How will 2014 European Society of Cardiology Congress influence our daily practice?

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ABSTRACT

European Cardiology Congress which was held in Barcelona in this year; was a meeting with striking results of the presented scientific studies. Herein, a brief overview of congress highlights is presented. *(Anadolu Kardiyol Derg 2014; 14: 669-73)*

Introduction

2014 European Society of Cardiology (ESC) congress, which was held in Barcelona, was a meeting that was full of scientific data which will influence our daily clinical practice. This meeting is currently regarded as the most crowded one among competitors. Due to constraints of Ministry of Health in Turkey and heavy work-load of the program, it might not be possible for many of participants to follow up all of the advances. Herein, some of the highlights of the 2014 ESC annual congress are presented under subtitles.

Heart failure

(Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure) PARADIGM-HF (1): This was the most remarkable study of ESC 2014. 8842 patients with heart failure with reduced ejection fraction (HFREF) were randomized to ARNI (LCZ696 200 mg bid) or enalapril (10 mg bid) after run-in period during which both agents were administered to all patients. **The study was prematurely stopped due to overwhelming benefit in the ARNI arm**. Cardiovascular mortality was reduced by 20%, HF related rehospitalization rate was reduced by 21% and finally total mortality was reduced by 16% along with an acceptable safety profile.

(Beneficial effects of long-term intravenous iron therapy with ferric carboxy maltose in patients with symptomatic heart failure and iron deficiency) CONFIRM-HF (2): 304 chronic HFREF patients were randomized 1:1 to intravenous iron therapy (ferric carboxy maltose) or placebo (double blind, therapy at basal, 6th month, 12th month, 24th month, 36th month, first two dose 500-2000 mg, then 500 mg). Whole group had mean hemoglobin of 12.4 gr/dL. After iron therapy, NYHA functional class, KCCQ scores, 6-minute walking distance, dyspnea score were improved in the active treatment arm compared to placebo. Furthermore, HF related rehospitalization was reduced by 61%, though, **the study was not powered to draw definitive conclusions.**

Neural Cardiac Therapy for Heart Failure (NECTAR-HF): HFREF patients with EF<35% and LVEDD>55 mm were considered for the study. All patients were implanted a generator into right pectoral pocket and a bipolar helix lead, which was wrapped around right vagus nerve, was then connected to generator. 95 patients were randomized 2:1 to active therapy arm and sham control. Echocardiographic parameters, blood tests, exercise tests were obtained at basal and at 6th month of follow up in 86 patients. After 3 months, stimulation threshold was increased up to 1.42±0.80 mA. **There was no change in echocardiographic parameters or biomarker levels**, though, there was slight improvement in quality of life scores.

(Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure) ANTHEM-HF: 80 HFREF patients with EF<%40, LVDD>55 mm were randomized to right vagus (n=29) and left vagus (n=31) stimulated device therapy. 59 patients were taken into uptitration phase. Vagal stimulation threshold was increased up to 2.0±0.6 mA. After 6 months, there was no difference between right or left vagus stimulation. In the

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whole group, **EF was increased 4.5%, LVESV decreased 4.1 mL, heart rate variability was increased by 17 msec, 6-minute walking distance was increased by 56 meters** (better with right vagus stimulation). The only handicap was noted as absence of "sham" control.

"MicroRNAs as non-invasive biomarkers of heart transplant rejection" (3): In this study, 113 patients who underwent cardiac transplantation were considered (60 patients in the derivation cohort, 53 patients in the validation cohort). Micro RNA expression was compared in patients who had rejection and in those who did not have rejection. There was differential expression in the levels of 4 microRNA, namely, miR-10a, miR-31, miR-92a, miR-155. Diagnostic performances were as follows: miR-10a (AUC=0.975), miR-31 (AUC=0.932), miR-92a (AUC=0.989), and miR-155 (AUC=0.998) (all p<0.0001). **Along with the very strong AUC, it is not surprising to expect a paradigm shift in the diagnosis of transplant rejection soon**.

For the detailed analysis of HF studies, latest HF bulletin of HF WG of TSC is recommended.

