The most important clinical trials presented at the HOT LINE sessions of the European Society of Cardiology Congress 2023

At the 9 scientific sessions of the HOT LINE Congress of the European Society of Cardiology 2023, the results of 29 randomized clinical trials were presented for the first time. The studies were devoted to various areas of cardiology, including the treatment of acute and chronic heart failure, cardiac arrhythmias, coronary heart disease, non-coronary myocardial diseases, the search for optimal diagnostic strategies, anticoagulant therapy, and treatment of COVID-19.

Keywords: clinical trials, cardiovascular diseases, treatment, diagnostics.

Conflict of interests: none declared.

Recieved: 19.03.2024
Accepted: 14.05.2024

STEP-HFpEF. Heart failure with preserved ejection fraction (HFpEF) is an increasingly common condition with particularly severe symptoms and functional impairment in obese individuals. In 529 patients with HFpEF and obesity, the results of semaglutide at a dose of 2.4 mg subcutaneously once weekly compared with placebo were observed for 52 weeks after randomization. The semaglutide group showed significant improvements according to Kansas City Cardiomyopathy Questionnaire quality of life (by 7.8 points; $p<0.001$), decreased body weight (by 10.7 %; $p<0.001$), increased 6-minute walk distance (by 20.3 m; $p<0.001$) and decreased C-reactive protein levels compared to placebo. Serious adverse events were reported in 13.3 % of participants in the semaglutide group and 26.7 % in the placebo group [1].

NOAH-AFNET 6. It is unclear whether episodes of frequent atrial pacing detected by an implanted device in the absence of atrial fibrillation (AF) require the initiation of anticoagulant therapy. Elderly patients with episodes (at least 6 minutes, mean 2.8 hours) of rapid (≥170 beats per minute) atrial rhythm detected by implantable devices and at least one risk factor for stroke were assigned to standard treatment with edoxaban (n=1270) or placebo (n=1266). The study was stopped early due to safety concerns at a mean follow-up of 21 months. The incidence of stroke was approximately 1 % per patient-year in both groups. There was no significant reduction in the incidence of cardiovascular death, stroke or systemic embolism with edoxaban compared to placebo ($p=0.15$), but a significant increase in the incidence of death from any

cause or major bleeding (p=0.03). In the study cohort, 18.2 % of patients developed electrocardiographically diagnosed atrial fibrillation during follow-up [2].

COP-AF. The perioperative risk of AF is thought to be related to inflammation, suggesting a potential benefit of anti-inflammatory drugs. Patients undergoing major non-cardiac thoracic surgery (lung lobe resection and others) received colchicine 0.5 mg (n=1608) or placebo (n=1601) 4 hours before surgery and twice daily for 10 days. During the 14-day follow-up, clinically significant perioperative atrial fibrillation was observed in 6.4 % and 7.5 % of cases (p=0.22), and myocardial damage in 18.3 % and 20.3 % (p=0.16) of patients receiving colchicine and placebo, respectively. Sepsis or infection was reported in 6.4 % of patients in the colchicine group and 5.2 % in the placebo group (p=0.14). Colchicine administration was significantly more associated with the development of non-infectious diarrhea (8.3 % vs. 2.4 % with placebo; p<0.001) [3].

QUEST. The 4 capsules of traditional Chinese medicine combination herbal medicine qiliqiangxin 3 times daily or placebo was added to standard therapy in 3110 patients with chronic heart failure (CHF) with reduced left ventricular ejection fraction (LV EF) (≤40 %). During a median follow-up of 18.3 months, the primary endpoint (rehospitalization for worsening HF or cardiovascular death) was observed in 25.02 % of patients in the qiliqiangxin group versus 30.03 % in the placebo group (p<0.001), and there was a significant reduction in the risk of each of the two endpoint components in the more active treatment group. No significant differences were observed between the matched groups in the incidence of all-cause mortality (14.21 % vs. 16.85 %) and the development of adverse events, including gastrointestinal symptoms, worsening renal function and increased liver enzyme levels [4].

