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Notable clinical trials and meta-analyzes presented in the HOT LINE of ESC Congress 2022

Results from 22 international multicentre clinical trials were presented in HOT LINE sessions at the recent European Congress of Cardiology. The studies focused on different areas of cardiology, including arterial hypertension, coronary heart disease, atrial fibrillation, lipid-lowering therapy, pharmacotherapy of heart failure, intensive care in cardiology and healthcare organisation in cardiology.
Keywords: clinical trials, meta-analyzes, cardiovascular diseases.

The **TIME** study included 21,104 patients with arterial hypertension (AH) (median age 65.1 years) who were randomized to receive all of their prescribed antihypertensive therapy in the morning (06:00–10:00) or evening (20:00–00:00). At a median follow-up of 5.2 years, the combined primary endpoint of vascular death or hospitalization for non-fatal myocardial infarction (MI) or non-fatal stroke was reported at a comparable incidence of 0.69 and 0.72 per 100 patient-years in the evening and morning dosing groups, respectively (RR 0.95 with 95% CI 0.83 to 1.10; p=0.53). No treatment safety issues were identified. Evening versus morning administration of regular antihypertensive medication did not differ in terms of major cardiovascular outcomes. Patients can be advised to take their regular antihypertensive medication at a time that is convenient for them. According to the authors, this conclusion is definitive, at least for drugs with a guaranteed duration of action of 24 hours. However, the study did not identify and take into account specific groups of patients with AH, such as those with daily blood pressure (BP) profiles of non-dippers, night-peakers, over-dippers, for whom the timing of antihypertensive medication intake may be of significant importance.

In the **SECURE** trial, 2499 patients (median age 76 years) who had had an MI within the previous 6 months were randomized to polypill therapy (aspirin 100 mg + ramipril 2.5, 5.0 or 10 mg + atorvastatin 20 or 40 mg) or conventional therapy. At a median follow-up of 36 months, the combined primary endpoint event rate (cardiovascular death, non-fatal type 1 MI, non-fatal ischemic stroke or urgent revascularisation) was 9.5% vs. 12.7% (RR 0.76 with 95% CI 0. 60 to 0.96; p=0.02), and death from cardiovascular events, non-fatal type 1 MI or ischemic stroke was 8.2% versus 11.7% (RR 0.70 with 95% CI 0.54 to 0.90; p=0.005) in the polypill and conventional treatment groups, respectively. The better results in the polypill group were attributed to better adherence to treatment and the incidence of adverse events was similar between groups. The results of SECURE may have important implications for secondary prevention in patients with recent MI, as prescribing the polypill (aspirin + ACEi + statin) at hospital discharge simplifies treatment, increases adherence to drug therapy and improves cardiovascular prognosis.

In the Danish population-based **DANCAVAS** study, men aged 65–74 years were invited (n=16 736) or not

invited (n=29 790) in a 1:2 ratio to undergo screening for subclinical cardiovascular disease. Randomization was based on computer-generated random numbers and stratified by municipality. Screening included computed tomography to determine coronary artery calcium index and detect aortic aneurysms, electrocardiography to diagnose atrial fibrillation (AF), upper arm and ankle BP measurement to detect peripheral arterial disease and AH, and blood tests to detect DM and hypercholesterolemia. In an intention-to-treat analysis after a median follow-up of 5.6 years, the incidence of death from any cause (primary endpoint) was 12.6% versus 13.1% in the invited and control groups, respectively (RR 0.95 with 95% CI 0.90 to 1.00; p=0.06). The risk ratios for stroke were 0.93 (95% CI 0.86 to 0.99), MI 0.91 (95% CI 0.81 to 1.03), aortic dissection 0.95 (95% CI 0.61 to 1.49) and aortic rupture 0.81 (95% CI, 0.49 to 1.35) in the invited group compared with the controls. After more than 5 years, an invitation to comprehensive cardiovascular screening was not associated with a significant reduction in mortality from any cause in men aged 65 to 74 years. The effect of invitation to screening may have been underestimated because only 63% of those invited attended.

