectively (HR 1.02; 95% CI 0.70–1.50) and unplanned hospitalization for heart failure occurred in 55.9% versus 61.8% respectively (HR 0.97; 95% CI 0.72–1.30).

In patients with severe secondary mitral regurgitation, percutaneous repair added to medical treatment does not significantly reduce the risk of death or hospitalization for heart failure at 2 years compared with medical treatment alone. On contrary, a similar COAPT study reported that percutaneous repair with the MitraClip device reduced the frequency of hospitalization for heart failure at 24 months. Mortality differed significantly in MITRA-FR and COAPT (34% and 46% at 2 years respectively), which may be either due to greater severity of cardiac disease in COAPT participants or to higher intensity of medical treatment in MITRA-FR. Assumingly, MitraClip may be beneficial in patients with severe secondary mitral regurgitation in the absence of significant LV dilation, who continue to be symptomatic despite the maximal medical treatment. COAPT and MITRA-FR investigators are planning to continue their observations up to 5 years.

The **DANAMI-2** trial [23] involved 1572 patients with STEMI who were randomized to receive PCI or fibrinolysis therapy. At 16 years death or re-hospitalization for MI (primary composite endpoint) occurred in 58.7% PCI compared with 62.3% with fibrinolysis (RR 0.86; 95% CI 0.76–0.98). No difference in all-cause mortality in two groups was observed, but cardiac death rates were significantly lower in the primary PCI group (18.3% versus 22.7% in fibrinolysis group; RR 0.78; 95% CI 0.63–0.98). The benefit of primary PCI compared with fibrinolysis in patients with STEMI — a reduction in the risk of death or re-hospitalization for MI — was sustained to 16 years.

HOT LINE Session 5

Data from 32 703 patients from 45 countries with chronic coronary syndrome enrolled in the prospective observational CLARIFY [24] registry with a 5-year follow-up, were analyzed. Characteristics and management of patients, as well as the determinants of achieved results were studied.

Frequency of composed primary endpoint (cardiovascular death or non-fatal MI) over a five-year follow-up period was 8.0% (8.1% in men and 7.6% in women). The main independent predictors of primary endpoint complications were previous hospitalizations for heart failure, current smoking, atrial fibrillation, residence in Central/South America, previous MI or stroke, current angina or peripheral artery disease. The association between angina and previous MI was determined (p=0.0016). Frequency of primary endpoint events was higher in patients with previous MI who also had stable angina (11.8% versus 8.2% in patients without angina; p<0.001), and patients without previous MI had no frequency difference of endpoint events independently of angina (6.3% in patients with stable angina and 6.4% in patients without stable angina; p<0.99). Evidence-based secondary prevention measures were successfully implemented in the registry patients.

Described characteristics of patients with chronic coronary syndrome patients show that patients with both angina and prior MI can be identified as a high-risk group despite intensive implementation of secondary prevention measures.

Patient data from **SWEDEHEART** registry [25] were analyzed to evaluate the effect of the long-term use of secondary prevention medications after CABG (statins, beta-blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors and antiplatelet therapy) on mortality.

The study involved all the patients who underwent CABG in Sweden from 200 to 2015 and survived at least 6 months after discharge (n=28.812). Six

months after discharge 93.9 % of patients received statins and 77.3 % eight years later. Figures for beta-blockers were 91.9 % and 76.4 %, for RAAS inhibitors 72.9 % and 65.9 %; for antiplatelets 93.0 % and 79.8 % respectively. These medications were administrated less often to patients aged 75 years and older. After adjustment for age, gender, comorbidities, and use of other secondary preventive drugs, treatment with statins (HR 0.56; 95 % CI 0.52–0.60], RAAS inhibitors (HR 0.78; 95 % CI 0.73–0.84), and platelet inhibitors (HR 0.74; 95 % CI 0.69–0.81) were individually associated with lower mortality risk (all $p < 0.001$). However, beta-blockers did not improve mortality (HR 0.97; 95 % CI 0.90–1.06; $p = 0.54$).