BUDAPEST-CRT Upgrade. *De novo* implantation of a defibrillator-enabled cardiac resynchronization therapy device reduces the risk of morbidity and mortality in patients with left bundle branch block, HF, and reduced EF. However, the benefit of switching patients with HF and reduced EF from right ventricular pacing to cardiac resynchronization therapy with defibrillation capability is unclear. The study included 360 patients with an implantable cardioverter-defibrillator and intermittent or continuous right ventricular pacing with a stimulated QRS complex duration of at least 150 m/s. The placement of an additional left ventricular stimulation lead implanted in the lateral branch of the coronary sinus (n=215) was associated with a lower risk of the primary endpoint. That included: hospitalization for heart failure, all-cause mortlity, or no reverse myocardial remodeling (32.4 % vs. 78.9 %; p<0.001) and HF hospitalization or all-cause mortality (10 % vs. 32 %; p<0.001) compared to the continued right ventricular pacing with defibrillation option group (n=145) over 12 months of follow-up. The incidence of procedure- or device-related complications was similar in both groups [5].

HEART-FID. Iron carboxymaltosate therapy has previously been shown to reduce symptoms and improve quality of life in HF patients with reduced LV EF and iron deficiency, but the effect of such treatment on outcomes required additional study. Intravenous iron carboxymaltosate (n=1532) every 6 months (as needed based on iron and hemoglobin levels) or placebo (n=1533) was added to the treatment regimen for chronic HF with reduced (≤40 %) LV EF in iron-deficient patients. At 12 months, there were no significant differences in all-cause mortality (8.6 % vs. 10.3 % of cases) and hospitalization for HF (13.3 % vs. 14.8 %) in the iron carboxymaltosate and placebo groups, respectively, although the 6-minute walk distance increased by 8 m in the iron group and by 4 m in the placebo group at 6 months (p=0.02). The incidence of serious adverse events during the treatment period was not significantly different between the two groups (27.0 % vs. 26.2 % of cases, respectively) [6].

FIRE. The benefit of complete coronary revascularization in elderly patients with myocardial infarction (MI) and multivessel stenoses remains unclear. Patients with MI and multivessel coronary artery stenoses (mean age 80 years) underwent percutaneous coronary intervention (PCI) with stenting of all arteries with hemodynamically significant stenosis (n=720) or only the culprit artery (n=725). The combined primary endpoint of death, myocardial infarction, stroke, or any revascularization procedure at 1 year was less frequent in the complete revascularization group (15.7 % vs. 21.0 % in the culprit artery stenting group; p=0.01), and the safety of the intervention (composite of stroke, bleeding, or acute kidney injury associated with the administration of radiopaque contrast) was comparable (p=0.37) [7].

ECLS-SHOCK. Extracorporeal membrane oxygenation is increasingly used in the treatment of cardio-

genic shock in patients with MI without evidence of its effect on mortality. Patients with MI, experiencing the cardiogenic shock, who were scheduled for early revascularization were treated with venoarterial extracorporeal membrane oxygenation plus conventional medical therapy (n=209) or conventional medical therapy alone (control group; n=208). The primary efficacy endpoint, death from any cause at 30 days, was observed in 47.8 % versus 49.0 % of patients in the full extracorporeal support group and the control group, respectively (p=0.81). In the first group, moderate or major bleeding was 2.44 times more frequent and peripheral vascular complications requiring intervention were 2.86 times more frequent [8].

STOPDAPT-3. Patients with acute coronary syndromes (75 %) or at high risk of bleeding were treated with prasugrel 20 mg once prior to PCI and, after randomization, continued to receive prasugrel monotherapy at a dose of 3.75 mg/day (n=2984) or a combination of prasugrel (3.75 mg/day) with aspirin (81-100 mg/day; n=2982) for 1 month. The antiplatelet monotherapy and dual therapy groups did not differ significantly in the frequency of Academic Research Consortium bleeding type 3 or 5 (4.47 % vs. 4.71 %; p=0.66 for superiority) and the cumulative incidence of cardiovascular death, MI, definite stent thrombosis, or stroke (4.12 % vs. 3.69 %; p=0.01 for non-inferiority) at 30 days. Antiplatelet monotherapy with prasugrel increased the risk of subacute definite or probable stent thrombosis by 3.4-fold and the risk of unplanned coronary revascularization by 83 %. The aspirin-free strategy with low-dose prasugrel showed no superiority over dual antiplatelet therapy with respect to major bleeding at 1 month after PCI, but no inferiority in regard to the risk of cardiovascular events. In addition, the aspirin-free strategy was associated with an excess of coronary events [9].