Acetazolamide, a carboanhydrase inhibitor that reduces sodium reabsorption in the proximal tubule, was evaluated for its potential to improve the efficacy of loop diuretics in the **ADVOR** trial in 519 patients with acute decompensated heart failure and signs of volume overload (oedema, pleural effusion or ascites), N-terminal brain natriuretic peptide levels greater than 1000 pg/ml or brain natriuretic peptide levels greater than 250 pg/ml. After randomization, acetazolamide (500 mg once daily) or placebo was added to the intravenous loop diuretic therapy at twice the oral maintenance dose. The primary endpoint of successful resolution of congestion, defined as no evidence of volume overload and no indication for increased diuretic therapy 3 days after randomization, was achieved in 42.2% of patients in the acetazolamide group and 30.5% in the placebo group (RR 1.46 with 95% CI 1.17 to 1.82; p<0.001). Death from any cause or rehospitalization for heart failure within 3 months of follow-up occurred in 29.7% of patients in the acetazolamide group and 27.8% in the placebo group (RR 1.07 with 95% CI 0.78 to 1.48). Treatment with acetazolamide was associated with greater cumulative diuresis and natriuresis. The incidence of renal dysfunction, hypokalemia and hypotension was similar between groups. More active diuretic therapy resulted in a shorter hospital stay (8.8 vs. 9.9 days; p=0.016). The addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure increases the rate of successful relief of congestion, indicating the importance of early aggressive therapy to ensure natriuresis.

The **BOX** study included 789 patients in coma after successful resuscitation for out-of-hospital cardiac arrest who were randomized according to a 2×2 factorial design to oxygen therapy to achieve an arterial blood partial pressure of oxygen of 9–10 kPa (68–75 mm Hg) or 13–14 kPa (98–105 mm Hg) and vasopressor/inotropic therapy to achieve a mean BP of 63 mm Hg or 77 mm Hg). The primary endpoint of death from any cause or hospital discharge with severe disability/coma was observed in 32.0% vs. 33.9% of patients in the lower vs. higher target arterial partial pressure of oxygen groups (RR 0.95 with 95% CI 0.75 to 1.21; p=0.69) and in 34% vs. 32% of patients in the lower vs. higher target mean arterial partial pressure of oxygen groups (RR 1.08 with 95% CI 0.84 to 1.37; p=0.56). Comparable variants of oxygen therapy intensity and use of vasopressor/inotropic therapy did not show significant differences in outcomes (death from any cause or discharge from hospital with severe disability/coma) within 90 days of successful resuscitation for out-of-hospital cardiac arrest.

In the **REVIVED-BCIS2** trial, 700 patients with LV dysfunction (ejection fraction of 35% or less) caused by coronary artery stenoses treatable by PCI and with the evidence of myocardial viability received PCI in addition to optimal medical therapy (PCI group) or optimal medical therapy alone (optimal medical therapy group) randomly. At a mean follow-up of 41 months, the combined primary endpoint (death from any cause or hospitalization for heart failure) occurred in 37.2% of patients in the PCI group and 38.0% in the optimal medical therapy group (RR 0.99 with 95% CI 0.78 to 1.27; p=0.96). At 6 and 12 months, there were no differences in mean LVEF between the two groups. Quality of life was better in the PCI group at 6 and 12 months, but this difference was lost at 24 months. In patients with severe ischemic LV systolic dysfunction who were receiving optimal medical therapy, myocardial revascularisation with PCI did not reduce the risk of death from any cause or hospi-

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talization for heart failure, nor did it improve LVEF or quality of life.

Allopurinol is a drug that lowers uric acid levels in the blood and is used to treat gout. The **ALL-HEART** trial enrolled patients with CHD aged over 60 years (mean age 72 years) with no history of gout. Patients were randomized to receive conventional therapy with the addition of allopurinol up to 600 mg/day (n=2853) or to continue therapy without allopurinol (n=2868). With a mean follow-up of 4.8 years, the event rate of the combined endpoint (non-fatal MI, non-fatal stroke or cardiovascular death) was similar in the conventional treatment group (11.3 %) and the addition of allopurinol (11.0 %; p=0.65), and all-cause mortality was not different between the two groups (p=0.77). ALL-HEART is the first large, prospective, randomized trial of the effect of allopurinol on major cardiovascular outcomes in patients with CHD without a history of gout and shows that allopurinol should not be recommended for secondary prevention of adverse events in this group of patients.

