

Dear friends of clinical journal club - load the latest 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 6-year-old boy is brought to clinic with a 2-year history of a nontender, mobile midline mass of the anterior neck which moves up with tongue protrusion and swallowing. Physical exam is shown. What is the most likely diagnosis? You are offered: Brachial cleft anomaly, Dermoid cyst, Goiter, Lymphadenopathy, and Thyroglossal duct cyst. Only one of these possibilities is a midline structure. Current U.S. and European guidelines recommend oral anticoagulation as a class IIa indication in patients with atrial fibrillation at intermediate risk for stroke; however, evidence from randomized trials is needed. Investigators conducted a multicenter, open-label, adjudicator-masked superiority trial in South Korea involving patients with atrial fibrillation and an intermediate risk of stroke (a score of 1 in men and 2 in women on the CHA2DS2-VASc scale). Patients were randomly assigned in a 1:1 ratio to receive either direct oral anticoagulant (DOAC) therapy or no anticoagulation. The primary end point was a composite of stroke, systemic embolism, major bleeding, or death from cardiovascular causes at 24 months. Anticoagulation provided the suspected stroke protection without serious bleeding. Narcolepsy type 1 is characterized by excessive daytime sleepiness, cataplexy, disrupted sleep, sleep paralysis, and hypnagogic or hypnopompic (hypnagogic) hallucinations. Oveporexton, an oral orexin receptor 2-selective agonist, reduced symptoms of narcolepsy type 1 in a previous phase 2 trial. Investigators conducted two phase 3, randomized, placebo-controlled trials evaluating the efficacy and safety of oveporexton over a period of 12 weeks. Participants 16 to 70 years of age with narcolepsy type 1 were randomly assigned to receive twice-daily oveporexton (1 mg or 2 mg) or placebo in the First Light trial and in the Radiant Light (2 mg) trial. The primary end point was the change from baseline to week 12 in mean sleep latency (the ability to stay awake under soporific conditions). Oveporexton kept the patients awake, compared to placebo. Transient insomnia was a side effect. Anitocabtagene autoleucel (anito-cel), a B-cell maturation antigen (BCMA)-directed autologous chimeric antigen receptor (CAR) T-cell therapy with a synthetic d-domain binder (ddBCMA), may have efficacy in patients with relapsed or

refractory multiple myeloma. In a phase 1 study, investigators evaluated the safety and efficacy of anito-cel (dose level 1, 100×10^6 CAR+ T cells; dose level 2, 300×10^6 CAR+ T cells) in patients with relapsed or refractory multiple myeloma who had received three or more lines of therapy previously or had triple-class refractory disease. Primary end points were adverse events during the treatment period and establishment of the recommended phase 2 dose. Anito-cel met its endpoint without disturbing safety issues. The Wiskott-Aldrich protein binds several critical cell-surface receptors to the actin cytoskeleton in hematopoietic progenitor cells. The Wiskott-Aldrich syndrome (WAS) is a rare, x-linked, life-threatening disease that features thrombocytopenia, severe eczema, and lethal infections because of defective lymphocytes. Etuvetidigene autotemcel (etu-cel) is an autologous gene therapy consisting of hematopoietic stem and progenitor cells that have been transduced ex vivo with a lentiviral vector encoding the WAS gene complementary DNA. Investigators integrated data from two prospective open-label clinical studies (a phase 1–2 study with 8 participants and a phase 3 study with 10 participants) and an expanded-access program with 9 participants to evaluate the efficacy and safety of etu-cel in patients with WAS. Ten years out, the results show that the effects of etu-cel are consistent with a sustained clinical benefit in persons with WAS. The N Engl J Med review is on the clinical uses of common genetic variants associated with common diseases. The patient-of-the-week is a 4-year-old boy with fatigue, imbalance, and frequent falls. He exhibits a positive Gower's sign. Targeted left ventricular lead placement is recommended in patients undergoing biventricular pacing for heart failure. A national, multicenter, double-blind trial from Denmark suggests that any advantage of targeted lead placement may be overdrawn. Acute heart failure in Africa has twice the mortality rate as in other developing areas. Lancet presents a large cohort study from 17 African countries. The heart-failure etiologies were not unique in Africa. Therapy needs to be implemented. Down's syndrome (trisomy of chromosome 21) patients may now live up to 60 years. They are afflicted by Alzheimer's syndrome at an early age. Lancet draws attention to the unappreciated natural history and clinical impact of epilepsy in these patients. A Lancet Commission reports on pandemic readiness (or the absence thereof) in a 54-page article. In Science Magazine we learn about adenosine receptors and noncanonical G $\beta\gamma$ -complex signaling in the heart. During heart failure progression,

extracellular adenosine levels are elevated and promote cardiac fibrosis. The drug, CGS15943, simultaneously antagonizes multiple AR subtypes, which converge on Gβγ signaling. Cardiac fibrosis was largely blocked. The AR-Gβγ signaling axis therefore represents a druggable target for cardiac fibrosis and potentially for fibrosis in other organs. In Washington Post, we encounter an injured pelican who seeks help from a Florida marine research facility. The bird receives the help it needs. Load down the file and join me again on September 30, 16:00 in English and 17:00 in German.

Sincerely, Fred Luft

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