ILUMIEN IV. Limited data were available on clinical outcomes after PCI in complex coronary artery lesions with optical coherence tomography versus standard coronary angiography. There was a significant difference in the minimum stent area (5.72±2.04 mm^2 vs. 5.36±1.87 mm^2; p<0. 001) with similar cumulative incidence of adverse outcomes — death from cardiac causes, MI or revascularization due to ischemia in the target artery area at 2 years (7.4 % and 8.2 % of cases; p=0.45), and stent thrombosis within 2 years (0.5 % vs. 1.4 % of cases; p=0.02) in the optical coherence tomography (n=1233) and angiography groups (n=1254), respectively [10].

OCTOBER. Patients with clinical indications for PCI and complex bifurcation lesions underwent myocardial revascularization using optical coherence tomography (n=600) or conventional coronary angiography (n=601). At a median follow-up of 2 years, the composite of primary endpoint events — cardiac death, MI, or target artery revascularization due to ischemia — was reported significantly less frequently in the optical coherence tomography-guided intervention group (10.1 % of patients) than in the conventional coronary angiography group (14.1 %; p=0.035). Procedure-related complications occurred at similar rates in the two groups (6.8 % and 5.7 % of cases, respectively) [11].

OCTIVUS. PCI was performed while using optical coherence tomography (n=1005) or intravascular ultrasound (n=1003) in patients with significant coronary artery lesions. After one year of follow-up, the incidence of the primary endpoint — death from cardiac causes, MI, or revascularization due to ischemia in the target artery area — was 2.5 % in the optical coherence tomography group and 3.1 % in the intravascular ultrasound group (p<0.001 for no less effective). The risk of contrast-induced nephropathy was similar in the two groups (p=0.85), and major procedural complications were lower in the optical coherence tomography group than in the intravascular ultrasound group (p=0.047), although no imaging procedure-related complications were observed [12].

ATTRibute-CM. A total of 421 elderly patients with transthyretin amyloid cardiomyopathy were prescribed akoramidis 800 mg twice daily (n=421) or placebo twice daily (n=211) for 30 months, with additional open-label use of tafamidis allowed at the discretion of the physician after 12 months. 14.5 % of patients receiving akoramidis and 21.8 % of patients receiving placebo were prescribed with tafamidis, which has previously been shown to be effective in this setting. The akoramidis group showed a statistically significant superiority in the risk of the primary combined endpoint with a hazard ratio of 1.772 (p<0.0001) in a hierarchical analysis that prioritized the endpoints in the following order: all-cause mortality, followed by the incidence of cardiovascular-related hospitalizations, subsequent change from baseline in the level of the N-terminal precursor of brain natriuretic peptide, subsequent change from baseline in the

6-minute walk distance. In addition, acoramidis was associated with a 50 % reduction in the relative risk of cardiovascular hospitalization (p<0.0001) [13].

ARREST. Patients with spontaneous circulatory recovery after out-of-hospital cardiac arrest without ST-segment elevation were transported by London Ambulance Service staff to one of 7 cardiac arrest centers (n=431) or to the geographically nearest emergency department (n=431) of 32 London hospitals. The primary endpoint (30-day all-cause mortality) was 63 % in the cardiac arrest center group and 63 % in the standard of care group (unadjusted hazard ratio 1.00; p=0.96). Only 2 % of patients in the cardiac arrest center group and 1 % in the standard of care group experienced serious adverse events, none of which were considered treatment-related. Thus, in patients without ST-segment elevation after successful out-of-hospital resuscitation, transfer to a specialized cardiac arrest center does not reduce mortality [14].

