was superior on change in HbA\textsubscript{1c} but only slightly better on change in bodyweight.\textsuperscript{11} When discussing the choice between a GLP-1 receptor agonist and an SGLT2 inhibitor, the effects in patients with cardiovascular disease also need to be considered, in agreement with current guidelines,\textsuperscript{32} but both treatment approaches have shown cardiovascular benefits (oral semaglutide in the PIONEER 6 trial\textsuperscript{3}), although their mechanisms of action probably differ considerably.

Oral semaglutide has not yet been approved by the medical authorities, but in April, 2019, new drug applications were filed for regulatory approval with both the US Food and Drug Administration and the European Medicines Agency. The PIONEER 4 study reported in The Lancet shows that the first oral GLP-1 receptor agonist has effects that are similar to those of one of the most widely used injectable agonists.

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Robotic-assisted training after stroke: RATULS advances science

The Robot Assisted Training for the Upper Limb after Stroke (RATULS) trial by Helen Rodgers and colleagues\textsuperscript{1} in The Lancet is, to the best of our knowledge, the largest study (n=770) in the field of robot-assisted arm training for people with stroke. Recruiting from four UK sites, this pragmatic, three-arm, randomised controlled trial compared robot-assisted training, enhanced upper limb training (EULT; matched in dose and frequency to robot-assisted training), and lower-dose usual care. The population for this study was 770 individuals aged at least 18 years (mean age 61 years [SD 14]; 468 [61%] men) with first-ever stroke (1 week to 5 years before enrolment) with moderate to severe upper limb impairment. The primary outcome was upper limb functional success at the end of the intervention (3 months), measured on the Action Research Arm Test (ARAT). Success was identified a priori, with four distinct success criteria (with improvement cutpoints ranging from 3 to 6 points on the ARAT) that varied according to baseline severity. Although not used previously, this approach aimed to more sensitively capture meaningful change relative to a patient’s starting point, which makes sense but needs further validation. An additional strength of the study is that interventions and intervention fidelity were well described.\textsuperscript{2}

Robot-assisted training did not improve upper limb function (assessed by ARAT) versus usual care (adjusted odds ratio [aOR] 1-17 [98·3% CI 0-70–1-96]) or versus matched-dose EULT (aOR 0·78 [98·3% CI 0·48–1·27]). Nor did usual care differ from EULT (aOR 1·51 [98·3% CI 0·90–2·51]). Although some secondary outcome analyses favoured higher-dose training (EULT or robot-assisted

For announcement of applications see https://www.novonordisk.com/bin/getPDF.2239031.pdf
training) over usual care, the effects were small. Serious adverse events were few (43 serious adverse events were reported for 39 participants in the robot-assisted training group, 42 were reported for 33 participants in the EULT group, and 29 were reported for 20 participants in the usual care group), none were trial related, and reporting bias is likely because of frequent contact between participants and clinical teams. The cost-utility analysis, not surprisingly, found higher costs for the more intensive treatments (robot-assisted training cost £5387 per participant, EULT cost £4451 per participant, and usual care cost £3785 per participant). Neither robot-assisted training nor EULT would be considered cost-effective at most levels of willingness to pay per quality-adjusted life-year (QALY) worldwide.

The promise of robotics as a powerful tool in the treatment of stroke and brain injury continues to excite stroke survivors, carers, researchers, developers, and funders. RATULS aimed to produce reliable and robust data to progress the field; harmonising treatment protocols, devices, and outcomes, including both functional (ARAT) and activities of daily living (ADL) outcomes. The investigators achieved these goals. The 2018 Cochrane systematic review of robot-assisted arm training, which included 45 trials with 1619 participants, reported significantly improved ADL scores (standardised mean difference [SMD] 0·31 [95% CI 0·09–0·50]) and arm function (SMD 0·32 [0·18–0·46]) at the end of training. A major caveat, however, was that variations in the intensity, duration, amount, and type of training, device type, participant characteristics, and measurements used across the range of trials included in the meta-analysis add considerable variability and lower evidence quality. RATULS, despite controlling many of these variables, did not show similar benefits in ADL or function over usual care.

