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Compound Name: Insulin
Molecular Form: C256H381N65O77S6
Molecular weight:5794 g/mol
CAS registration: 9004-10-8
ATC code: ATC Code not found
IUPAC name: (4S)-4-[[2-[[(1R,6R,12S,15S,18S,21S,24S,27S,30S,33S,36S,39S,42R,47R,50S,53S,56S,59S,62S,65S,68S,71S,
Solubility: Solubility not found
Physical description: Physical description not found
Melting point: Melting Point not found
Decomposition: Decomposition not found
Half life: Biological Half-life not found
Reactivity: Reactivity not found

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Pharmacodynamics: URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/34267380/ Paragraphs: The 1993 publication of the Diabetes Control and Complications Trial112 and 1998 United Kingdom Prospective Diabetes Study113–115 demonstrated definitive relationships between glycemic control and microvascular complications and showed that lower A1cs were associated with higher rates of severe hypoglycemia. These observations spurred efforts focused on improving exogenously administered insulin's pharmacokinetic and pharmacodynamic properties (absorption rate, time to peak and duration of action). URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/34413118/ Paragraphs: Insulin icodec is a novel, long-acting insulin analog designed to cover basal insulin requirements with once-weekly subcutaneous administration. Here we describe the molecular engineering and the biological and pharmacological properties of insulin icodec.. A number of in vitro assays measuring receptor binding, intracellular signaling as well as cellular metabolic and mitogenic responses were used to characterize the biological properties of insulin icodec. To evaluate the pharmacological properties of insulin icodec in individuals with type 2 diabetes, a randomized, double-blind, double-dummy, active-controlled, multiple-dose, dose escalation trial was conducted.. In vitro cell-based studies showed that insulin icodec activates the same dose-dependent IR-mediated signaling and metabolic responses as native human insulin (HI). The affinity of insulin icodec for the insulin-like growth factor-1 receptor was proportionately lower than its binding to the IR, and the in vitro mitogenic effect of insulin icodec in various human cells was low relative to HI. The clinical pharmacology trial in people with type 2 diabetes showed that insulin icodec was well tolerated and has pharmacokinetic/pharmacodynamic properties that are suited for once-weekly dosing, with a mean half-life of 196 hours and close to even distribution of glucose-lowering effect over the entire dosing interval of 1 week.. The molecular modifications introduced into insulin icodec provide a novel basal insulin with biological and pharmacokinetic/pharmacodynamic properties suitable for once-weekly dosing.. Introducing strong, reversible binding to albumin, together with reduced insulin receptor (IR) affinity to slow down clearance, ensures that insulin icodec forms a circulating albumin-bound depot, which is essentially inactive, from which insulin icodec can slowly and consistently activate IRs, resulting in a long half-life suitable for once-weekly administration. A clinical pharmacology trial demonstrates that insulin icodec has a half-life of 196 hours and a glucose-lowering effect that is close to evenly distributed throughout the week, thus making it indeed suitable for once-weekly dosing.. To

evaluate the pharmacological properties of insulin icodec in individuals with type 2 diabetes, a randomized, double-blind, double-dummy, active-controlled, multiple-dose, dose escalation trial was conducted. Eligible participants had type 2 diabetes, were treated with any insulin (total daily dose 0.3–1.0 U/kg), aged 18–64 years, with glycosylated hemoglobin (HbA1c) ≤9.0 % (75 mmol/mol) and were not using oral antidiabetic drugs or GLP-1RAs (subjects on insulin therapy in combination with metformin were allowed in cohort 3, but metformin was washed out for ≥3 weeks prior to first trial product administration in these subjects).. Within each of three subsequent cohorts, participants were randomized to once-weekly insulin icodec (cohort 1: 12 nmol/kg; cohort 2: 20 nmol/kg; cohort 3: 24 nmol/kg) plus once-daily placebo or once-daily insulin degludec (0.4 U/kg; corresponding to 16.8 nmol/kg/week) plus once-weekly placebo for 5 weeks (all by subcutaneous injection in the thigh at ~20:00 hours using a NovoPen4 pen device; Novo Nordisk A/S, Bagsværd, Denmark) (online supplemental figure 1). Data on insulin degludec are not included, but pharmacodynamic data have been presented elsewhere.26 The decision to proceed to the next cohort was made by an internal trial safety group after review of blinded interim safety, pharmacokinetic and pharmacodynamic data.. Total serum insulin icodec concentration (both the free and albumin bound) was measured using a specific assay at prespecified time points from predose until 36 days after the last weekly insulin icodec dose (online supplemental table 1). Steady-state pharmacodynamic properties were assessed during two 24-hour automated euglycemic glucose clamps (ClampArt, Profil, Neuss, Germany; target of 5.5 mmol/L) at steady state on day 2 (24–48 hours) and day 7 (144–168 hours) after the last weekly insulin icodec dose in week 5 (ie, days 30 and 35 of the treatment period; online supplemental figure 1).. Pharmacokinetic dose proportionality was evaluated by linear regression of log(AUC0-168h) on log(dose), where AUC0-168h was derived after the last insulin icodec dose and a slope of 1 corresponds to dose proportionality (the power model). Pharmacokinetic trough values to steady state and full-week glucose-lowering effect profiles in week 5 were predicted for each individual using a pharmacokinetic–pharmacodynamic model. Model parameters were estimated for each individual based on insulin icodec pharmacokinetic data from the first dose until day 65 and 24-hour glucose clamp data in week 5 (days 30 and 35).. In the clinical pharmacology trial, 38 individuals were randomized to receive insulin icodec 12 nmol/kg (n=13), 20 nmol/kg (n=13) or 24 nmol/kg (n=12). The 38 individuals (33 men) had a mean±SD age of 57.8±4.3 years, body weight of 93.9±13.3 kg, body mass index of 29.9±2.8 kg/m2, HbA1c of 7.4%±0.6% and duration of diabetes of 14.4±6.7 years with comparable treatment groups (online supplemental table 2). In cohort 3, seven participants (58.3%) used metformin at screening.. Results supported dose-proportionality for AUC0-168h as the slope of log(AUC0-168h) versus log(dose) was not statistically significantly different from 1 (0.83 (0.56; 1.10)95% CI). Model-predicted pharmacodynamic data of a 1 week dosing interval at steady state indicated rather consistent glucose-lowering effect of insulin icodec throughout the week at clinically relevant doses (figure 2C). The distribution of glucose-lowering effect of insulin icodec over a week at steady state was determined as the daily proportion of the total weekly model-predicted glucose-lowering effect.. Pharmacokinetic and pharmacodynamic properties of insulin icodec in individuals with type 2 diabetes. (A) Model-predicted serum insulin icodec trough concentration during initiation of once-weekly dosing. The dashed line indicates the threshold for clinical steady state of serum insulin icodec and the shaded area indicates serum insulin icodec concentrations considered as clinical steady state. Circles indicate individual values (n=38). (B) Mean observed total serum insulin icodec concentration (the vast majority being albumin-bound) during week 5 of once-weekly dosing.. Results from the clinical pharmacology trial support the model illustrated in figure 3. As shown in figure 2B, the geometric mean half-life was 196 hours, that is, just longer than 1 week. As a consequence of the long half-life, insulin icodec builds up during the first weeks of once-weekly dosing until reaching a plateau. The median tmax was 16 hours, and a peak to trough difference could be observed when measured as total insulin icodec (bound and unbound to albumin). However, the mean glucose-lowering effect of insulin icodec demonstrated a close to even distribution over the entire dosing interval of 1 week (figure 2C).. This is clearly illustrated in figure 3B, where it can be seen that during the first week, despite the administration of a full dose of insulin icodec, the model-predicted pharmacodynamic effect is considerably less, suggesting that it should be safe to add a loading dose as was investigated in the phase II trial.38. Technical assistance was provided by Annette F Bjerre,