Stable coronary artery disease

(Ivabradine in stable coronary artery disease without clinical heart failure) SIGNIFY (4): 19.102 patients with stable coronary artery disease having resting heart rate of >70 bpm, but without HF, were enrolled and randomized 1:1 to ivabradine (n=9550, up to 10 mg bid with a target hart rate 55-60 bpm) or placebo (n=9552) on top of standard therapy. Of note, there was angina of CCS class II or more in 12.049 patients. After 3 months, mean heart rate was 60.7±9.0 bpm in the ivabradine arm, versus, 70.6±10.1 bpm in the placebo arm. After a median follow up of 27.8 months, primary end point, which was a composite of death from cardiovascular causes or nonfatal myocardial infarction, was noted to be similar in both arms (6.8%-6.4%, p=0.2). In the subgroup of patients with angina, primary end point of death from cardiovascular causes or nonfatal myocardial infarction was more frequently encountered in the ivabradine arm. Nevertheless, bradycardia was more frequently observed in the ivabradine arm (18.0% vs. 2.3%, p<0.001). Along with this large scale trial, it could be concluded that **there is no room for ivabradine in the management of stable coronary artery disease.** Of note, this finding should not dissuade physicians to administer ivabradine in patients with HFREF along with clear-cut benefit observed in this group of patients.

Fractional Flow Reserve-Guided PCI for Stable Coronary Artery Disease (FAME 2) (5): In this study, 1220 patients with angiographically documented stable coronary artery disease were evaluated. 888 patients with fractional flow reserve (FFR)≤0.80 were randomized 1:1 to PCI plus medical therapy arm (n=447) and only medical therapy (n=441). Remaining 332 patients with FFR>0.80 were enrolled into registry arm. Primary endpoint was composite of total mortality, nonfatal MI, unplanned hospitalization leading to urgent revascularization. Study was prematurely terminated. Primary endpoint was 8.1% versus 19.5% respectively in FFR guided PCI plus medical therapy arm versus only medical therapy arm (p<0.001). This reduction was driven by a lower rate of urgent revascularization in the FFR guided PCI plus medical therapy arm (4.0% vs. 16.3%; p<0.001), along with no significant between-group differences in the rates of death and myocardial infarction. Composite endpoint in the registry arm was similar to FFR guided PCI plus medical therapy arm (%9, p=0.72). One of the interesting subgroup analyses was time-dependent differential effect on outcomes. During the first 7 days, hazard ratio for primary endpoint in FFR guided PCI plus medical therapy over medical therapy alone was 2.49, whereas, between 7 days-2 years, it was 0.29 (p for interaction <0.001). Furthermore, combined endpoint of death or MI yielded similar trends as hazard ratio of 9.01 for the first 7 days, and 0.56 between 8 days and 2 years (p=0.04). Of note, most of the primary endpoints in the first seven days were due to periprocedural MI. In conclusion, it was shown that **FFR guided treatment plan improves outcomes in patients with stable coronary artery disease.**

Acute coronary syndrome

(Effect of darapladib on major coronary events after an acute coronary syndrome): SOLID-TIMI 52 Çalışması (6): Efficacy and safety of darapladib, as an oral, selective inhibitor of the Lipoprotein-associated phospholipase A2 (Lp-PLA2) enzyme, was evaluated in patients after an acute coronary syndrome (ACS). 13.026 patients with an ACS [non-ST-elevation or ST-elevation myocardial infarction (STEMI)] were randomized to either once-daily darapladib (160 mg) or placebo within 30 days of hospitalization for an index ACS event and were followed up for a median of 2.5 years. The primary end point which was the composite of coronary heart disease death, MI, or urgent coronary revascularization for myocardial ischemia was similar in both arms [16.3% vs. 15.6% at 3 years; hazard ratio (HR), 1.00 p=.93]. No difference was observed between the two arms for other secondary end points, either. Whereas, agent specific side effects were more common in the active treatment arm. **In conclusion, darapladib is useless after ACS.**

(Prehospital ticagrelor in ST-segment elevation myocardial infarction) ATLANTIC (7): Ticagrelor as a P2Y12 receptor antagonist was shown to be more efficient compared to clopidogrel previously. However, this efficiency was not tested in terms of rapidity of action. Hence, in this study, prehospital (in the ambulance) administration of ticagrelor was tested against usual in-hospital administration (in the catheterization laboratory) with the aim to improve coronary reperfusion and the clinical outcome. 1862 patients with STEMI of less than 6 hours were randomized 1:1 to prehospital ticagrelor versus in-hospital ticagrelor. Median time difference of 31 minutes between the two arms did not yield any difference in the end points which include ST-segment elevation resolution and the rates of major adverse cardiovascular events. Definite stent thrombosis was less frequently observed in prehospital ticagrelor than in the in-hospital ticagrelor, though, the numbers were too small (0.2% vs. 1.2%).

Safety profile with regard to any bleeding outcome was similar in both arms. **Administration of ticagrelor in the ambulance in patients with acute STEMI did not improve outcomes**, but, it is a safe alternative.