ADVENT. The comparative efficacy and safety of pulsed field ablation-based pulmonary vein isolation and conventional thermoablation in patients with paroxysmal AF have not been evaluated. Patients with paroxysmal AF refractory to antiarrhythmic drugs underwent pulsed-field catheter ablation (n=305) or conventional radiofrequency or cryoballoon (thermal) catheter ablation (n=302) to isolate the pulmonary vein orifices. At 1 year follow-up, the primary efficacy endpoint of freedom from primary procedure ineffectiveness, documented atrial tachyarrhythmia after a 3-month blinded period, antiarrhythmic drug use, cardioversion, or repeat ablation was reported in 73.3 % versus 71.3 % of cases in the pulsed-field and thermal ablation groups, respectively (p>0.999 for no less efficacy). The primary safety endpoint (acute and chronic serious device and procedure-related adverse events) was reported at the same rate in the matched groups (p>0.999 for no less safety) [15].

MULTISTARS AMI. In patients with ST-segment elevation MI (STEMI) and multivessel coronary stenoses, the optimal timing of complete revascularization remained unknown. Hemodynamically stable patients with STEMI and multivessel coronary heart disease (CHD) underwent immediate multivessel PCI (emergency group; n=418) or first intervention on the "culprit" artery followed by staged multivessel intervention on the "non-culprit" arteries within 19 to 45 days after the index procedure (staged group; n=422). During 1-year follow-up, the sum of events for the primary end point-death from any cause, non-fatal MI, stroke, unplanned revascularization due to ischemia, or hospitalization for HF was 8.5 % in the immediate treatment group compared with 16.3 % in the staged group (p<0.001 for not less effective and p<0.001 for superiority). The risk of death from any cause, stroke, and hospitalization for HF was similar in the matched groups. Serious adverse events were observed in 104 patients in the emergency group and 145 in the stage group [16].

CASTLE HTx. The prognostic role of catheter ablation in patients with symptomatic AF and end-stage HF remained unknown. In a single-center study, patients with symptomatic AF and New York Heart Association functional class II-III HF with EF ⩽35 % received catheter ablation to restore sinus rhythm and medical therapy (n=97) or medical therapy alone (n=97). At a median follow-up of 18 months, the primary endpoint of death from any cause, left ventricular assist device implantation or urgent heart transplantation occurred in 8 % and 30 % of patients, respectively (p<0.001), and death from any cause occurred in 6 % and 20 % of patients in the ablation and medical therapy groups, respectively. Procedure-related complications were observed in 3 patients in the ablation group and 1 patient in the medical therapy group [17].

FRAIL-AF. In frail patients with atrial fibrillation receiving vitamin K antagonists, the appropriateness of switching to direct oral anticoagulants remains unclear. Patients with non-valvular AF and frailty aged ⩾75 years (mean age 83 years) with a glomerular filtration rate ⩾30 ml/min/1.73 m^2 were switched to direct oral anticoagulants (n=662) or continued on vitamin K antagonists (n=661). After 12 months of follow-up, major and clinically significant bleeding (primary endpoint) occurred in 15.3 % vs. 9.4 % of cases (p=0.00112), and the incidence of thromboembolic complications was 2.4 % vs. 2.0 % in the direct oral anticoagulant and vitamin K antagonist groups, respectively. In frail elderly patients with AF, switching from adequate vitamin K antagonist therapy to direct oral anticoagulant therapy should not be considered in the absence of obvious indications [18].

OPT-BIRISK. Patients undergoing PCI for acute coronary syndromes (ACS) at high bleeding risk and high ischemic risk received dual antiplatelet therapy (clopidogrel plus aspirin) for 9 to 12 months,

followed by 9 months of clopidogrel plus aspirin (n=3850) or clopidogrel plus placebo (n=3850), followed by 3 months of aspirin alone. The risk of type 2, 3, or 5 bleeding according to the Bleeding Academic Research Consortium classification was lower in the aspirin-free group (2.5 % vs. 3.3 %; p=0.03) over 9 months of treatment. The cumulative risk of all-cause mortality, MI, stroke or clinically driven revascularization was also lower in the aspirin-free group (2.6 % vs. 3.5 %; p=0.02), and all-cause mortality was 0.3 % vs. 0.5 % of cases (p>0.05) [19].