Marianne B Jensen, Pia Jensen, Lenette S Jørgensen, Anette Kirstine Lauridsen, Gitte Norup, Jette E Svendsen and Lene Walander. The authors would like to thank the principal investigator of the clinical pharmacology trial, Ulrike Hövelmann, MD, Profil, Neuss, Germany and all other investigators at Profil for conducting the clinical pharmacology trial, which was sponsored by Novo Nordisk. Medical writing support was provided by Carsten Roepstorff, PhD, CR Pharma Consult, Copenhagen, Denmark funded by Novo Nordisk. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/34850005/ Paragraphs: Design of “first-generation” insulin analogues over the past 3 decades has provided pharmaceutical formulations with tailored pharmacokinetic (PK) and pharmacodynamic (PD) properties. Application of a molecular tool kit—integrating protein sequence, chemical modification, and formulation—has thus led to improved prandial and basal formulations for the treatment of diabetes mellitus. Although PK/PD changes were modest in relation to prior formulations of human and animal insulins, significant clinical advantages in efficacy (mean glycemia) and safety (rates of hypoglycemia) were obtained.. The present year marks both the centennial of insulin’s discovery (1921) (1) and the golden anniversary of its high-resolution structure (2). Whereas the former’s therapeutic effect was immediate, clinical translation of structural advances has occurred only gradually (3). Indeed, unmet clinical needs in the treatment of type 1 and type 2 diabetes (T1D and T2D) represent continuing sources of therapeutic innovation. In this review we highlight a creative interplay between basic science and molecular pharmacology.. In T2D broader clinical considerations led to insulin’s deemphasis in current treatment algorithms (12, 18); preferred agents (whether oral or injected) mitigate hypoglycemic risk, avoid weight gain (or induce weight loss), and may be cardioprotective (19, 20). These include metformin as a first-line agent with subsequent addition of one of several classes (dipeptidyl peptidase 4 inhibitors, sulfonylureas, glucagon-like peptide 1 [GLP-1] receptor agonists, or SGLT2 inhibitors) (21-24). For T2D patients requiring insulin therapy, investigational approaches envision further optimization of pharmacokinetic (PK) and pharmacodynamic (PD) properties (such as ultrarapid or ultrabasal), providing glucose-responsivity as a “smart” insulin analogue (25, 26), possible organ-selective insulin analogues, and bias insulin agonists.. Insulin activity profiles and representative structures. A, Pharmacodynamic profiles: a, ultra-rapid-acting reformulations Fiasp and URLi (Table 1); b, first-generation prandial formulations (Humalog, Novolog, and Apidra); c, “regular” wild-type formulation; d, neutral protamine Hagedorn insulin is an intermediate-duration microcrystalline formulation; e and f basal analogue formulations Levemir and Lantus (see Table 1; different depot-precipitation mechanisms); g, Tresiba (see Table 1) provides more than 24 hours’ duration; h, initial target profile for novel once-a-week analogues.. Given this growing global health need, we envisage a third-generation of insulin analogues: combining the present desiderata of properties with ultrastability. Such efforts are likely to require further structural analysis of degradation mechanisms, including metastable partial folds and amyloid. The rugged landscape of protein folding and misfolding, for the present a foundational topic in biophysics, may thus emerge as a new translational frontier in molecular pharmacology.

Overview of Efficacy: URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/33325008/ Paragraphs: Glucagon-like peptide 1 (GLP-1) based therapy is an established treatment option for the management of type 2 diabetes mellitus (T2DM) and is recommended early in the treatment algorithm owing to glycaemic efficacy, weight reduction and favourable cardiovascular outcomes. Glucose-dependent insulinotropic polypeptide (GIP), on the other hand, was thought to have no potential as a glucose-lowering therapy because of observations showing no insulinotropic effect from supraphysiological infusion in people with T2DM.. Pre-clinical trials and phase 1 and 2 clinical trials indicate that tirzepatide has potent glucose lowering and weight loss with adverse effects comparable to those of established GLP-1 receptor agonists. The long-term efficacy, safety and cardiovascular outcomes of tirzepatide will be investigated in the SURPASS phase 3 clinical trial programme. In this paper, we will review the pre-clinical and phase 1 and 2 trials for tirzepatide in the management of T2DM and give an overview of the SURPASS clinical trials.. The clinical efficacy, safety and tolerability of tirzepatide has been reported in phase 1 and phase 2 clinical trials (Table 2).. The SURPASS clinical trial programme aimed to assess the efficacy and safety of tirzepatide as a treatment to improve glycaemic control in people with T2DM (Table 3) [34–42]. The SURPASS phase 3 clinical trials include

six global, two Japanese and one Asia–Pacific studies. These trials include anti-hyperglycaemic therapy-naïve patients (patients treated with diet and lifestyle alone) as well as patients on various oral anti-hyperglycaemic agents (metformin, sulfonylurea, pioglitazone, SGLT2 inhibitor and/or insulin).. Diabetes care has evolved over the last two decades, shifting from a glucocentric approach to multifactorial intervention with the aim of minimising CV morbidity and mortality. International guidelines recommend the choice of anti-hyperglycaemic therapy based not only on the degree of hyperglycaemia but also on the presence or absence of CV disease, renal disease and obesity. GLP-1 RAs and SGLT2 inhibitors have gained popularity due to their clinical efficacy and favourable CV outcomes. Despite these developments, there are still unmet needs for people living with diabetes, especially those with obesity.. Tirzepatide has demonstrated greater HbA1c reduction (− 2.4% with 15 mg tirzepatide) and superior weight loss (− 11.3 kg with tirzepatide 15 mg) with comparable adverse effects versus the GLP-1 RA dulaglutide in phase 2 trials. Of note, semaglutide, currently regarded as the most potent GLP-1 RA, demonstrated 1.5–1.8% HbA1c reduction and 4.5–6.5 kg weight reduction [1]. It is not possible to compare the efficacy of tirzepatide and semaglutide with available data from phase 2 trials; however, the SURPASS-2 trial will directly compare the efficacy and safety of tirzepatide versus semaglutide with the potential for superiority of tirzepatide, particularly with respect to weight reduction.. However, the SCALE study was not designed to compare the efficacy of liraglutide 3 mg versus 1.8 mg. In the SCALE insulin trial, liraglutide 3 mg was associated with a HbA1c reduction of 1.1% compared to placebo (0.6%) [45]. Of interest, a higher dose of dulaglutide for glucose lowering was recently approved by the FDA [46] following the AWARD-11 trial which demonstrated HbA1c reduction of 1.9% and 1.7% and weight reduction of 5 kg and 4.3 kg with dulaglutide 4.5 mg and 3 mg QW respectively [47].. Some SURPASS clinical trials include SGLT2 inhibitors as concomitant therapy (e.g. SURPASS-3 and -4). SGLT2 inhibitors have a favourable effect on weight and CVD outcomes. It would be interesting to see the combined effect of tirzepatide and SGLT2 inhibitors on efficacy and CVD outcomes. Of interest, the combined use of once weekly exenatide and dapagliflozin resulted in superior HbA1c reduction and greater weight loss compared to the exenatide group and the dapagliflozin group [48]. Therefore, one can argue that tirzepatide might not be solely responsible for favourable results.. None of the SURPASS trials are designed to compare tirzepatide against SGLT2 inhibitors. Further study comparing tirzepatide against SGLT2 inhibitors would be of use in clinical decision-making. Since the 2008 publication of FDA guidance on anti-hyperglycaemic therapy, medications for diabetes should not only be efficacious in reduction in HbA1c but should also have favourable CV outcomes (at least no negative CV impact). The SURPASS-CVOT trial will provide long-term data on the CV safety as well as efficacy of tirzepatide.. SYNERGY-NASH is a randomized, double-blind, placebo-controlled phase 2 study comparing the efficacy and safety of tirzepatide in patients with non-alcoholic steatohepatitis (NASH) [50].. Tirzepatide, a dual GIP/GLP-1 receptor agonist, is a new incretin-based therapy for type 2 diabetes. The degree of HbA1c reduction and weight reduction observed in pre-clinical, phase 1 and 2 clinical trials has not previously been observed in diabetes clinical trials. The comprehensive phase 3 SURPASS clinical trial programme will confirm comparable efficacy, safety and cardiovascular outcomes of tirzepatide in the management of T2DM diabetes. The SURPASS trials will also provide insight into understanding of incretin hormones, particularly the role of GIP in energy metabolism. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/26773015/ Paragraphs: However, recent findings have highlighted the substantial impact that obesity and MetS parameters have on immunity and pathogen defense, including the disruption of lymphoid tissue integrity; alterations in leukocyte development, phenotypes, and activity; and the coordination of innate and adaptive immune responses. These changes are associated with an overall negative impact on chronic disease progression, immunity from infection, and vaccine efficacy. This review presents an overview of the impact that obesity and MetS parameters have on immune system function.. Several studies have further demonstrated the complications of obesity after influenza exposure. Diet-induced obesity has been shown to impair memory CD8+ T cell responses to an influenza virus infection, resulting in increased mortality, viral titers in lung, and worsened lung pathology (37). These adverse effects were associated with an obesity-induced failure to maintain influenza-specific CD8+ memory T cells, which are essential in ensuring vaccine efficacy (37). Accordingly, obesity has been shown to increase the risk of vaccine