The **DELIVER** trial included 6263 patients with CHF and LVEF greater than 40 % who were receiving standard therapy to which dapagliflozin 10 mg/day or placebo was added after randomization. During a median follow-up of 2.3 years, the primary endpoint event of worsening heart failure (unplanned hospitalization for heart failure or urgent care visit for heart failure) or cardiovascular death occurred in 16.4 % of patients in the dapagliflozin group and 19. 5 % in the placebo group (RR 0.82 with 95 % CI 0.73 to 0.92; p<0.001), including worsening heart failure in 11.8 % vs. 14.5 % (RR 0.79 with 95 % CI 0.69 to 0.91) and cardiovascular death in 7.4 % vs. 8.3 % (RR 0.88 with 95 % CI 0.74 to 1.05) of patients, respectively. Symptom severity was significantly lower in the dapagliflozin group than in the placebo group. The results were similar in patients with LVEF of 60 % or more and less than 60 % with and without DM. The incidence of adverse events did not differ between groups. Dapagliflozin reduces the combined risk of worsening heart failure or CVD mortality in patients with heart failure and moderately reduced or preserved LVEF.

A pooled meta-analysis of two trials of dapagliflozin, **DAPA HF** and **DELIVER**, in participants with heart failure and different ranges of LVEF (⩽40 % and >40 %) was prespecified to examine the effect of treatment on endpoints and to test the consistency of the drug effect over a wide range of ejection fractions. The prespecified endpoints were death from cardiovascular causes; death from any cause; total number of hospitalizations for heart failure; and the sum of the major CVEs — death from cardiovascular causes, MI or stroke. A total of 11,007 participants with an average LVEF of 44 % were included. Dapagliflozin reduced the risk of death from cardiovascular causes (RR 0.86 with 95 % CI 0.76 to 0.97; p=0.01), death from any cause (RR 0.90 with 95 % CI 0.82 to 0.99; p=0.03), total hospitalizations for heart failure (RR 0.71 with 95 % CI 0.65 to 0.78; p<0.001) and major CCO (RR 0.90 with 95 % CI 0.81 to 1.00; p=0.045). There was no evidence that the effect of dapagliflozin differed by LVEF. In a pooled meta-analysis of patients with heart failure across the entire range of LV ejection fractions, dapagliflozin reduced the risk of death from cardiovascular causes and hospitalization for heart failure, severe CVEs.

After preliminary meta-analyzes of the **DELIVER** and **EMPEROR-Preserved** trials in chronic heart failure (CHF) with preserved or moderately reduced LV EF patients, outcomes in CHF with reduced LV EF patients (DAPA-HF and EMPEROR-Reduced) and those hospitalized with worsening heart failure regardless of LV EF (SOLOIST-WHF) were included in further statistical analysis. Among 12,251 participants in the DELIVER and EMPEROR-Preserved studies, sodium-glucose cotransporter type 2 inhibitors reduced the pooled risk of cardiovascular death or first hospitalization for heart failure (RR 0.80 with 95 % CI 0.73 to 0.87) with a concomitant reduction in the risk of both components of this primary endpoint (cardiovascular death — RR 0.88 with 95 % CI 0.77 to 1.00; first hospitalization for heart failure — RR 0.74 with 95 % CI 0.67 to 0.83). When the results of 5 studies involving 21,947 patients were summarised, sodium-glucose cotransporter type 2 inhibitors reduced the risk of cardiovascular death or hospitalization for heart failure (RR 0.77 with 95 % CI 0.72 to 0.82), cardiovascular death (RR 0.87 with 95 % CI 0.79 to 0.95), first hospitalization for heart failure (RR 0.72 with 95 % CI 0.67 to 0.78) and all-cause mortality (RR 0.92 with 95 % CI 0.86 to 0.99).

For each of the endpoints evaluated, the effects of treatment with type 2 sodium-glucose cotransporter inhibitors were consistently observed in heart failure trials with moderately reduced or preserved LV EF and in all 5 trials selected for meta-analysis. The effect of treatment on primary endpoint events was generally

similar in all 14 subgroups studied. Sodium-glucose cotransporter 2 inhibitors reduce the risk of cardiovascular death and hospitalization for heart failure in a wide range of patients with heart failure, supporting the role of these drugs as first-line therapy for heart failure regardless of LV EF or treatment setting.