Frequency of secondary prevention medications use after CABG was high in the early post-operative period but decreased significantly. It is essential to use statins, RAAS inhibitors, and platelet inhibitors after CABG, and the use of beta-blockers may be questioned.

The majority of randomized trials on the use of implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death in patients with HFrEF were conducted at the end of the twentieth century. The study investigated the association of ICD and mortality rates in a HFrEF cohort receiving modern treatment. Patients from the **Swedish Heart Failure Registry** [26] who met the European Society of Cardiology criteria for primary prevention of sudden cardiac death with an ICD. The association between ICD use, 1-year and 5-year all-cause and cardiovascular mortality was assessed by Cox regression models in predetermined groups.

Of 16.702 patients who met the criteria only 1599 (10 %) had an ICD implanted. ICD use was associated with a reduction of all-cause mortality risk within 1 year (HR 0.73; 95 % CI 0.60–0.90) and 5 years (HR 0.88; 95 % CI 0.78–0.99). The similar results were observed in all subgroups, including the patients with and without CAD, men and women aged <75 and ⩾75, in those with earlier and later enrollment in Swedish Heart Failure Registry, and in patients with and without cardiac resynchronization therapy.

In a modern HFrEF population, ICD is underused, although it significantly reduces short-term and long-term mortality in all the clinical and demographic subgroups. These finding support better implementation of ICD in systolic CHF.

The **PURE** [27,28] prospective study presents findings from 155.722 participants (21 countries, 5 continents, except Australia) aged 35–70 years, who were enrolled in 2005–2016 with a following follow-up (median = 9.5 years). The investigators compared causes of death in high-income, middle-income, or low-income countries, modifiable risk factors effect on cardiovascular disease events (cardiovascular death, MI, stroke and heart failure) and mortality. According to the findings, mortality was caused by cardiovascular events in 43 %, 42 % and 23 % of cases, and by cancer in 15 %, 30 %, 55 % in high-income, middle-income, or low-income countries, respectively. All-cause mortality rates, adjusted for age and gender, decreased with the increase in income — 13.3, 6.9 and 3.4/1000 patient-years in high-income, middle-income, or low-income countries respectively. When analyzed separately, low income was associated with increased mortality from cardiovascular and respiratory diseases, traumas and infections; and with decreased mortality from cancer. Mortality from cardiovascular causes to mortality from cancer ratio was 3.0, 1.3 and 0.4 in high-income, middle-income, or low-income countries, respectively. The most important cardiovascular disease risk factor was arterial hypertension, followed by high LDL level and air pollution. Smoking, bad diet, poor education and abdominal obesity also increased cardiovascular disease risk. Behavioral and metabolic risk factors were predominant risk factors in high-income countries, and poor education and air pollution were predominant in middle-income and low-income countries.

Most cardiovascular disease cases and deaths can be prevented by adequate control of metabolic and behavioral risk factors in households and individuals. National healthcare policies should focus on risk factors of greatest significance in the specific groups of countries. In low-income and middle-income countries, the greatest benefit can be achieved by smoking limitations, blood pressure control, healthcare investments and better availability of medication for modifiable risk factors correction.

HOT LINE Session 6

The **RAPID-TnT** study [29] investigated the use of earlier high-sensitivity troponin (hs-cTnT) assays to safely exclude MI in patients presented into the emergency department with ACS. Patients were randomly assigned to receive care guided either by the early (0/1-hour) hs-cTnT assessment protocol with exclusion criteria <5 ng/L (n = 1646) or by standard (0/3-hour) assessment protocol with exclusion criteria < 29 ng/L (n = 1642). Participants in the 0/1-hour arm were more likely to be discharged earlier compared with

the standard arm (45.1% versus 32.3% respectively; p<0.001), and the median length of stay was shorter (4.6 hours versus 5.6 hours respectively, p<0.001). Over the 30-day follow-up period primary endpoint events (all-cause death or MI) occurred with the same frequency in both arms (1.0% in the 0/1-hour arm versus 1.0% in the standard arm; RR 1.06; 95% CI 0.53–2.11; non-inferiority p-value=0.06, superiority p-value=0.867). Among the discharged patients, the negative predictive value for the 0/1-hour protocol was 99.6% (95% CI 99.0–99.9%) for 30-day risk of death or MI.