failure, including the vaccines for hepatitis B (70), tetanus (72), and influenza (17).. The impact of obesity on immunity further extends to other chronic conditions. In the NHANES 2005–2006 cohort, obesity was associated with an increased prevalence of allergic disease in children that was primarily driven by allergic sensitization to food (75). Individuals who are obese are also at an increased risk of developing different types of cancers, including colon, breast, liver, pancreatic, and leukemia. Obesity is also associated with poorer cancer treatment efficacy and greater cancer-related mortality (128). URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/36372278/ Paragraphs: In addition, several human clinical trials related to CNS diseases are progressing or have been completed (Table 2), with initial phases of trials in PD showing efficacy (13). Incretin mimetics exhibit pleiotropic signaling effects in a variety of different cell types (14), but their potent anti-inflammatory properties, together with their neurotrophic and neuroprotective features, make them ideal for treating neurodegenerative disease. Within this review article we provide a brief overview of incretin mimetic drugs, both FDA-approved and in clinical and preclinical trials (Tables 1 and 2), and underscore their potent anti-inflammatory capacity that makes them ideal candidates for repurposing and investigation in clinical trials for neurodegenerative conditions.. GLP-1R agonists in clinical trials for repurposing to treat neurodegenerative diseases. Drugs in red (approved in the United States) or green (approved abroad) have been approved for metabolic disease treatment, and those in blue are in clinical trials for metabolic disease treatment. Only Bydureon®, Byetta®, and Victoza® have completed interventional clinical studies and demonstrated efficacy in treating a neurodegenerative disease.. More recent research has investigated the use of drugs that target a combination of secretin receptors (GLP-1R, GIPR, and GcgR) to treat T2DM. In 2009, a dual GLP-1R/GcgR agonist was pioneered for treating metabolic disorders in rodents (30). Later, in 2013, a dual GLP-1R/GIPR agonist, termed “twincretin”, demonstrated efficacy in animal models and humans with T2DM in reducing glycosylated hemoglobin A1c (HbA1c), an average measure of blood sugar levels over the duration of several months (31).. SAR4411255 demonstrated a terminal half-life of 3.5–6.1 hours, which is a relatively short exposure for a proposed once daily subcutaneously administered drug, and doses up to 150 ug were well tolerated, with the most frequent treatment-emergent adverse events being gastrointestinal, in accord with other GLP-1R agonists. Maintaining an appropriately balanced agonism among the three receptor subtypes (GLP-1, GIP, and Gcg) is key for single molecule triagonists to optimize efficacy across measures of glucose and body weight-lowering action, as well as to maintain tolerability across organ systems.. A further phase 1 trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of HM15211 in obese subjects with nonalcoholic fatty liver disease (NAFLD) has been reported as NCT03744182 (66 participants, aged 18–65 years). Finally, an ongoing phase 2 study to evaluate efficacy, safety and tolerability of HM15211 treatment for 12 months in subjects with biopsy confirmed non-alcoholic steatohepatitis (NASH) has been reported as NCT04505436 (217 participants, aged 18–70 years, across multiple US sites with a proposed completion date of November 2025).. Although the dual GLP-1R/GIPR agonist Tirzepatide is the only FDA-approved incretin multi-agonist, unimolecular incretin receptor multi-agonists will likely dominate as treatment options in the future due to growing evidence of their increased efficacy over single GLP-1R agonists (15, 35, 40, 41). Several multi-agonist incretin analogues are in the preclinical or clinical trial phases (Table 1) and are likely to be approved over the coming decade to treat both obesity and diabetes. Interestingly, recent research is unraveling the nuances in intracellular biased agonism these drugs may have, including preferential cAMP and other intracellular pathway induction (42, 43).. Although not GLP-1R agonists, DPP-IV inhibitors block the action of DPP-IV and therefore reduce the rate of breakdown of GLP-1 and GIP, consequently raising levels of endogenous incretins and promoting healthy incretin hormone signaling. Numerous DPP-IV inhibitors are FDA-approved for the treatment of T2DM, and DPP-IV inhibition has demonstrated efficacy in reducing neuroinflammation and AD markers—DPP-IV inhibition in an STZ-induced rat model of AD elevated GLP-1 levels and decreased levels of amyloid-β, total tau, phosphorylated tau, and pro-inflammatory cytokines TNF-α and IL-1β in a dose-dependent manner (243).. Dual agonists also offer numerous other neuroprotective benefits including reduced oxidative stress and improved memory function, synaptic health, and neurogenesis in mice (252), as well as neuroprotective and antioxidant properties in rodent models of TBI (12, 100, 251). Interestingly, the human dose of liraglutide (single GLP-1R agonist) and twincretin (dual GLP-1R/GIPR agonist) in T2DM

is the same: 1.8 mg subcutaneously daily. In the preclinical evaluation of twincretin in concussive head injury by Bader and colleagues (100), a direct comparison was made to liragultide treatment—a 247.6 μg/kg dose of liraglutide in mouse, which translates to a 1.8 mg dose in an 88.8 kg human, provided similar efficacy to a 5-fold lower dose of twincretin (50 μg/kg) to mitigate TBI-induced neuroinflammation, neuronal loss and behavioral impairments.. GLP-1R agonists liraglutide (Victoza®), semaglutide (Ozempic®, Rybelsus®), exenatide (Bydureon®, Byetta®, PT320, NLY01), and lixisenatide (Adlyxin®/Lyxumia®) have been FDA-approved or are in trials for the treatment of T2DM and are currently being investigated to determine their potential efficacy in treating neurodegenerative diseases. Only trials of liraglutide and exenatide have reached completion. In a phase 2 clinical trial investigating liraglutide treatment in patients with AD, 6 months of liraglutide treatment significantly increased glucose transport at the BBB, elevating the cerebral metabolic rate for glucose and reversing the abnormalities in brain glucose transport commonly associated with AD pathology (274).. Another trial that is currently in progress investigates the safety and efficacy of liraglutide in treating patients with PD (279).. At present, exenatide is the most prevalent GLP-1R agonist in clinical trials for AD and PD treatment. In an 18-month phase 2 clinical trial investigating the safety and efficacy of exenatide (administered as BID Byetta®) in treating early AD, extracellular vesicles isolated from the patients exhibited reduced amyloid-β–42 concentrations with exenatide treatment (257). However, in the same study, there were no significant differences between exenatide treatment and placebo in patients' cognition, cortical thickness and volume, or biomarkers of AD in CSF or plasma (257).. This was a small double-blind, randomized, placebo-controlled clinical trial whose primary outcome was to assess safety and tolerability. A total of 18 patients completed the study, and partial outcomes were available on 21 patients prior to the premature termination of the study when the sponsor withdrew provision of drug and matched placebo pens. Exenatide proved to be well-tolerated but the study was underpowered to truly evaluate markers of efficacy and drug action (257). Hence, further research is required to elucidate the effects of exenatide and related drugs in AD patients.. A sustained-release exenatide phase 2, multi-center clinical trial involving a once weekly and once every other week administration (PT320; Peptron; NCT04269642) has recently been completed in South Korea that largely follows the clinical protocol of Foltynie and colleagues (13), and results are awaited. This trial, likewise, evaluates the contents of brain-enriched exosomes to define biomarkers of drug response. Additional clinical trials for exenatide and alike drugs in neurodegenerative disease treatment are currently underway (Table 2).. Finally, albeit it not a classical neurodegenerative disorder, studies by Sinclair and colleagues (294) demonstrated the efficacy of exenatide in reducing hypertension in a rat model of hydrocephalus, which has relevance to the human disorder of idiopathic intracranial hypertension for which effective pharmacological treatments are currently lacking (295). The choroid plexus expresses an abundance of GLP-1Rs and GLP-1R agonists reduce the activity of Na+/K+ ATPase, a marker of CSF secretion and, thereby, intracranial pressure (294).. An abundance of research in cellular and animal model systems highlights the potential for GLP-1R agonists in reducing neuroinflammation and treating neurodegenerative diseases. Many GLP-1R agonists have already been approved by the FDA for the treatment of diabetes and obesity and could be repurposed for the treatment of neuroinflammation and neurodegeneration. This repurposing will require additional research in human clinical trials to confirm the safety, tolerability, and efficacy of each drug in reducing neuroinflammation in the human brain, as well as reveal the implications for neurodegenerative disease treatment.. Several clinical trials have been completed or are currently underway to investigate the utility of GLP-1R agonists in treating neurodegenerative diseases, and the use of exosomes to evaluate biomarkers of drug target engagement and biological cascades involved in disease progression would provide valuable insight into drug action. In future research on the development of effective incretin receptor-stimulating drugs for reducing neuroinflammation as well as mitigating disease progression via multiple potential neurotrophic/protective actions, important considerations should include BBB penetration and the demonstrated enhanced efficacy of multi-agonism relative to single agonism agents. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/36631836/ Paragraphs: Insulin sensitization drugs are a new treatment modality for PCOS. We searched PubMed, Google Scholar, Elsevier, and UpToDate databases in this review, and focused on the pathogenesis of IR in women with PCOS and the pathophysiology of IR in various tissues. In addition, the review provides a