The **INVICTUS** trial enrolled 4531 patients with AF and echocardiographically confirmed rheumatic heart disease, CHA_2DS_2-VASc thromboembolic risk of at least 2, mitral valve area of 2 cm^2 or less, spontaneous left atrial echocontrast or left atrial thrombus. Patients were randomized to receive standard doses of rivaroxaban or a dose-adjusted vitamin K antagonist. With a mean follow-up period of 3.1 years, the risk of the primary endpoint: a combination of stroke, systemic embolism, MI, or death from vascular (cardiac or noncardiac) or unknown causes, was higher in the rivaroxaban group than in the vitamin K antagonist group (OR 1, 25 with 95% CI 1.10 to 1.41). That included a higher risk of death (RR 1.23 with 95% CI 1.09 to 1.40) and ischemic stroke (RR 1.53 with 95% CI 1.06 to 2.20) in the rivaroxaban group, and the incidence of bleeding was similar between the two anticoagulant therapy options. Vitamin K antagonists should remain the standard of care for AF associated with rheumatic heart disease because of their advantage in preventing mortality.

Oral Factor XIa inhibitors may modulate coagulation and prevent thromboembolic complications without significantly increasing the risk of bleeding. In the phase 2 **PACIFIC AMI** trial in 1601 patients (median age 68 years), the oral factor XIa inhibitor asundexian at doses of 10, 20 or 50 mg or placebo once daily for 6–12 months was added to treatment with aspirin and ticagrelor or prasugrel, PCI, within 5 days of the diagnosis of MI after randomization. Asundexian produced a dose-dependent inhibition of XIa activity that was greater than 90% at the 50 mg dose. At a median follow-up of 368 days, Bleeding Academic Research Consortium type 2, 3 or 5 bleeding events occurred in 7.6%, 8.1%, 10.5% and 9.0% of patients receiving asundexian 10, 20 or 50 mg and placebo, respectively. Cumulative ischemic complications (cardiovascular death, MI, stroke or stent thrombosis) occurred in 6.8%, 6.0%, 5.5% and 5.5% of patients in the asundexian 10, 20 or 50 mg and placebo groups, respectively. In patients with recent MI, three doses of asundexian, when added to aspirin and a P2Y12 receptor inhibitor, dose-dependently and almost completely inhibited factor XIa activity without significantly increasing the incidence of bleeding or reducing the incidence of ischemic events. These data support the evaluation of asundexian at a dose of 50 mg/day in patients with MI in a phase 3 clinical trial with adequate statistical power.

The Phase 2b PACIFIC-Stroke dose-finding study of the oral Factor XIa inhibitor asundexian enrolled patients with acute (48 hours after symptom onset) non-cardioembolic ischemic stroke aged 45 years or older who were on antiplatelet monotherapy or dual antiplatelet therapy and were able to undergo brain MRI. After randomization, 1808 participants received asundexian 10 mg (n=455), 20 mg (n=450) or 50 mg (n=447) or placebo (n=456) once daily. At 26 weeks, the primary efficacy outcome (dose-response relationship on the combined incidence of occult MRI brain infarcts and recurrent symptomatic ischemic stroke) was met in 19% of patients in the placebo group, compared to 19% in the 10 mg asundexian group, 22% in the 20 mg asundexian group and 20% in the 50 mg asundexian group (p=0.80), while the primary safety outcome (major or clinically significant minor bleeding as defined by the International Society on Thrombosis and Haemostasis) was observed in 2%, 4%, 3% and 4% of patients, respectively. Factor XIa inhibition with asundexian in patients with acute non-cardioembolic ischemic stroke did not reduce the cumulative incidence of occult brain infarction or ischemic stroke or increase the major or clinically significant minor bleeding compared with placebo.

Digital smart devices are capable of detecting AF, but the effectiveness of this type of digital screening has not been directly compared with conventional care in detecting treatment-significant AF. The **eBRAVE-AF** trial randomized 5551 insured individuals (mean age 65 years, 31% women) without AF at baseline to digital screening (n=2860) or usual care (n=2691). In the digital screening group, participants used a certified app on their smartphone to detect pulse wave abnormalities. Abnormal results were assessed with an external ECG recorded with a loop recorder over 14 days. The primary endpoint was AF first diagnosed within 6 months and treated with oral anticoagulants by an independent physician not involved in the study. After 6 months, participants were invited to enter the second phase of the study with reverse allocation for secondary analyzes. The primary endpoint of the study was met as digital screen-

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ing more than doubled the detection rate of treatment-significant AF in both phases of the study, with an odds ratio of 2.12 (95% CI 1.19 to 3.76; p=0.010) and 2.75 (95% CI 1.42 to 5.34; p=0.003) in phases one and two, respectively. The digital screening technology used offers significant advantages in AF detection over conventional management and has potential for widespread application due to its accessibility on common smartphones. Further studies are needed to test whether digital AF screening leads to better AF management outcomes.