The early (0/1-hour) hs-cTnT assessment protocol which was tested in clinical settings enables earlier discharge of patients with suspected ACS, without worsening the 30-day outcomes. Recent findings suggest the possibility of future changes in suspected ACS patient management.

A randomized, open-label, phase 3b **ENTRUST-AF PCI** study [30] involved patients with atrial fibrillation (AF) requiring oral anticoagulation, who had undergone successful PCI for stable CAD or ACS. Patients were randomized from 4 to 5 days after PCI to either edoxaban (60 mg once daily) plus a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor depending on the investigators' preferences) for 12 months or a vitamin K antagonist (VKA) plus a P2Y12 inhibitor and aspirin (100 mg once daily) for 1–12 months. The edoxaban dose was later reduced to 30 mg once daily if one or more factors (creatinine clearance 15–50 mL/min, weight ⩽60 kg, or concomitant use of potent P-glycoprotein inhibitors) were present. At 12 months the primary safety endpoint events (major or clinically relevant non-major bleeding) occurred in 17% (annualized event rate 20.6%) of patients in the edoxaban group and in 20% (annualized event rate 25.6%) of patients in the VKA group (HR 0.83; 95% CI 0.65–1.05; non-inferiority p-value p=0.0010, superiority p-value p=0.1154). Annualized primary efficacy endpoint event rate (cardiovascular disease, stroke, systemic embolism, MI or stent thrombosis) was 7.3% in the edoxaban group and 6.9% in the VKA group (HR 1.06; 95% CI 0.71–1.69).

In patients with AF who had PCI double antiplatelet edoxaban-based therapy was non-inferior for safety (bleeding risk) compared with the standard triple antithrombotic VKA-based regimen, without significant difference in ischemic events rate.

In an open-label **POPular Genetics** study [31] patients who had undergone primary PCI were randomized to undergo an early genetic testing (n=1242) or to standard treatment with ticagrelor or prasugrel (n=1246). It is known that CYP2C19*2 or CYP2C19*3 alleles are associated with reduced transformation of clopidogrel into its active form. Patients in the genetic testing group who tested positive for CYP2C19*2 or CYP2C19*3 alleles were treated with ticagrelor or prasugrel, and those who tested negative were treated with clopidogrel. At 12 months a total of poor clinical outcomes (primary combined endpoint: death from all causes, MI, stent thrombosis, stroke or major bleeding) occurred in 5.1% in the genetic testing group versus 5.9% in the standard therapy group (p<0.001 for non-inferiority). PLATO major or non-major bleeding rate was 9.8 in the genetic testing group and 12.5% in the standard therapy group (HR 0.78; 95% CI 0.61–0.98; p=0.04).

In patients who had PCI the strategy of genetic testing with CYP2C19 genotype evaluation for oral P2Y12 inhibitor selection was non-inferior compared with standard regimen with ticagrelor or prasugrel in preventing thrombotic events at 12 months.

The DAPA study [32] that began in 2004 was stopped early in 2013 due to slow enrollment of patients who had STEMI. It was originally planned to investigate the reduction in mortality ICD implantation (n=131) compared with medical therapy only (n=135). During a median follow-up of 9 years all-cause mortality rate was 24.4% in the PCI group compared with 35.5 in the medical therapy group (HR 0.58; 95% CI 0.37–0.91; p=0.02); cardiac death occurred in 11.5% versus 18.5% respectively (HR 0.52; 95% CI 0.28–0.99; p=0.04), and including the death from the heart failure — 3.1% versus 5.9 respectively.

The limitations of this study were low statistical power, transition of patients between groups and questionable inclusion criteria.

The next European Society of Cardiology Congress will take place in Amsterdam, Netherlands from the 29th of August to the 2nd of September 2020.

Conclusions

This article presents the materials from the European Society of Cardiology 2019 which were of particular interest according to the authors opinion. More information about the Congress is available on https://www.escardio.org. New scientific findings made in the well-planned and accurately conducted randomized clinical studies will undoubtfully have a great influence on medical practice.

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