comprehensive overview of the current progress in the efficacy of insulin sensitization therapy in the management of PCOS, providing the latest evidence for the clinical treatment of women with PCOS and IR.. There have been conflicting conclusions regarding the efficacy of the choice of optimal exercise mode in improving insulin sensitivity in women with PCOS. The heterogeneity of PCOS necessitates individualization of treatment options, and it appears that exercise combined with additional dietary/drug intervention is better for improving insulin sensitivity than either intervention alone [149–151].. Inositol is a compound with nine forms (sugar alcohols), of which inositol (MI) and d-chiral inositol (DCI) are the most abundant forms present in humans, playing important biological roles in mediating various effects of insulin. Several scientific studies have confirmed that it has excellent insulin sensitization efficiency in women with PCOS and promotes ovulation [180]. Given that inositol administration is safe and effective in ameliorating the reproduction and metabolism of patients with PCOS, it may be used not only as a treatment for infertile women but also as a preventive treatment during pregnancy [180–183].. IR in different PCOS tissues can selectively affect metabolic or mitotic pathways in many tissues, including the ovaries. Therefore, effective prevention and treatment options should be evaluated to improve IR in PCOS patients. Lifestyle interventions and insulin sensitization therapy can be effective strategies for improving insulin sensitivity, while increasing ovulation and reducing androgen levels. Among all of the insulin sensitizers, metformin is the most widely used in PCOS. However, all mentioned drugs for PCOS are still off-label and further studies with larger sample sizes are needed to evaluate the efficacy of these new treatments and provide new insights into the molecular mechanisms of IR in PCOS. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/36834836/ Paragraphs: Preclinical and clinical evidence has revealed that the administration of ERAs reduces kidney fibrosis, inflammation and proteinuria. Currently, the efficacy of many ERAs to treat kidney disease is being tested in randomized controlled trials; however, some of these, such as avosentan and atrasentan, were not commercialized due to the adverse events related to their use. Therefore, to take advantage of the protective properties of the ERAs, the use of ETA receptor-specific antagonists and/or combining them with sodium-glucose cotransporter 2 inhibitors (SGLT2i) has been proposed to prevent oedemas, the main ERAs-related deleterious effect.. The majority of the antagonists here described are still under investigation in ongoing clinical trials, while others are not used in clinical practice because of lack of efficacy or due to the presence of adverse events related to their use that compromise the safety of patients. Therefore, to take advantage of these compounds with clear beneficial effects (Table 2), therapeutic approaches under study are the combination of ERAs with other nephroprotective drugs such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) and the use of dual drugs such as sparsentan that blocks at the same time angiotensin-II type 1 and endothelin receptors.. Darusentan was promising because reduced blood pressure in resistant hypertension patients in early clinical studies but unfortunately failed to achieve efficacy in phase III clinical studies [32]. Other examples of ETA selective antagonists are sitaxentan, ambrisentan, avosentan, atrasentan, macitentan and zibotentan (Table 2). Currently, sitaxentan, ambrisentan and macitentan are approved to treat pulmonary arterial hypertension [21,34,35] while avosentan, atrasentan and zibotentan have been proposed as therapeutic agents in kidney disease [19,24,36].. Atrasentan is an oral selective ETA inhibitor with a selective ETA:ETB blockade ratio of 1200:1 [40] and 1800-fold selectivity for ETA [39]. In patients with diabetes and chronic kidney disease, atrasentan reduces the risk of renal events and albuminuria [19,22,41]. Currently, it is under study in an ongoing phase 2 clinical trial to evaluate the efficacy and safety of atrasentan in patients with proteinuric glomerular diseases (AFFINITY: Atrasentan in Patients with Proteinuric Glomerular Diseases—NCT04573920).. [94,95]. A recent post-hoc analysis of patients receiving atrasentan and SGLT2i in the SONAR trial revealed that weight increase (a surrogate marker of fluid overload) was reduced in patients receiving both atrasentan and SGLT2i [96]. New trials with prespecified kidney outcomes that evaluate the synergistic effects of the combination will shed light upon the future of ERAs in the treatment of chronic kidney disease. The currently ongoing ZENITH-CKD trial (NCT04724837), for example, will evaluate the efficacy of the combination of zibotentan and dapagliflozin in the treatment of CKD.. As reviewed here, the concentration of ET-1 is increased in pathological conditions, such as diabetes or hypertension, causing sustained vasoconstriction that ultimately leads to kidney damage. The ERAs show clear renoprotective effects in

preclinical experimental models and in human mainly by hemodynamic effects but also by restoring podocyte injury, reducing mesangial matrix accumulation, fibrosis and inflammation which reduces glomerular permeability and proteinuria. However, the use of ERAs in clinical practice to prevent kidney disease is narrow because some ERAs failed to demonstrate efficacy in phase III randomized clinical trials and/or produced adverse events such as oedemas.

Pharmacodynamics Drug Interaction: URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/34267380/ Paragraphs: Achievements are also viewed through the lens of patients impacted by insulin therapy and the evolution of insulin pharmacokinetics and delivery over the past 100 years. Finally, we reflect on the future of insulin therapy and diabetes treatment, as well as challenges to be addressed moving forward, so that the full potential of this transformative discovery may be realized.. However, it took nearly another century to link the polyuria and polydipsia of diabetes mellitus with excessive glucose in both the blood and urine11. The first working evidence that the pancreas controlled carbohydrate metabolism would not come until 1889, when German scientists Oskar Minkowski and Joseph von Mering performed pancreatectomies on dogs who then developed hyperglycemia and diabetes12. Almost 20 years before Minkowski and von Mering's seminal work, the first detailed histologic studies of the pancreas were published by Paul Langerhans, as a medical student.. Although exogenously administered regular insulin was lifesaving, its pharmacokinetics did not mirror that of endogenously produced human insulin. Administered insulin molecules self-associate into hexamers, which must dissociate into dimers and then monomers before entering the circulation, with typical delays of 60–90 min from injection to peak action. This contrasts with the circulating endogenous insulin peak action of approximately 15–30 min after the start of food ingestion. In addition to the delay in action, these first insulins were all short acting (Fig. 2) and required multiple injections per day.. a, The native structure of human proinsulin. b, Representative pharmacokinetic profiles of available insulins administered subcutaneously. c, Structural changes of insulin analogs and years of introduction in the USA including rapid-acting insulin analogs (green boxes) and long-acting insulin analogs (red boxes)96,106,151–154.. Subsequently, Genentech and Lilly agreed to commercialize this new insulin and Humulin R and N insulins came to market in 1983. Novolin R (Novo Nordisk) followed in 1991 and Insuman R (Hoechst) in 1997. Although this represented an improvement in source, these insulins were still zinc-based formulations with slower pharmacokinetic profiles than natively secreted insulin.. The 1993 publication of the Diabetes Control and Complications Trial112 and 1998 United Kingdom Prospective Diabetes Study113–115 demonstrated definitive relationships between glycemic control and microvascular complications and showed that lower A1cs were associated with higher rates of severe hypoglycemia. These observations spurred efforts focused on improving exogenously administered insulin's pharmacokinetic and pharmacodynamic properties (absorption rate, time to peak and duration of action).. This has been accomplished over time (Fig. 2) using recombinant DNA technology and genetic engineering, and adding excipients. Tweaking amino acid sites/composition in the native insulin molecule changed the pharmacokinetics and permitted faster absorption, earlier peak action and faster offset. In 1988 a synthetically designed insulin was produced by replacing the B28 proline with aspartic acid, which favored a molecular conformation leading to rapid dissociation of dimerized insulin chains. The first rapid-acting insulin, insulin lispro (produced by inverting the B29 lysine and B28 proline), came to market in 1996.. Next was aspart in 2000, and then glulisine in 2004. An ultrarapid-acting version of insulin aspart was subsequently developed by adding nicotinamide and l-arginine as excipients that improve the insulin's stability and rate of absorption116. An ultrarapid insulin lispro has also been developed by using a prostacyclin analog to enhance vasodilation and absorption and citrate to enhance local vascular permeability.. In addition to efforts focused on disease modification, there are continuing efforts to improve insulin therapies and there is still much to be refined in our approach to exogenous insulin delivery. There is a hope for development of better insulins including: insulins with even faster pharmacokinetics, once-weekly insulin, oral insulin and, ultimately, glucose-responsive 'smart' insulins that increase circulating concentrations under conditions of hyperglycemia. Additional technological advancements on the horizon include improved algorithms for automated insulin delivery devices, implantable devices and dual-hormonal systems that combine automated delivery of insulin