ARAMIS. Hospitalized patients with symptomatic acute myocarditis and elevated cardiac troponin levels on standard therapy were compared to subcutaneous administration of the interleukin-1 receptor antagonist anakinra 100 mg once daily (n=57) or placebo (n=60) during hospitalization. The primary efficacy endpoint, the number of days free of myocarditis complications after hospital discharge, averaged 30 days in the anakinra group and 31 days in the placebo group. The safety endpoint, the number of serious adverse events within 28 days of discharge, was observed in 12.1 % of patients receiving anakinra and 10.2 % of patients receiving placebo, also with no significant differences between groups [20].

DANPACE II. Patients with sick sinus syndrome (n=539) were initially implanted with pacemakers programmed to a base rate of 60 beats per minute (bpm) with rate-adaptive pacing or a base rate of 40 bpm without rate-adaptive pacing. At 2 years, remote monitoring showed no differences between groups in the number of AF episodes lasting longer than 6 minutes (46 % each), longer than 6 hours or longer than 24 hours, frequency of progression to persistent or permanent AF, cardioversion for AF, or death from any cause. In addition, quality of life and 6-minute walk test scores at 12 months were similar in both groups. Significantly more patients in the 40 bpm pacing group experienced syncope or presyncope (22 %) compared to the 60 bpm pacing group (13 %). For this reason, or because of chronotropic incompetence, 23 % of patients required pacing reprogramming to a higher rate [21].

RED-CVD. In 650 patients with chronic obstructive pulmonary disease (COPD) and/or type 2 diabetes mellitus (DM) in primary care, a diagnostic intervention consisting of three steps was assessed: 1) symptom assessment using a questionnaire; 2) physical examination, determination of N-terminal brain natriuretic peptide precursor levels, and electrocardiogram recording; and 3) at the discretion of the primary care physician, referral to a cardiologist if abnormalities were detected (n=624) or usual care (n=592). Patients progressed to the next stage if they accumulated a number of points above a certain threshold. At one year, the rates of new diagnoses of cardiovascular disease (8.0 % vs. 3.0 %), HF (4.5 % vs. 1.5 %), AF (2.1 % vs. 0.8 %), and CHD (2.6 % vs. 1.4 %) were higher in the intervention group than in the usual care group. An easy-to-use active diagnostic strategy more than doubled the number of newly-found cases of CH, AF, and CHD in patients with COPD and/or type 2 DM in primary care compared with usual care, which may facilitate timely initiation of treatment for emerging cardiovascular conditions [22].

NITRATE CIN. Contrast-induced nephropathy (CIN) during coronary angiography and/or PCI is a long-standing problem. Researchers have searched for years for a method other than hydration to prevent such renal injury, and one after another these attempts have failed (examples include intravenous sodium bicarbonate and oral N-acetylcysteine). In patients with ACS without ST-segment elevation referred for invasive coronary angiography and at risk for CIN (more than half of patients had chronic kidney disease at baseline and 45 % had DM), the efficacy of potassium nitrate at a dose of 12 mmol (n=319) and potassium chloride (placebo; n=321) in capsules once daily for 5 days was compared. In the inorganic nitrate group, compared with placebo, there was a significant reduction in the risk of CIN (creatinine elevation ≥26.5 μmol/L within 48 hours or ≥1.5 times within a week) of 9.1 % vs. 30.5 %, (p<0.0001), procedural MI (2.7 % vs. 12.5 %; p=0.003) and major cardiovascular complications within a year (9.1 % vs. 18.1 % of cases; p=0.001) [23].

DICTATE-AHF. Patients with type 2 DM and an estimated glomerular filtration rate (eGFR) of at least 25 mL/min/1.73 m^2 hospitalized for acute decompensated HF with hypervolemia and receiving intravenous loop diuretics were treated with dapagliflozin at a dose of 10 mg/day for the first 24 hours (n=119) or standard therapy (n=119). After 5 days or up to the day of hospital discharge, there was no advantage of dapagliflozin in influencing the ratio of weight change in kg/dose of loop diuretic in mg. However, dapagliflozin significantly increased 24-hour natriuresis (p=0.025) and 24-hour diuresis (p=0.005), shortened

time to cessation of intravenous diuretic therapy (p=0.006) and time to hospital discharge (p=0.007). Early initiation of dapagliflozin was safe in regard to all DM and cardiovascular outcomes, and there were no between-group differences in change in eGFR from baseline to study end, incidence of adverse events, in-hospital mortality, symptomatic hypotension, hypoglycemia, genitourinary infections, or severe hypokalemia [24].