In the **FOURIER** study, the PCSK9 inhibitor evolocumab, when added to statins, significantly reduced LDL cholesterol levels and the risk of CVE in patients with atherosclerotic CVD and was safe and well tolerated over a mean follow-up of 2.2 years. The **FOURIER-OLE** study was designed to address the lack of large-scale long-term follow-up of this therapy by continuing the use of evolocumab (n=3355) in an open-label setting compared to placebo (n=3280). With a median follow-up of 5.0 years and a maximum exposure to evolocumab from randomization in FOURIER of 8.4 years, the incidence of serious adverse events, muscle symptoms, new-onset DM, haemorrhagic stroke and neurocognitive decline did not exceed that of the corresponding parameters in the placebo group, with a sustained LDL reduction of <40 mg/dL in 63.2% of patients. At the follow-up period of the FOURIER-OLE, patients initially randomized to the evolocumab group had a reduced cumulative risk of CVD death, MI, stroke, hospitalization for unstable angina or coronary revascularisation (RR 0.85 with 95%, CI 0.75 to 0.96; p=0.008), the risk of CVD death, MI or stroke by 20% (RR 0.80 with 95%, CI 0.68 to 0.93; p=0.003) and CVD death by 23% (RR 0.77 with 95%, CI 0.60 to 0.99; p=0.04) compared to placebo. Long-term LDL lowering with everolocumab is associated with a consistently low incidence of adverse events and a reduced incidence of CCO for more than 8 years, similar to placebo.

Statin therapy is widely used and effective in preventing atherosclerotic CVD, but concerns remain that it may cause muscle pain or weakness. **The Cholesterol Treatment Trialists' Collaboration meta-analysis** included 19 large, randomized, double-blind trials of statins versus placebo (n=123,940) and 4 double-blind trials of more and less intensive statin therapy (n=30,724). During a median follow-up of 4.3 years, 27.1% of those receiving statins compared with 26.6% of those receiving placebo reported muscle pain or weakness (OR 1.03 with 95% CI 1.01 to 1.06). During the first year of statin therapy, there was a relative increase in the incidence of muscle pain or weakness (RR 1.07 with 95% CI 1.04 to 1.10), which corresponds to an absolute excess incidence of 11 events per 1000 person-years, meaning that only one in 15 ([1.07–1.00]/1.07) of these reports of statin therapy were actually related to statins. After 1 year of follow-up, there was no excess incidence of first-time muscle symptoms in the statin group compared with placebo (RR 0.99 with 95% CI 0.96 to 1.02). High-intensity statin regimens (atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day) were associated with a higher risk of muscle symptoms than low-intensity and moderate-intensity statin regimens at 1 year follow-up compared with placebo (RR 1.05 with 95% CI 0.99 to 1.12). There was no clear evidence that the risk differed for individual statin molecules or in different clinical situations. Statin therapy causes a small, clinically insignificant increase in mean blood creatine kinase levels. Statin treatment causes a small increase in patient complaints of muscle pain, most of which are mild. The majority (>90%) of all reports of muscle symptoms in patients treated with statins are not statin-related. The risk of muscular symptoms is much lower than the known cardiovascular benefits of statins.

ARB and BB are widely used in the treatment of Marfan syndrome in attempt to reduce the rate of progression of aortic root dilatation accompanying this pathology. **The Marfan Treatment Trialists' Collaboration** meta-analysis included 10 randomized comparisons of ARB versus control or ARB versus BB in patients with Marfan syndrome who had not previously undergone aortic surgery (n=1442). The primary endpoint was the annual rate of change in aortic root Z-score (sinuses of Valsalva) adjusted for body surface area. At a median follow-up of 3 years, ARB administration approximately halved the annual rate of change in aortic root Z-score (mean annual increase of 0.07 in the ARB group versus 0.13 in controls; p=0.012). Prespecified subgroup analyzes showed that the effects of ARB were particularly significant in patients with pathogenic fibrillin-1 variants compared with those without it, and there was no evidence to suggest that the effect of ARB varied with BB use (p=0.54 for heterogeneity). Three trials (n=766) compared ARB with BB in eligible participants. At a