and glucagon133,134. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/34413118/ Paragraphs: In vitro cell-based studies showed that insulin icodec activates the same dose-dependent IR-mediated signaling and metabolic responses as native human insulin (HI). The affinity of insulin icodec for the insulin-like growth factor-1 receptor was proportionately lower than its binding to the IR, and the in vitro mitogenic effect of insulin icodec in various human cells was low relative to HI. The clinical pharmacology trial in people with type 2 diabetes showed that insulin icodec was well tolerated and has pharmacokinetic/pharmacodynamic properties that are suited for once-weekly dosing, with a mean half-life of 196 hours and close to even distribution of glucose-lowering effect over the entire dosing interval of 1 week.. The molecular modifications introduced into insulin icodec provide a novel basal insulin with biological and pharmacokinetic/pharmacodynamic properties suitable for once-weekly dosing.. Beagle dogs weighing 9–18 kg were not offered food for at least 12 hours prior to dosing subcutaneously in the neck with the different insulin analogs. Blood samples were drawn regularly for 7–14 days. Time points for blood sampling were prespecified for each analog depending on the expected pharmacokinetic profile. Plasma samples were analyzed for the respective insulin analog by luminescent oxygen channeling immunoassay (AlphaLISA) using antibodies specific for each analog tested.25 Plasma concentration–time profiles were analyzed by non-compartmental pharmacokinetics analysis using WinNonlin Professional.. Within each of three subsequent cohorts, participants were randomized to once-weekly insulin icodec (cohort 1: 12 nmol/kg; cohort 2: 20 nmol/kg; cohort 3: 24 nmol/kg) plus once-daily placebo or once-daily insulin degludec (0.4 U/kg; corresponding to 16.8 nmol/kg/week) plus once-weekly placebo for 5 weeks (all by subcutaneous injection in the thigh at ~20:00 hours using a NovoPen4 pen device; Novo Nordisk A/S, Bagsværd, Denmark) (online supplemental figure 1). Data on insulin degludec are not included, but pharmacodynamic data have been presented elsewhere.26 The decision to proceed to the next cohort was made by an internal trial safety group after review of blinded interim safety, pharmacokinetic and pharmacodynamic data.. Pharmacokinetic dose proportionality was evaluated by linear regression of log(AUC0-168h) on log(dose), where AUC0-168h was derived after the last insulin icodec dose and a slope of 1 corresponds to dose proportionality (the power model). Pharmacokinetic trough values to steady state and full-week glucose-lowering effect profiles in week 5 were predicted for each individual using a pharmacokinetic–pharmacodynamic model. Model parameters were estimated for each individual based on insulin icodec pharmacokinetic data from the first dose until day 65 and 24-hour glucose clamp data in week 5 (days 30 and 35).. Furthermore, the amino acid modifications confer molecular stability by minimizing enzymatic degradation.11 15 Finally, the threonine in position B30 of HI has been deleted; however, the desB30 has no influence on the IR affinity. Altogether, these molecular changes have been demonstrated to impart a long half-life as seen by the pharmacokinetic profile of insulin icodec in dogs following a single subcutaneous injection (online supplemental figure 2).. A key consideration when developing insulin analogs is to ensure that the modifications to achieve the desired pharmacokinetic profile do not unfavorably alter the biological responses. Several in vitro studies were therefore conducted to demonstrate that insulin icodec retains the biological properties of native HI. Similar assays have been previously used to assess the biological characteristics and in vitro safety profiles of various long-acting basal insulin analogs (insulin glargine, detemir and degludec).23 27 28 From the displacement curves for binding to the solubilized hIR, it can be seen that insulin icodec fully displaces the HI tracer to the same extent as HI (figure 1B).. Pharmacokinetic and pharmacodynamic properties of insulin icodec in individuals with type 2 diabetes. (A) Model-predicted serum insulin icodec trough concentration during initiation of once-weekly dosing. The dashed line indicates the threshold for clinical steady state of serum insulin icodec and the shaded area indicates serum insulin icodec concentrations considered as clinical steady state. Circles indicate individual values (n=38). (B) Mean observed total serum insulin icodec concentration (the vast majority being albumin-bound) during week 5 of once-weekly dosing.. It has previously been demonstrated that increasing the length of the fatty acid side chain gives rise to a longer half-life as observed with insulin detemir,30 insulin degludec23 and oral insulin 338.11 15 For illustrative purposes, the pharmacokinetic profile of insulin icodec has been compared with these acylated basal insulin analogs in dogs (online supplemental figure 2), where an increase in half-life was observed going from C14 to C16, C18 and C20 fatty acids, reflecting the increasing albumin binding affinity.. For insulin detemir and insulin

degludec, the fatty acid side chain also contributes to the formation of larger soluble self-association forms: dihexamers for insulin detemir and multihexamers for insulin degludec, which occur in the subcutis at the injection site. However, insulin icodec was intentionally formulated not to promote the formation of multimers at the injection site. For a protein drug, multimers with an absorption time longer than a week may not be desirable due to the risk of reduced bioavailability.. Pharmacokinetic modelling of serum insulin icodec trough concentrations during initiation of once-weekly dosing (figure 2A) demonstrates the build-up of an albumin-bound depot. After 3–4 weekly injections, steady state is reached in the majority of individuals at which time the rate of clearance essentially matches the administered dose. Figure 3 provides a schematic illustration of the sequence of events leading to steady state. With the first injection (panel A1), a week's dose of insulin icodec is administered into the subcutis, where hexamers dissociate into monomers that are absorbed into the circulation, binding to albumin.

Clinical Studies: URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/34413118/ Paragraphs: In vitro cell-based studies showed that insulin icodec activates the same dose-dependent IR-mediated signaling and metabolic responses as native human insulin (HI). The affinity of insulin icodec for the insulin-like growth factor-1 receptor was proportionately lower than its binding to the IR, and the in vitro mitogenic effect of insulin icodec in various human cells was low relative to HI. The clinical pharmacology trial in people with type 2 diabetes showed that insulin icodec was well tolerated and has pharmacokinetic/pharmacodynamic properties that are suited for once-weekly dosing, with a mean half-life of 196 hours and close to even distribution of glucose-lowering effect over the entire dosing interval of 1 week.. IR and insulin-like growth factor-1 receptor (IGF-1R) binding studies were performed essentially as described previously.17 Briefly, receptor affinities were determined by competition scintillation proximity assays using either solubilized IRs or IGF-1Rs in the absence or presence of HSA. Concentration-response relations from the binding assays were analyzed using a four-parameter logistic model18 assuming common slope and basal and maximum response.. A key consideration when developing insulin analogs is to ensure that the modifications to achieve the desired pharmacokinetic profile do not unfavorably alter the biological responses. Several in vitro studies were therefore conducted to demonstrate that insulin icodec retains the biological properties of native HI. Similar assays have been previously used to assess the biological characteristics and in vitro safety profiles of various long-acting basal insulin analogs (insulin glargine, detemir and degludec).23 27 28 From the displacement curves for binding to the solubilized hIR, it can be seen that insulin icodec fully displaces the HI tracer to the same extent as HI (figure 1B).. Overview of in vitro assays demonstrating that insulin icodec has retained the same biological effects as human insulin. Results supported dose-proportionality for AUC0-168h as the slope of log(AUC0-168h) versus log(dose) was not statistically significantly different from 1 (0.83 (0.56; 1.10)95% CI). Model-predicted pharmacodynamic data of a 1 week dosing interval at steady state indicated rather consistent glucose-lowering effect of insulin icodec throughout the week at clinically relevant doses (figure 2C). The distribution of glucose-lowering effect of insulin icodec over a week at steady state was determined as the daily proportion of the total weekly model-predicted glucose-lowering effect.. The reduced IR binding affinity of insulin icodec contributes to the long half-life by reducing the clearance rate, since insulin clearance occurs primarily via IR-mediated internalization. Importantly, the low IR affinity does not translate into reduced potency but rather results in a slow rate of insulin action since the low receptor affinity means it will take longer for each insulin molecule to initiate receptor activation before it can be cleared. Thus, insulin icodec remains fully potent, but much slower and longer acting compared with native HI.. Results from the clinical pharmacology trial support the model illustrated in figure 3. As shown in figure 2B, the geometric mean half-life was 196 hours, that is, just longer than 1 week. As a consequence of the long half-life, insulin icodec builds up during the first weeks of once-weekly dosing until reaching a plateau. The median tmax was 16 hours, and a peak to trough difference could be observed when measured as total insulin icodec (bound and unbound to albumin). However, the mean glucose-lowering effect of insulin icodec demonstrated a close to even distribution over the entire dosing interval of 1 week (figure 2C).. For the non-clinical studies, data associated with this work are present in the paper. Data and reagents may be made available, on reasonable request, from Novo