PUSH-AHF. Treatment of acute HF with natriuresis control in patients 2, 6, 12, 18, 24, and 36 hours after initiation of intravenous loop diuretics with possible dose adjustment (n=150) was compared with standard therapy (n=160). During the first 24 hours, natriuresis was significantly higher by an average of 63 mmol/L in the natriuresis-controlled group (p=0.0061), but the risk of all-cause death or hospitalization for heart failure at 180 days was the same as in the conventional treatment group (31 % in both groups; p=0.698). There were no significant differences between the two groups in terms of length of hospital stay, risk of electrolyte disturbances or worsening of renal function [25].

RIGHT. Patients undergoing primary PCI for STEMI with bivalirudin received postprocedural anticoagulant therapy within 4 hours of the procedure (n=1494): 1) unfractionated heparin at 10 U/kg/hour intravenously with dose adjustment to maintain an activated clotting time of 150-220 s or 2) enoxaparin at a dose of 40 mg once daily subcutaneously or 3) bivalirudin 0.2 mg/kg/hour intravenously or placebo (ie, no anticoagulant therapy; n=1495) for ≥48 hours. At 30 days, there was no difference in the cumulative incidence of the primary efficacy endpoint (all-cause death, non-fatal MI, non-fatal stroke, definite stent thrombosis, or urgent revascularization of any artery at 30 days) between the anticoagulation and placebo groups (p=0.988). However, there was a significant interaction between the primary efficacy endpoint and the type of anticoagulant used (p=0.015 for interaction). Enoxaparin reduced the risk of adverse events by 54 % compared to placebo, while unfractionated heparin increased the risk by 3.71-fold and bivalirudin by 1.24-fold. The incidence of the primary safety endpoint (major bleeding type 3-5 according to the Bleeding Academic Research Consortium within 30 days) did not differ between the two groups compared (p=0.511), and there was no significant interaction between the three anticoagulants (p=0.679 for interaction) [26].

ONCO DVT. The optimal duration of anticoagulant therapy for isolated distal deep vein thrombosis in cancer patients remained undetermined because such treatment may increase the risk of bleeding in addition to its presumed benefit. Active cancer patients with isolated distal deep vein thrombosis were treated with edoxaban (60 mg once daily or 30 mg once daily if creatinine clearance was 30-50 mL per minute or body weight ≤60 kg or in those receiving concomitant treatment with potent P-glycoprotein inhibitors) for 12 months (n=296) or 3 months (n=305). After one year, the primary endpoint, a composite of symptomatic recurrent venous thromboembolism or related death, was reported in 1.0 % vs. 7.2 % of cases (p<0.001), and major bleeding according to International Society on Thrombosis and Hemostasis criteria in 9.5 % vs. 7.2 % of cases in the 12-month and 3-month therapy groups, respectively [27].

The meta-analysis of the **DARE-19**, **RECOVERY**, and **ACTIV-4A** studies. Participants in the three trials who were hospitalized for COVID-19 received either additional sodium-glucose cotransporter type 2 inhibitors (n=3025) or conventional treatment/placebo alone (n=3071) after randomization. The primary endpoint of all-cause mortality within 28 days occurred in 11.7 % and 12.4 % of patients in the sodium-glucose cotransporter type 2 inhibitor and conventional treatment or placebo groups, respectively (p=0.33). There were also no significant differences in the risk of progression of acute kidney injury, need for dialysis, conversion to invasive mechanical ventilation, extracorporeal membrane oxygenation within 28 days, in-hospital mortality (p=0.37), or 90-day mortality (p=0.18). These results do not support the use of type 2 sodium-glucose cotransporter inhibitors as standard of care in this clinical setting, but also do not seem to justify the routine withdrawal of these drugs prescribed for other indications (HF, chronic kidney disease or type 2 DM) during COVID-19.

Conflict of interests: none declared.

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