median follow-up of 3 years, the annual change in aortic root Z-score was similar in the matched groups (0.08 in the ARB group versus 0.11 in the BB group; p=0.48), whereas the difference in the annual change in aortic root Z-score between the ARB and control groups was 0.09 (p=0.042). In people with Marfan syndrome and without previous aortic surgery, ARB reduced the rate of increase in aortic root Z-score by about half, including those taking BB. The beneficial effects of BB and ARB are comparable, and their combination from the time of diagnosis will provide a greater reduction in the rate of aortic dilation than monotherapy, which over several years of therapy may delay the need for aortic surgery.

The **PANTHER** meta-analysis included 7 studies — ASCET, CADET, CAPRIE, DACAB, GLASSY, HOST-EXAM and TiCAB — conducted in 492 centres in Europe, Asia and North America. After exclusion, the final study population included 24,325 patients (mean age 64.3 years, 21.7% women) with confirmed CHD, of whom 12,178 received monotherapy with P2Y12 inhibitors (clopidogrel in 62% or ticagrelor in 28% of cases) and 12,147 received aspirin monotherapy. The mean duration of treatment was 557 days. The primary endpoint of the study (death from CVD, MI or stroke) occurred in 5.5% of patients in the P2Y12 inhibitor group versus 6.3% of patients in the aspirin group (RR 0.88 with 95% CI 0.79 to 0.97; p=0.014). The incidence of major bleeding type 3 or 5 according to the Bleeding Academic Research Consortium was similar when comparing P2Y12 inhibitor or aspirin antiplatelet therapy regimens (1.2% vs. 1.4%; p=0.23). When ischemic and haemorrhagic outcomes were combined, there was a lower cumulative risk of these adverse events in the P2Y12 inhibitor group, 6.4% versus 7.2% of cases in the aspirin group (RR 0.89 with 95% CI 0.81 to 0.98; p=0.020). Antiplatelet therapy is indicated after MI, PCI, stroke and coronary artery bypass graft surgery to prevent recurrent events. Based on these findings, long-term P2Y12 inhibitor monotherapy is preferable to long-term aspirin monotherapy in the secondary prevention of CHD.

Several randomized controlled trials have compared transradial and transfemoral access for the invasive treatment of CHD, with the former showing a lower mortality rate. **The Radial Trialists' Collaboration** meta-analysis included data from 7 randomized trials using transradial (n=10,775) or transfemoral (n=10,825) access. The mean age of patients was 63.9 years, 31.9% were female, 95% had ACS and 75.2% had undergone PCI. The primary endpoint (all-cause mortality at 30 days) was less frequent with transradial (1.6%) versus transfemoral (2.1%) access (RR 0.77 with 95% CI 0.63 to 0.95; p=0.012), and major bleeding at 30 days was also less frequent (1.5% versus 2.7%; RR 0.55 with 95% CI 0.45 to 0.67; p<0.001). Subgroup analysis of mortality showed consistent results except for baseline haemoglobin level (p=0.033), indicating superiority of transradial access in patients with significant anaemia, but not in those with mild or no anaemia. After adjustment, transradial access remained associated with a 24% RR reduction in all-cause mortality and a 51% reduction in major bleeding. In the invasive treatment of CHD, transradial access was associated with lower rates of all-cause mortality and major bleeding at 30 days compared with transfemoral access. The positive effect of transradial access on mortality is seen in patients with anaemia. The reduced risk of major bleeding only partially explains the reduction in mortality.

The efficacy and safety of prophylactic use of full-dose anticoagulant and antiplatelet therapy in patients with critically severe COVID-19 remained uncertain. In the open-label, controlled **COVID-PACT** trial with a 2×2 factorial design and blinded endpoint adjudication, 390 patients with COVID-19 in the ICU were randomized to treatment with full or standard prophylactic doses of anticoagulants. If antiplatelet therapy was not indicated, patients were also randomized to receive clopidogrel or no antiplatelet therapy. The primary efficacy endpoint (death related to venous or arterial thrombosis, pulmonary embolism, clinically evident deep vein thrombosis (DVT), type 1 MI, ischemic stroke, systemic embolism or acute limb ischemia and clinically silent DVT before hospital discharge or within 28 days) was achieved less frequently in the full-dose anticoagulant group compared to the standard-dose group (9.9% versus 15.2% of cases, RR 0.56 with 95% CI 0.32 to 0.99; p=0.046). The primary safety endpoint of fatal or life-threatening bleeding occurred in 2.1% of patients on the full dose and 0.5% of patients on the standard dose of anticoagulants (p=0.19); the secondary safety endpoint of moderate/severe bleeding occurred in 7.9% and 0.5% of patients, respectively (p=0.002). There were no differences in all-cause mortality between the full-dose and standard-dose anticoagulant