Nordisk A/S under a materials transfer agreement. For the clinical trial, individual participant data will be shared in data sets in a deidentified/anonymized format. Datasets from Novo Nordisk sponsored clinical research completed after 2001 for product indications approved in both the EU and USA will be shared. Trial protocol and redacted Clinical Trial Report will be available according to Novo Nordisk data sharing commitments. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/26798030/ Paragraphs: Two review authors independently extracted data, assessed studies for risk of bias, and evaluated overall study quality utilising the GRADE instrument. We assessed the statistical heterogeneity of included studies by visually inspecting forest plots and quantifying the diversity using the I^2 statistic. We synthesised data using random■effects model meta■analysis or descriptive analysis, as appropriate.. We found five randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) with a total of 201 participants. Most trials did not report on type of diabetes. Younger diabetic participants and children were underrepresented in our included trials (one trial only). Participants in four trials received treatment with insulin lispro, and one trial with 45 participants investigated insulin aspart. The average follow■up as measured by mean hospital stay ranged between two and seven days.. Key results. Our results are most relevant for adults with mild or moderate diabetic ketoacidosis due to undertreatment of diabetes. No deaths occurred. Time to resolution of diabetic ketoacidosis from the start of therapy did not differ substantially between the two insulin treatment schemes (approximately 11 hours). Hypoglycaemic (low blood sugar) episodes were comparable: 118 per 1000 participants for intravenous insulin compared with 70 per 1000 participants for subcutaneous insulin lispro (no statistically significant difference).. Our results were limited by mostly low■ to very low■quality evidence, mainly because the number of included trials and participants was low. Further research is very likely to have an important impact on our findings.. The basic mechanism for the development of DKA is a reduction in the effective insulin concentration and increased counter■regulatory (catabolic or stress) hormones like glucagon, catecholamine, cortisol, and growth hormone. The hyperglycaemia of DKA results from increased hepatic glucose production (gluconeogenesis and glycogenolysis) and impaired peripheral glucose utilisation. Ketone bodies result from a marked increase in the free fatty acid release from adipocytes, with a resulting shift toward ketone body synthesis in the liver.. The route of administration of insulin in the management of DKA has been debated since the early 1970s. Alberti 1973 reported the results of low■dose intramuscular insulin in the management of people with DKA. They found that an initial average bolus dose of 16 units followed by 5 to 10 units of intramuscular regular insulin per hour was effective in correcting hyperglycaemia and acidaemia. Later in the 1970s, Fisher and colleagues reported a greater decline in blood glucose and ketone body levels in the first two hours of therapy with intravenous insulin as compared to intramuscular or subcutaneous insulin (Fisher 1977).. Hypoglycaemia is an inherent adverse effect of insulin treatment. Additionally, insulin therapy is associated with injection site reactions, generalised sensitivity reactions, and electrolyte imbalances such as hypokalaemia. Concern has been raised regarding potential mitogenic effects of insulin analogues, but evidence is controversial (Hemkens 2009; Kurtzhals 2000). Insulin lispro and insulin aspart, like human insulin, are rated category B for pregnancy use, which means that well■controlled trials in pregnant women are lacking, while insulin glulisine is category C, because only animal reproduction studies have been performed with it (Home 2012).. Two systematic reviews comparing rapid■acting insulin analogues with intravenous infusion of regular insulin in the treatment of mild to moderate DKA have been published (Mazer 2009; Vincent 2013). Both reviews provide an overview of the studies located, however there are some limitations. Firstly, the comprehensiveness of systematic literature searches was suboptimal. The literature search in Vincent 2013 was restricted exclusively to the PubMed database. Secondly, assessments of risk of bias of studies were not specified (Mazer 2009; Vincent 2013).. We continuously applied a MEDLINE (via Ovid) email alert service to identify newly published studies using the same search strategy as described for MEDLINE (for details on search strategies see Appendix 1). After supplying the final review draft for editorial approval, the Cochrane Metabolic and Endocrine Disorders Group performed a complete updated search on all databases available at the editorial office and sent the results to the review authors. Should we have identified new trials for inclusion, we evaluated these, incorporated the findings into our review, and resubmitted another review draft (Beller 2013).. We planned to evaluate any newly identified studies for inclusion, incorporate the findings into our review,

and resubmit another review draft (Beller 2013).. For trials that fulfilled our inclusion criteria, two review authors (CAC, LCL) independently abstracted relevant population and intervention characteristics using standard data extraction templates (for details see Characteristics of included studies; Table 3; Appendix 2; Appendix 3; Appendix 4; Appendix 5;Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12), with any disagreements to be resolved by discussion, or, if required, by a third review author (NDF).. We have provided information including trial identifier about potentially relevant ongoing trials in Characteristics of ongoing studies and in Appendix 5 ('Matrix of study endpoints (publications and trial documents)'). We attempted to identify the protocol of each included trial, either in trials registers, publications of study designs, or both, and specified data in Appendix 5.. We emailed authors of included trials to enquire as to whether they would be willing to answer questions regarding their trials. Appendix 13 shows the results of this survey. We thereafter sought relevant missing information on the trial from the primary author(s) of the article, if required.. We judged 'Risk of bias' criteria as 'low risk', 'high risk', or 'unclear risk' and evaluated individual bias items as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011a). We have presented a 'Risk of bias' graph and a 'Risk of bias summary'. We assessed the impact of individual bias domains on trial results at the endpoint and trial levels. In case of high risk of selection bias, we would have marked all endpoints investigated in the associated trial as 'high risk'.. We assessed outcome reporting bias by integrating the results of 'Examination of outcome reporting bias' (Appendix 6) and 'Matrix of study endpoints (publications and trial documents)' (Appendix 5) (Kirkham 2010). This analysis formed the basis for the judgement of selective reporting (reporting bias).. Where standard deviations for outcomes were not reported and we did not receive information from trial authors, we planned to impute these values by assuming the standard deviation of the missing outcome to be the average of the standard deviations from those studies where this information was reported. We wanted to investigate the impact of imputation on meta■analyses by means of sensitivity analysis.. In the event of substantial clinical or methodological heterogeneity, we did not report trial results as the pooled effect estimate in a meta■analysis.. Had we included 10 trials or more investigating a particular outcome, we would have used funnel plots to assess small■study effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. We therefore planned to interpret results carefully (Sterne 2011).. Unless there was good evidence for homogeneous effects across studies, we primarily summarised low risk of bias data by means of a random■effects model (Wood 2008). We interpreted random■effects meta■analyses with due consideration of the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009), which specifies a predicted range for the true treatment effect in an individual study (Riley 2011). In addition, we performed statistical analyses according to the statistical guidelines presented in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011a).. We have presented the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results. Two review authors (CAC, NDF) independently rated the quality for each outcome. We have presented a summary of the evidence in 'Summary of findings' (SoF) tables, which provide key information about the best estimate of the magnitude of the effect, in relative terms and absolute differences for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome, and the rating of the overall confidence in effect estimates for each outcome.. We created the SoF tables based on the methods described in the Cochrane Handbook for Systematic Reviews of Interventions by means of the table editor in Review Manager (RevMan), including Appendix 12 'Checklist to aid consistency and reproducibility of GRADE assessments' to help with standardisation of the 'Summary of findings' tables (Higgins 2011a; Meader 2014; RevMan 2014). Alternatively, we used the GRADEproGDT software and present evidence profile tables as an appendix (GRADEproGDT 2015). We have presented results on the outcomes as described in the Types of outcome measures section.. If meta■analysis was not possible, we presented results in a narrative form in the SoF table.. We also tested the robustness of the results by repeating the analysis using different measures of

effect size (RR, OR, etc.) and different statistical models (fixed■effect and random■effects models).. For a detailed description of the included trials, see Characteristics of included studies, Characteristics of excluded studies, and Characteristics of studies awaiting classification.. The electronic search strategies retrieved a total of 645 citations. After duplicates were excluded, two review authors (CAC, LCL) independently assessed the remaining titles and abstracts. We obtained the full text of 23 potentially relevant trials, seven of which we deemed potentially appropriate for inclusion in the analysis. Of these, two trials are awaiting classification, one trial was published as an abstract only, and another trial was registered in ClinicalTrials.gov with the status "This study has been completed", but no trial results were posted and no publication is available.. We have provided information about these trials in Characteristics of studies awaiting classification.. For a detailed description of the included studies, see Characteristics of included studies. The following is a succinct overview.. Overview of study populations. Trials were conducted in the USA (Umpierrez 2004a; Umpierrez 2004b), Brazil (Della Manna 2005), Turkey (Ersöz 2006), and India (Karoli 2011) (see Characteristics of included studies for details). In the US and Brazilian trials, participants were treated with subcutaneous insulin managed in regular medicine wards, in Umpierrez 2004a and Umpierrez 2004b, or in the emergency department, in Karoli 2011, and the participants treated with intravenous insulin were managed in the intensive care unit (Karoli 2011; Umpierrez 2004a; Umpierrez 2004b).. A total of 201 participants were randomised and exposed to trial insulins in the included studies. All five trials recruited people who had a DKA episode (Della Manna 2005; Ersöz 2006; Karoli 2011; Umpierrez 2004a; Umpierrez 2004b). One trial included paediatric and adolescent participants (60 DKA episodes in 46 participants) with a median age of 11 years (range 3 to 17 years) (Della Manna 2005); the other trials included either type 1 or type 2 diabetic adults with a DKA episode (Ersöz 2006; Karoli 2011; Umpierrez 2004a; Umpierrez 2004b).. Subcutaneous rapid■acting insulin analogues injections varied across studies. Four trials used lispro at given dosages: injection regimens were either 0.15 IU every two hours without bolus (Della Manna 2005), or 0.075 IU/kg every hour, preceded by a bolus injection of intravenous regular insulin (0.15 IU/kg) (Ersöz 2006), or 0.1 IU/kg every hour, preceded by an initial subcutaneous bolus of insulin lispro (0.3 IU/kg) (Umpierrez 2004a), or initial subcutaneous bolus of insulin lispro (0.3 IU/kg), followed by 0.2 IU/kg one hour later and then 0.2 IU/kg every two hours (Karoli 2011).. We excluded 16 trials after evaluation of the full publication. We have provided reasons for exclusion of studies in Characteristics of excluded studies. The main reasons for exclusion were inappropriate interventions and non■randomised study design.. For details on risk of bias of included trials, see Characteristics of included studies.. For an overview of review authors' judgements about each risk of bias item for individual trials and across all trials, see Figure 2 and Figure 3.. We did not perform subgroup analyses because there were not enough studies to estimate effects in various subgroups.. We could not perform preplanned analyses excluding unpublished trials because we included only published studies in this review. We were unable to perform sensitivity analyses with regard to risk of bias because all studies were of high or unclear risk of bias in various domains.. We did not draw funnel plots due to limited number of studies (n = 5).. This systematic review analysed the evidence from all published randomised controlled trials (RCTs) of subcutaneous rapid■acting insulin analogues in the treatment of diabetic ketoacidosis (DKA). We included five trials with a total of 201 participants in this review. The results of our review suggest that there is no substantial difference in the time to resolution of DKA between the subcutaneous rapid■acting insulin analogues lispro or aspart and intravenous regular insulin in adult participants.. In terms of hypoglycaemia and length of hospital stay, the results obtained with subcutaneous rapid■acting insulin analogues and regular insulin were comparable in both adults and children. No deaths occurred. Data on morbidity and socioeconomic effects were limited. None of the trials reported on adverse events other than hypoglycaemia, patient satisfaction, or glycosylated haemoglobin A1c.. The trials analysed in this review were conducted in four different countries, three of which could be considered as low■ or middle■income countries. Notably, most participants representing the high■income Western region were of African■American ethnicity. Younger diabetic participants and children were underrepresented in our trial cohorts. Based on the inclusion criteria of the analysed trials, the results are most relevant to adults with a mild or moderate DKA episode due to poor compliance with diabetes therapy.. The risk of bias across several domains was unclear for the majority of included studies. This was due mainly to there being insufficient information to permit