The investigators raise some points for consideration in future trials, including the need for better ways of determining the most effective dose of treatment, with dose considerations including length of each session, total number of sessions, and their schedule (sessions per day or week) as well as the intensity of training within a session. In addition to the robot-assisted training dose, the investigators question what should be paired with robot-assisted training in future trials to enhance functional outcomes. Although the interventions in this trial were built using best evidence and expert opinion, arguably, the potential for 36 sessions over 3 months of a 45-min dose of robot-assisted treatment (or EULT) to deliver substantial changes in function or ADL was low. Meta-analyses suggest much higher doses of training are required to appreciably change outcome.1

A further point to consider is the time to the start of training after stroke. In RATULS, the median time from stroke to baseline was 240 days (IQR 109–549). In addition to identifying the optimal dose of training to test in future trials, refining the target group for training is crucial and is a recovery research priority.2 Given the well known non-linear pattern of recovery, individuals at an early phase after stroke are likely to respond differently to those with chronic stroke and associated secondary changes.3,4 In the Cochrane review, the treatment effect for patients treated in the first 3 months after stroke with robot-assisted arm training was equal to an SMD of 0·40 (95% CI 0·10 to 0·70) compared with an SMD of 0·19 (–0·13 to 0·50) for patients treated with robot-assisted arm training after 3 months of stroke.5 Although time since stroke was not a significant factor in RATULS subgroup analyses, the subgroup samples were small and the question remains of who best to target, and when, to optimise outcome.

There are more than ten different devices available for robot-assisted arm therapy. Devices are needed that deliver substantially better functional outcomes than current care. RATULS shows that large, well conducted, multisite trials using one of these devices is possible—learning from this and getting the fundamentals right for future trials is imperative to advance the field.

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We declare no competing interests.

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Maternal mortality is an international health-care crisis. A staggering 830 women die daily from pregnancy-related complications globally—over 300,000 per year. Pre-eclampsia affects approximately 2–8% of pregnancies worldwide and is a leading cause of maternal morbidity and mortality. The Global Strategy for Women’s, Children’s and Adolescents’ Health aims to reduce global maternal mortality to less than 70 per 100,000 livebirths by 2030. In order to accomplish this goal, new treatments to prevent hypertensive disorders of pregnancy are urgently needed.

Pre-eclampsia is a result of several pathological mechanisms, including abnormal placentation, uteroplacental ischaemia, vascular disorders of the placenta, insulin resistance, systemic maternal inflammation, endothelial dysfunction, and an imbalance of angiogenic and anti-angiogenic factors. Maternal factors and biomarkers can predict adverse pregnancy outcomes and have been coupled with interventions to prevent pre-eclampsia, with aspirin yielding the most promising results.

In 2017, Ho and colleagues reported that a placental peptide hormone elabela (also known as apela, toddler, or ela) might be implicated in the pathogenesis of pre-eclampsia. In all vertebrates, elabela is encoded by the elabela gene, initially considered to be a non-coding transcript. This hormone competes with apelin for the apelin receptor and is involved in embryogenesis during zebrafish development. Using mouse models, Ho and colleagues showed that elabela deficiency resulted in placental dysfunction, characterised by thin labyrinths with poor vascularisation, increased apoptosis, and reduced proliferation, as well as delayed syncytiotrophoblast differentiation. Elabela-deficient mice developed pre-eclampsia-like symptoms such as hypertension, proteinuria, glomerular endotheliosis, and low birth weight (ie, intrauterine growth restriction). Infusion of elabela into such mice normalised their pre-eclampsia-like symptoms, indicating that this hormone probably acts systemically and might offer a potential treatment.

In humans, elabela localised to the placenta during the first and third trimesters. Elabela was also found to facilitate invasion in trophoblast cell cultures, suggesting that the hormone has a role in the transformation of the spiral arteries, which are defective in women with pre-eclampsia. The mechanisms whereby elabela might regulate placental function are shown in the figure (pathway shown in black). The putative mechanisms whereby elabela deficiency might cause pre-eclampsia include impaired placental vascular function, apoptosis, and oxidative stress and are shown in red.

Reducing maternal mortality: can elabela help in this fight?

Figure: Elabela during pregnancy

The mechanisms whereby elabela may regulate placental function are shown in black. The putative mechanisms whereby elabela deficiency may cause pre-eclampsia include impaired placental vascular function, apoptosis, and oxidative stress and are shown in red.

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