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groups (RR 0.91 with 95% CI 0.56 to 1.48; p=0.70). There were no differences in the incidence of the primary efficacy or safety endpoints with clopidogrel compared to no antiplatelet therapy. In patients with severe COVID-19, full-dose anticoagulation, but not clopidogrel, reduced the risk of thrombotic complications with an increased incidence of bleeding and no apparent effect on mortality. Enrolment was stopped in early March 2022 (≈50 % of planned enrolment) due to declining admissions to intensive care units with a diagnosis of COVID-19.

COVID-19 is associated with dysregulation of the immune response and hypercoagulability. The open-label, controlled **ACT** trial with a 2×2 factorial design enrolled 2749 patients from 62 centres in 11 countries who were hospitalized with symptoms of laboratory-confirmed COVID-19 and randomized (1:1) to receive anti-inflammatory therapy with colchicine at a dose of 1.2 mg followed by 0.6 mg 2 hours later and then 0.6 mg twice daily for 28 days (n=1304) or conventional treatment (n=1307). For the second time, patients were randomized (1:1) to receive antithrombotic therapy with a combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily for 28 days (n=1063) or usual care (n=1056). After 45 days of follow-up, 28.2 % of patients in the colchicine group and 27.2 % of patients in the control group had a primary endpoint event (need for high-flow oxygen therapy, ventilation or death) (OR 1.04 with 9 5% CI 0.90 to 1.21; p=0.58), and the other primary endpoint event (MI, stroke, acute limb ischemia or pulmonary embolism) was reported in 26.4 % of patients in the rivaroxaban + aspirin group versus 28.4 % in the control group (RR 0.92 with 95 % CI 0.78 to 1.09; p=0.32). The results were confirmed by the subgroup analysis and were independent of vaccination status, baseline disease severity and time from symptom onset to randomization. Adverse reactions, mainly gastrointestinal, leading to discontinuation were observed in 0.61 % of patients in the colchicine group. Bleeding was observed in 1.6 % of patients in the rivaroxaban plus aspirin group versus 0.66 % in the control group (p=0.042), but the incidence of major bleeding was not significantly different — 0.19 % versus 0.57 % (p=0.18). In addition, there were no serious adverse events in the rivaroxaban plus aspirin group that led to discontinuation of study treatment. In patients hospitalized for COVID-19, neither colchicine nor rivaroxaban plus aspirin prevented disease progression or death.

The open-label, controlled, 2×2 factorial **ACT** trial enrolled 3917 outpatients from 48 centres in 11 countries with symptomatic, laboratory-confirmed COVID-19 with a high risk of disease progression. The participants were randomized (1:1) to receive anti-inflammatory therapy with colchicine 0.6 mg twice daily for 3 days followed by 0.6 mg once daily for 25 days (n=1939) or usual treatment (n=1942). Secondly, patients were randomized (1:1) to receive antithrombotic therapy with aspirin 100 mg once daily for 28 days (n=1945) or usual care (n=1936). After 45 days of follow-up, the primary endpoint (hospitalization or death) occurred in 3.4 % of patients in the colchicine group and 3.3 % in the control group (OR 1.02 with 95 % CI 0.72 to 1.43; p=0.93). The other primary endpoint (major thrombosis, hospitalization or death) occurred in 3.0 % of patients in the aspirin group and 3.8 % in the control group (RR 0.80 with 95 % CI 0.57 to 1.13; p=0.21). The results were consistent across all predefined subgroups and were independent of vaccination status, timing of randomization from symptom onset and timing of enrolment in relation to pandemic phase. Serious adverse reactions occurred in 1.8 % of patients in the colchicine group and 1.4 % in the control group; 1.6 % of patients in the aspirin group versus 1.6 % in the control group, but none of these events led to discontinuation of the study medication. The results do not support the use of colchicine or aspirin to prevent COVID-19 progression or death in outpatients.

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