judgement of either a low or high risk of bias, despite attempts to contact the trial authors. According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, the quality of the evidence was low or very low for most clinically important outcomes (see Table 1; Table 2). The available data were thus too few and inconsistent to provide firm evidence about the effects of subcutaneous rapid■acting insulin analogues in people with DKA.. We believe that our search for RCTs has been comprehensive. However, we cannot exclude the possibility that studies with negative findings remain unpublished. Also, we did not systematically search the grey literature.. Our analyses suggest that, on the basis of mostly low■ to very low■quality evidence, there are neither advantages nor disadvantages when comparing the effects of subcutaneous rapid■acting insulin analogues (insulin lispro, insulin aspart) versus intravenous regular insulin for treating DKA. These results are most relevant to adults with a mild or moderate DKA episode due to poor compliance with diabetes therapy. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/33945208/ Paragraphs: Diabetic ketoacidosis (DKA) is an acute, life■threatening metabolic complication of feline diabetes mellitus (DM), and mortality rates range from 17 to 50%.1, 2, 3, 4, 5, 6 Despite this, studies are scarce, and current treatment recommendations are mostly extrapolated from experiences in people and dogs. The 3 cornerstones of therapy are rehydration, correction of electrolyte imbalances, and insulin administration to reduce ketone and glucose concentrations. Published insulin treatment regimens include intermittent IM administration of regular insulin2, 7 or glargine,8 continuous rate infusion of regular insulin1, 3, 5, 9 or lispro,1, 6 the combinations of SC glargine with intermittent IM regular insulin5 or the combination of SC and IM glargine.8 The relatively small number of patients included in the studies and limited comparisons between different protocols precludes evidence■based recommendations regarding which protocol is superior, and additional research is required.. Several studies in ketoacidotic diabetic human patients have shown that IM17 or even SC18, 19 bolus treatment protocols are safe and an effective treatment option. The objective of this prospective block■randomized study was to compare the basal■bolus glargine regimen with a regular IV insulin protocol and to demonstrate its utility in the treatment of feline DKA.. The results of our study in cats with naturally occurring DKA corroborate the findings of Marshall et al,8 who showed that the basal■bolus administration of glargine insulin is a safe and effective alternative to the regular insulin CRI protocol currently used by most experts in the field.3, 4, 36, 37 Furthermore, as already shown by Gallagher et al,5 the application of this simplified basal■bolus protocol decreased time to improvement of hyperglycemia and to discharge, without affecting survival rate or incidence of adverse events.. Although it could be argued that this more rapid decrease in glucose concentrations, likely caused by the higher insulin concentrations achieved within the first hours in the glargine group, would increase the risk of serious complications such as cerebral edema, several studies in dogs and cats suggest that this concern is unwarranted.36, 38, 39 It has been demonstrated in cats with diabetic ketosis that despite significant decreases of blood glucose concentrations > 120% within the first 72 hours of conventional therapy, sodium, the major determinant of serum tonicity, increases and effective osmolality stays relatively constant, minimizing large osmotic shifts.39 None of the cats in our study exhibited clinical signs suggestive of hypoglycemia or cerebral edema.. DKA treatment is traditionally guided by changes in blood glucose concentrations and blood gas analysis. The results of our study suggest that, as in human patients41 and in dogs,42 β■OHB measurements are a useful adjunct for monitoring response to therapy and eliminate the need for frequent blood gas analyses, which are not specific for ketone production, are labor intensive and, therefore, expensive. Additionally, β■OHB measurements facilitate rapid reevaluation of the diagnosis in cats with low ketone concentrations but ongoing metabolic acidosis.. The results of blood gas analysis did not influence insulin dose in any cat.. The median time for resolution of ketonemia in our CRI■group was 42 hours, compared to 62 and 68 hours in 2 previous studies.1, 5 A possible explanation is the use of a different protocol for adjustment of insulin and glucose administration. In contrast to the previous studies, insulin infusion was not decreased at glucose concentrations < 16.8 mmol/L (300 mg/dL)1 or < 13.9 mmol/L (250 mg/dL),5 but insulin administration rate was kept constant until target β■OHB concentrations were reached. To allow for intensive insulin treatment, 5% glucose solutions were administered when glucose concentrations fell below 10 mmol/L (180 mg/dL).. This is in line with the latest treatment guidelines in decompensated diabetic children,19 in which a decrease of insulin dose of < 0.05 to 0.1 unit/kg/h is only recommended after DKA has resolved or hypoglycemia is

impending, despite the use of 10% or even 12.5% glucose solutions. The early reduction of the CRI■insulin dose in the cited studies1, 5 possibly delayed the resolution of ketonemia and could explain why more key indicators were significantly different between the 2 protocols in Gallagher et al's5 study.. Two retrospective studies compared outcome in cats treated with either 0.05 or 0.1 units/kg/h.4, 9 Whereas the higher insulin dose reduced the odds of poor outcome defined as deaths in the first study,4 no differences were found in the second.9 Neither of the studies compared time until resolution of ketoacidosis or ketonemia.. A topic of debate in human medicine is whether to routinely start SC administration of a long■acting basal insulin (eg, glargine insulin) at the onset of DKA management. The rationale is to provide stable background insulin concentration and to avoid reoccurrence of hyperglycemia during the transition time to SC insulin.18, 48 A common concern raised with SC insulin administration in dehydrated patients is SC insulin accumulation and sudden release after rehydration.49 A meta■analysis of 4 studies in human patients suggests that this concern is likely unwarranted.. The addition of SC glargine insulin to standard protocols using IV infusion of regular insulin significantly decreased the time to resolution of DKA, without increasing the risk of adverse events.50 Interestingly, Shankar et al51 proposed that the positive effects are caused by yet to be described mechanisms, other than just increased total daily insulin dose. Based on evidence in human and feline patients, some veterinary specialists are combining IV regular insulin infusions with twice■ daily SC glargine insulin injections.37 Prospective randomized studies are required to more conclusively estimate the benefit of adding SC insulin glargine to DKA protocols for cats.. To avoid adverse events associated with hypophosphatemia such as hemolytic anemia, IV phosphorus supplementation (potassium■phosphate) was a fixed part of our treatment protocol. Severe depletion of phosphorus may lead to ATP depletion in erythrocytes, causing failure of actin and myosin fibers in the cell membranes to maintain normal biconcave structure and deformability.27 In our protocol, phosphorus was preventatively administered by providing 25% of potassium as potassium■phosphate. Consequently, hypophosphatemia was observed in only 50% of the cats, compared to 80%,8 67%,1 and 65%4 in previous studies, in which phosphorus was administered exclusively to hypophosphatemic patients.. Several important limitations must be recognized when interpreting the results of our study. The major limitation was that due to stringent criteria for inclusion, the number of cats included was lower than initially planned. A sample size calculation, assuming a power of 80% and a 5% significance level, revealed that a minimum of 37 cats in each treatment group would have been needed to show a 12■hour difference until resolution of ketonemia. In the future, multisite studies are recommended to provide sufficient power.. In conclusion, although the study was underpowered to detect differences in time until resolution of ketonemia, the results suggest that the basal■bolus administration of insulin glargine is a useful alternative to the current standard CRI■protocol for the management of DKA in cats. It is simple and associated with a shorter time to first improvement of hyperglycemia and decreased hospitalization time. Additionally, β■OHB measurements using hand■held ketone meters are a useful adjunct for monitoring response to therapy and eliminate the need for frequent blood gas analyses.. Further studies are required to evaluate the benefits and disadvantages of IM bolus vs CRI protocols and to compare choices of fluid therapy in management of feline DKA. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/27434027/ Paragraphs: We systematically searched multiple databases (PubMed, EMBASE, OVID, BIOSIS, Web-of-Knowledge, CAB, CINAHL, Cochrane Library, SIGLE, Faculty1000) for randomised controlled feeding trials published by 26 Nov 2015 that tested effects of macronutrient intake on blood glucose, insulin, HbA1c, insulin sensitivity, and insulin secretion in adults aged ≥18 years. We excluded trials with non-isocaloric comparisons and trials providing dietary advice or supplements rather than meals. Studies were reviewed and data extracted independently in duplicate.. Prior knowledge has been limited by several factors, including focus on limited metrics to assess glucose-insulin homeostasis (e.g., fasting glucose alone), rather than studying multiple relevant outcomes, such as HbA1c, fasting insulin, insulin resistance, insulin secretion capacity, and post-challenge measures [8]; insufficient statistical power in many smaller trials to confirm important effects; and difficulties in evaluating results of individual trials due to multiple and varying changes in several macronutrients simultaneously. [8,13]. Study exclusions were insufficient information on macronutrient composition or glycaemic outcomes, studies of supplements or dietary advice only, and studies of acute (single meal) post-prandial effects only. We searched PubMed,