TASTE-1 (Outcomes 1 year after thrombus aspiration for myocardial infarction) (8): Routine intracoronary thrombus aspiration before PCI in patients with STEMI was shown not to reduce short-term mortality previously. Clinical outcomes at 1 year were presented in the ESC congress. 7244 patients with STEMI had been randomized to manual thrombus aspiration followed by PCI or to PCI alone. The primary end point of all-cause mortality at 30 days was similar in both. Total mortality at 1 year was another prespecified secondary end point of the trial. Total mortality rates were 5.3% and 5.6% in the thrombus-aspiration group and the PCI-only groups respectively (p=0.57). All other endpoints were also identical in both arms irrespective of grade of thrombus burden and coronary flow before PCI. Routine thrombus aspiration before PCI in patients with STEMI did not reduce major adverse cardiovascular events (MACE) either at 1st month or at the 1st year. **In conclusion, routine thrombus aspiration in STEMI seems useless, though, bail-out efforts were not tested appropriately.**

(Complete versus Lesion-only PRimary PCI Trial) CvLPRIT: In this study, 296 patients with STEMI were randomized 1:1 to complete revascularization (n=150) arm versus PCI only in infarct related artery (IRA, n=146) arm. MACE rates were significantly lower in the complete revascularization arm than in PCI only in IRA arm (10%-21.2%, p=0.009). On the other hand, contrast volume and procedural time were significantly more in the complete revascularization arm than in (250 versus 190 mL, p<0.001 and 55 versus 41 minutes, p=0.001 respectively). **In conclusion, contrary to existing guidelines, complete revascularization in patients presenting with STEMI was shown to be superior to PCI only in the IRA arm**. These results put up more evidence in favor of PRAMI (9).

(Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction) FAMOUS-NSTEMI (10): FFR is a game changer in patients with stable coronary artery disease. However, it has not been tested in ACS patients previously. In this study, 350 patients with non-ST segment elevation myocardial infarction (NSTEMI) were randomized 1:1 to FFR-guided management or standard care (angiography guided). FFR result was disclosed to the operator in the FFR-guided group (n=176) and was kept blinded to the angiography-guided group (n=174). Of note, median time from the index episode of myocardial ischaemia to angiography was 3 days. Integrating FFR result into decision making resulted in final decision of medical therapy more frequently (22.7% vs. 13.2%, p=0.022). Unblinding to FFR yielded a change in treatment strategies (PCI versus bypass versus medical therapy) not only in one direction but also in every direction (from PCI to medical therapy or from medical to PCI or bypass to medical) in 21.6% of patients. After 1 year, revascularization rate was lower in the FFR-guided group (79.0% vs. 86.8%, p=0.054). Quality of life outcomes did not differ between the groups. **In patients with NSTEMI, integrating FFR into clinical decision making process resulted in lower rate of revascularization compared to standard care without a trade off in quality of life or other MACE.**

Arrhythmia

(Optimal Method and Outcomes of Catheter Ablation of Persistent AF) STAR AF-2: In this study; 589 patients with persistent AF were randomized 1:4:4 to receive pulmonary vein isolation alone (PVI, n=67) versus PVI plus ablation of left atrial parts that produce complex fractionated electrograms (PVI+electrograms, n=263) versus PVI plus ablation of linear lesions in the left atrium (PVI+lines, n=259) with aim to identify which method is the best with regard to outcomes. Pulmonary vein isolation was successful in 97% of all patients. Procedural time was significantly shorter for the PVI alone group (167 mins) compared to other arms (229 and 223 mins respectively; p<0.001). After 1.5 years, freedom from AF recurrence was similar among three arms (59% for PVI alone, 48% for PVI+electrograms, and 44% for PVI+lines; p=0.15). Furthermore, repeat ablation was performed in 29% of the patients, though; the results did not change after two ablations, either. On the other hand, with regard to safety outcomes, some high-risk complications were more frequently noted in plus groups compared to PVI only arm. **In conclusion, PVI alone achieves outcomes which are comparable to addition of more complex procedures in persistent AF. Addition of further procedure seems to increase procedural time with no additional benefit over PVI alone at a cost of increased complications.**

Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation [X-VeRT(11)]: In this study, 1504 patients with atrial fibrillation undergoing elective cardioversion were randomized 2:1 to rivaroxaban (20 mg once daily, 15 mg if creatinine clearance was between 30 and 49 mL/min) or dose-adjusted warfarin. Early cardioversion (target period of 1-5 days after randomization) versus delayed cardioversion (3-8 weeks) was also evaluated. Composite of stroke, transient ischaemic attack, peripheral embolism, myocardial infarction, and cardiovascular death was noted in 0.51% in the rivaroxaban group and in 1.02% in the warfarin group (risk ratio 0.50; 95% C:0.15-1.73). In the early cardioversion arm, 0.71% patients experienced composite outcome in the rivaroxaban group, whereas, 1.08% of the patients in the VKA group experienced composite outcome. Time to cardioversion was shorter in the rivaroxaban arm compared to warfarin arm (22 days vs. 30 days, p<0.001). With regard to safety, rivaroxaban was similar to warfarin (0.6% vs. 0.8%, risk ratio 0.76; 95% CI 0.21-2.67). **In conclusion, data coming from this randomized trial seems to prove efficacy and safety of rivaroxaban as compared to warfarin along with a better profile when early cardioversion strategy was sought**.

