Dear friends of clinical journal club - load the file down at https://www.mdc-berlin.de/cjc. This website also gives you access to my seminar on Wednesdays 16:00 English and 17:00 German. You need to click on *Besprechung beizutreten*. If it fails to work immediately, keep on clicking.

A 66-year-old man with chronic obstructive pulmonary disease presented to the emergency department with a 2-week history of shortness of breath and cough and 5 days of left flank pain. Two days before presentation, he had noted the appearance and rapid expansion of a mass on his left side. Computed tomography of the chest is shown. What is the underlying etiology? You are offered: Autoimmune pleuritis, Empyema necessitans, Hematoma, Mesothelioma, and Soft tissue sarcoma of the chest wall. Notice the gas patterns within the pus. An appropriate duration of dual antiplatelet therapy after percutaneous coronary intervention for acute myocardial infarction that has been treated with guideline-recommended complete revascularization and a contemporary drug-eluting stent remains unclear. Guidelines indicate a dual platelet inhibition for the first year. Investigators conducted a multicenter, open-label, randomized trial at 40 European sites. Adults with acute myocardial infarction who had undergone successful complete revascularization within 7 days after the infarction and had subsequently completed 1 month of dual antiplatelet therapy with no ischemic or major bleeding events were randomly assigned to transition to a P2Y12 inhibitor as monotherapy or to continue dual antiplatelet therapy for an additional 11 months. In this study P2Y12 monotherapy was non-inferior to dual-platelet therapy and caused less bleeding. However, other investigators also pursued this issue. Adults with acute myocardial infarction who had undergone successful complete revascularization within 7 days after the infarction and had subsequently completed 1 month of dual antiplatelet therapy with no ischemic or major bleeding events were randomly assigned to transition to a P2Y12 inhibitor as monotherapy or to continue dual antiplatelet therapy for an additional 11 months. The two ranked primary outcomes, assessed through 12 months, were a composite of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization (tested for noninferiority, with a noninferiority margin of 2.5 percentage points) and major or clinically relevant nonmajor bleeding (tested for superiority). In this study, P2Y12 monotherapy was not non-inferior to dual antiplatelet therapy in the first year.

Approximately half the worldwide population is at risk for dengue. No antiviral prophylaxis or treatment options are available. In a phase 2a, double-blind, randomized trial, investigators assigned healthy adults to receive oral mosnodenvir once daily as a low dose (40-mg loading dose followed by 10-mg maintenance dose), medium dose (200 mg followed by 50 mg), or high dose (600 mg followed by 200 mg) or matched placebo. Loading doses were given for 5 days and maintenance doses for 21 days. In a controlled human infection model, participants received subcutaneous inoculation of an under-attenuated dengue virus serotype 3 (DENV-3) strain (rDEN3Δ30) on the day of the first maintenance dose (day 1). The primary efficacy end point was the DENV-3 RNA load. The highest mosnodenvir dose provided protection against DENV-3. Angiopoietin-like protein 3 (ANGPTL3) inhibits lipoprotein and endothelial lipases. ANGPTL3 loss-of-function genetic variants are associated with decreased levels of low-density lipoprotein cholesterol and triglycerides and a decreased lifetime risk of atherosclerotic cardiovascular disease. Investigators conducted an ascending-dose phase 1 trial to assess the safety and efficacy of CTX310, a lipid-nanoparticle–encapsulated clustered regularly interspaced short palindromic repeats–Cas9 endonuclease (CRISPR-Cas9) messenger RNA (mRNA) and guide RNA targeting hepatic ANGPTL3 to induce a loss-of-function mutation. Adults who had uncontrolled hypercholesterolemia, hypertriglyceridemia, or mixed dyslipidemia and were receiving maximally tolerated lipid-lowering therapy received a single intravenous dose of CTX310 (0.1, 0.3, 0.6, 0.7, or 0.8 mg per kilogram of body weight). The primary end point was adverse events, including dose-limiting toxic effects. This single-shot Crispr-Cas9 gene therapy appears to be effective. Hereditary hemorrhagic telangiectasia (HHT or Morbus Osler) involves mutations along the activin receptor-like kinase signaling pathway (endoglin and others), a TGF-beta family member. In a proof-of-concept, multicenter, double-blind, placebo-controlled trial, investigators evaluated the safety and efficacy of oral engasertib, a new, allosteric, selective PI3 kinase-AKT inhibitor, in patients with HHT. Patients were randomly assigned in a 1:1:1 ratio to receive engasertib at a dose of 30 mg, engasertib at a dose of 40 mg, or placebo once daily for 12 weeks. The primary outcomes were the frequency and severity of adverse events. Key secondary outcomes included the frequency and duration of epistaxis. Engasertib was well tolerated and reduced

nosebleeds. An open-label extension is ongoing. The N Engl J Med review is on the decline of basic history taking and physical examination skills amongst students and trainees. The mystery patient of the week is a 57-year-old woman with visual disturbances, diplopia, and right-arm shaking. The Lancet presents a proof-of-concept study on transcutaneous transseptal mitral valve replacement. The results are encouraging. Factor XI, the Rosenthal factor, is responsible for hemophilia-C, a not severe bleeding disorder. Regeneron has developed two antibodies against factor XI. These antibodies are now compared to enoxaparin and to apixaban after knee operations. Factor XI inhibition appears to protect against thrombosis with minimal bleeding issues. Oral insulin can induce tolerance. Type-1 diabetes is involved in auto-antibody formation. Oral insulin or placebo were given to young children with a high risk of type-1 diabetes. The endpoint was the development of two or more type-1 diabetes antibodies. Also studied were development of type-1 diabetes or protection from type-1 diabetes. The primary hypothesis was negative, but the news was not all bad. The Lancet review is on contemporary non-invasive imaging for coronary artery disease. CT coronary angiography seems to be the best. Next, the Lancet presents a fascinating article on the US health-care system. In the last 40 years, the number of doctors has doubled. But the number of so-called health-care managers has increased 20-fold. In Science Magazine we learn about targeted protein degradation and discover that methods now exist to target transmembrane and extracellular proteins. Washington Post advises us to take a “fart walk” after heavy meals. There will be no oral presentation this week but please review the files anyway. Join me on December 10 for another comprehensive clinical journal club.

Sincerely, Fred Luft

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