Prospective Registry of Patients Using the Wearable Defibrillator (WEARIT-II Registry): Arrhythmic risk could poten-

tially be transient in some patients who are referred to ICD implantation. In this case, wearable cardioverter defibrillator can help decision making process. In this registry, 2000 patients who were referred to implantation of wearable cardioverter defibrillator were enrolled. Median age was 62 years, median EF was 25%, and women comprised 30% of the whole cohort. 40.3% of patients were suffering from ischemic cardiomyopathy. Median wearable cardioverter defibrillator wear time was 90 days with a median daily use of 22.5 hours. Sustained ventricular tachycardia was recorded in 41 patients. Inappropriate wearable device shock was rare (0.5%). The most frequent reason not to implant an ICD following WCD wear was improvement in left ventricular ejection fraction. **In conclusion, it seems wearable devices can potentially prevent unnecessary ICD implantations, and also identify patients who really need ICD**.

ELECTRa (European Lead Extraction ConTRolled) Registry: Transvenous Lead Extraction (TLE) is a contemporary iatrogenic problem secondary to device era. Since, objective data concerning indication, success rate and safety of TLE are still lacking, this registry was undertaken. In this multicentric registry of patients undergoing TLE, acute and long-term safety of TLE were evaluated and complication rate was evaluated according to lead extraction workload of the center (high volume >2.5 pts/month and low volume centres <=2.5 pts/month). 3524 patients were evaluated. Mean age was 65 years (72% male). There were several types of devices. Almost 50% of extractions were related to infection. Clinical success rate of extraction was 95.5%. Death rate overall was 1.4% (1.2% in high volume centres and 2.5% in low volume centres). Major complications were noted in 2.7% (2.5% for high volume centres while 3.9% for low volume centres). **In conclusion, it seems TLE is relatively successful procedure with a low complication rate. Worthwhile mentioning is almost 50% difference in mortality and complication rates between low volume versus high volume centers**.

Pericarditis&Pericardial effusion

Post-Operative Pericardial Effusion-2 (POPE-2): In this study, 8140 consecutive postoperative patients were screened by transthoracic echocardiography for presence of moderate to large post-operative pericardial effusion (POPE). 197 consecutive patients with moderate to large POPEs (grade 2 or higher) between 7 and 30 days after cardiac surgery were randomized to colchicine (n=98, 1 mg bid loading if patient weighs at least 70 kg and then 1 mg/day maintenance for 14 days, if patient is less than 70 kg, no loading was done) or placebo (n=99) for 14 days. Change in pericardial effusion grade after treatment was the primary end point along with a secondary endpoint of cardiac tamponade. Mean age was 64 years, and 86% were male. After 14 days of treatment, placebo and colchicine arms were similar with regard to mean decrease in POPE grade from baseline (p=0.23). There were 13 cases of cardiac tamponade, with 7 in the placebo group and 6 in the colchicine group (p=0.80).

In conclusion, among postoperative patients with moderate to large pericardial effusion 6.6% develops cardiac tamponade, and **colchicine is of no benefit in either prevention of tamponade or treatment of effusion. Of note, diclofenac, an NSAID, had also failed in this indication in POPE-1 (12).**

Colchicine for Prevention of the Post-pericardiotomy Syndrome and post-operative atrial fibrillation (COPPS-2) Çalışması (13): Cardiac surgery is known to be associated with post-pericardiotomy syndrome, post-operative atrial fibrillation (AF), and post-operative effusions. In this study, 360 consecutive candidates for cardiac surgery, 180 for each arm, were randomized to receive colchicine (0.5 mg twice daily in patients ≥70 kg or 0.5 mg once daily in patients <70 kg) or placebo between 48-72 hours before surgery and continued for 1 month after surgery. Patients without baseline sinus rhythm were not considered. Mean age 67.5±10.6 years, 69% were men, and 36% had planned valvular surgery. Post-pericardiotomy was observed in 19.4% patients in colchicine arm versus in 29.4% in placebo (absolute difference, 10.0%; 95% CI, 1.1%-18.7%; number needed to treat=10). Post-operative AF was recorded in 41.2% patients in placebo arm versus 27.0% of patents in colchicine arm (absolute difference, 14.2%; 95% CI, 3.3%-24.7%). Adverse events were more common in colchicine arm than in placebo arm (20.0% vs. 11.7%). **There was no benefit of colchicine with regard to postoperative effusions**. On the other hand, frequent gastrointestinal side effects (14.4% vs 6.7%) would reduce potentially small benefit of colchicine in this group of patients.

Miscellaneous

(Statin Therapy in Cardiac Surgery) STICS: Perioperative statin therapy was shown to be associated with improved outcomes in small studies. In this large scale study, 1922 patients in sinus rhythm who were referred to elective cardiac surgery were randomized to 20 mg rosuvastatin (n=960) or placebo (n=962). Mean age was 59.4 years. Treatment began 8 days before the surgery and was continued for 5 days postoperatively. All patients were followed up for development of AF by Holter ECG for 5 days, and troponin levels were obtained to evaluate myocardial injury. Post-operative AF was similar in both groups (21% vs. 20%), and troponin levels were comparable in both groups (p=0.72). **In conclusion, there was no benefit of perioperative statin therapy, at least rosuvastatin, with regard to postoperative AF development or myocardial injury. This large scale trial will probably bring about end of statins in this indication.**

Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated daily statin (ODYSSEY COMBO II study): Alirocumab, one of the human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), is being tested for the treatment of hypercholesterolaemia and for the reduction of cardiovascular (CV) events. In this phase 3 study, patients were randomised 2:1 to either alirocumab 75 mg subcutaneously every 2 weeks or ezetimibe 10 mg daily. Alirocumab and placebo injections were administered as a single 1 mL using a

prefilled pen. A "treat to target" approach with alirocumab achieved significantly greater (~30% absolute) reductions in LDL-C vs. ezetimibe with a similar frequency of adverse effects.

There were several ongoing trials with "ocumab" family agents. Some of them were presented in different sessions in the ESC 2014. It seems a paradigm shift will occur later or sooner.

Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis (14): Atrial fibrillation (AF) and HF frequently coexist and it is relatively well established that presence of AF is known to be associated with poorer prognosis. Beta-blockers are strictly indicated in HFREF, though, there are some efficacy concerns for the subgroup of patients with AF. Authors, in this study, extracted individual patient data from 10 randomized controlled trials evaluating use of beta-blockers in HFREF cohort. Outcome data were meta-analyzed in patients with or without AF. 18.254 patients with HFREF were assessed, (76% in sinus rhythm, 17% in AF at baseline). Total mortality was 16% and 20.7% in patients in sinus rhythm and in patients with AF respectively (follow up of 1.5 years), as expected. However, there was a differential effect of beta blockers with regard to basic rhythm. There was a significant reduction in mortality rate in patients in sinus rhythm (HR 0.73, 0.67-0.80; p<0.001), whereas, there was overall neutral effect of beta blockers in patients with AF (HR 0.97, 0.83-1.14; p=0.73). Trends were similar in all other outcomes. **Discussions with regard to exposing HFREF patients with AF to unnecessary load of beta-blockers** which, in this analysis, were shown to have a neutral effect, were on the way. Whether we should really push on not only initiation but also uptitration of beta-blockers in HFREF patients with AF remains to be established. Of note, this meta-analysis gives insight only those who are in AF during initiation of such therapy, and hence, does not give any information about the patients who developed new AF under chronic beta blockade.

Battery-free pacemaker: This was one of the most striking studies, presented in the ESC 2014. An energy-harvesting device was extracted from an automatic wrist watch and encased in plastic housing with eyelets to allow suture to the epicardium of a 60 kg pig. Results showed that the device generated, just by the motion of the heart, a mean output power of 52 microwatts - the energy consumption of modern pacemakers is known to be around 10 microwatts. Adrian Zurbuchen, from the University of Bern, stated that 'This answers our core question that **heart motion can be converted into electrical energy that exceeds power requirements of modern pacemakers**". This group is planning to reduce the size and weight of the prototype to make it more sensitive to heart motion. It seems, in near future, heart will be the generator of its pacemaker, will even be able give defibrillator shock itself when needed.

In conclusion overall, 2014 ESC Congress was a meeting, full of inspiring and paradigm-shifting scientific data. There are several other presentations, which deserve to be mentioned. I have, herein, tried to summarize the ones that drew my attention most. I think, along with the published guidelines during the congress, ESC will keep serving as an evidence-based guide for physicians in the cardiovascular area.

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