EMBASE, OVID, BIOSIS, Web-of-Knowledge, CAB, CINAHL, Cochrane Library, SIGLE, and Faculty 1000, without language restriction, for all publications up until 26 November 2015. Search terms included each of the dietary macronutrients and metabolic measurements of interest.. Between-arm correlations in trials using either crossover or Latin-square design were estimated and incorporated in meta-analysis by using reported p-values and outcome measures based on the function of within-individual correlations, interventional effects, their standard errors or deviations, and p-value [15,16]. Missing information on covariates (trans fat, dietary fibre), within-trial correlations, or precise post-intervention statistics (e.g., results expressed only as “$p > 0.05$”; standard deviations of post-intervention values [17]) was imputed with a multiple imputation approach to incorporate the uncertainty in our estimation by generating ten imputed datasets and pooling the estimates [18].. In post hoc analyses, we explored heterogeneity by extent of provision of all daily meals (full/partial). Each characteristic was tested as a potential source of heterogeneity by testing a standard Q-statistics for stratum-specific effects on the selected outcome for exchanging carbohydrate with SFA, MUFA, or PUFA, exchanging SFA with MUFA or PUFA, and exchanging MUFA with PUFA. For stratification by continuous variables, the median value across studies was used. To avoid false positive findings due to multiple testing of these exploratory interactions on the four outcomes, the $\alpha = 0.05$ was adjusted for the family-wise false-discovery rate [22].. To assess publication bias or bias specific to small studies in multiple-treatment meta-regression, we utilized influence analyses [15]. Meta-regressions were repeated after excluding each single trial individually, with each new meta-regression finding plotted against the square root of the excluded trial’s effective sample size, accounting for within-trial correlations [26]. The resulting plots were inspected visually for patterns of bias by trial size; using linear regression to determine whether observed deviations were statistically significant, analogous to Egger’s test [15]; and using a non-parametric Wilcoxon rank test to examine whether estimates were symmetrical around the main estimate.. To evaluate robustness of the main findings, we repeated meta-analyses using random effects in five selected strata, which were significant sources of heterogeneity: trials conducted in Western nations; trials of adults with diabetes; trials of adults without diabetes; trials providing whole meals; and trials with blinding of meals provided (S4 Table). Findings using random effects were generally similar, with some results having wider CIs and failing to achieve statistical significance (e.g., for HbA1c); most results being statistically significant in both fixed-effects and random-effects models, in particular for 2 h insulin, HOMA-IR, and AIR; and rarely some findings being significant in random-effects but not fixed-effects models.. The results of this systematic review and meta-analysis of randomised controlled feeding trials provide, to our knowledge, the most robust available evidence for the effects of dietary fats and carbohydrate on diverse glucose-insulin metrics. We identified divergent relationships of specific dietary fats with different measures of glucose-insulin homeostasis. For example, only energy intake substitution with PUFA was linked to lower fasting glucose, lower HbA1c, improve HOMA-IR, and improve insulin secretion capacity.. Meta-analyses of omega-3 supplementation as well as dietary intakes and blood biomarker levels of omega-3 PUFA demonstrate no significant effects on fasting glucose or incident diabetes [40,41]. Together with our results, these findings suggest that metabolic benefits of PUFA relate to omega-6 PUFA or total PUFA, and not omega-3 PUFA alone.. Our findings advance the field by exploring interactions using all currently available data from feeding trials, which generate hypotheses to be tested in new studies, including studies of gene-diet interactions across diverse populations, controlled trials of glucose-insulin biomarkers, and prospective studies of clinical events.. Our investigation has several strengths. Our systematic search, rigorous screening, and data extraction protocols made it unlikely that any large studies or relevant data were missed or erroneously extracted. In addition, the large number of identified studies makes it unlikely that any single study, whether included or missed, would appreciably alter our findings. We focused on randomised, controlled trials using feeding interventions, maximizing inference for true biological effects. We examined different replacement scenarios among major macronutrients, providing novel insights for the most relevant replacements; confirmed robustness of our findings in sensitivity analyses and adjusted for between-arm differences in protein, trans fat, and dietary fibre, reducing the influence of variation in these factors.. For instance, our results should not be extrapolated to potential effects of carbohydrate in fruit, legumes, or minimally processed whole grains. Trials inconsistently provided information on food sources of macronutrients (e.g., specific oils) or

cooking methods; future studies should evaluate whether these characteristics modify physiologic effects. Most trials were in North America and Europe, and findings may not be generalisable to other world regions. Our analysis evaluated relatively few trials measuring C-peptide, post-challenge glucose and insulin, ISI, and AIR, and did not evaluate outcomes specific to peripheral or hepatic insulin sensitivity, not capturing the potential effects of fatty acids on insulin sensitivity of specific tissues.. Unmeasured sources of heterogeneity may exist, such as effects of genes and cooking methods. Therefore, our meta-analysis highlights the gaps in knowledge for potential effect-modifiers for various metrics of glucose-insulin homeostasis. Our results and available evidence support the importance of further experimental studies and large, adequately powered feeding trials examining ISI and AIR. Meta-analyses can be influenced by small study bias; yet, influence analysis did not support the presence of such bias, and findings for our main endpoints were based on large numbers of trials, making it unlikely that inclusion of any unpublished trials would substantially alter the results.. In conclusion, this systematic review and meta-analysis provides novel quantitative evidence for effects of major dietary fats and carbohydrate on glucose-insulin homeostasis. The results support guidelines to increase MUFA intake to improve glycaemia and insulin resistance, with possibly stronger effects among patients with type 2 diabetes, and to increase PUFA intake in the general population to improve long-term glycaemic control, insulin resistance, and insulin secretion capacity, in place of SFA or carbohydrate. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/35179802/ Paragraphs: Moreover, fasting and feeding schedule may interfere with the circadian rhythm and hence sleep length and quality 12 and in addition, poor sleep has been associated with insufficient glycaemic control. 13 The majority of the available data on intermittent fasting and sleep derives from Ramadan studies and were inconclusive with regard to sleep duration and sleepiness of people. 14. Main exclusion criteria contain active, known malignancies within the last year (excluding intraepithelial neoplasia of prostate, gastrointestinal tract and basalioma), pregnancy or intention of becoming pregnant, breastfeeding, a history of any chronic disease process that could interfere with interpretation of study results, new hormonal supplementation or contraceptive hormonal medication changes in the last 2 months, type 1 diabetes mellitus or other forms of diabetes mellitus, an acute or chronic inflammatory disorder, alcohol abuse with more than 15 standard drinks per week, overnight shifts or intake of illicit substances.. Previously, intermittent fasting was shown to cause weight loss of 3%–8% over 3–24 weeks and to reduce waist circumference by 4%–7%, which indicates that people lost some abdominal fat, associated with insulin resistance and related diseases. 37 Although reducing insulin resistance is beneficial in people with diabetes, it also bears the risk of hypoglycaemia in people treated with insulin. Data from Ramadan studies are available, showing mitigation of hypoglycaemia during Ramadan using the flash glucose monitoring system.. All procedures performed in studies involving human participants are in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Overview of Safety: URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/33325008/ Paragraphs: Pre-clinical trials and phase 1 and 2 clinical trials indicate that tirzepatide has potent glucose lowering and weight loss with adverse effects comparable to those of established GLP-1 receptor agonists. The long-term efficacy, safety and cardiovascular outcomes of tirzepatide will be investigated in the SURPASS phase 3 clinical trial programme. In this paper, we will review the pre-clinical and phase 1 and 2 trials for tirzepatide in the management of T2DM and give an overview of the SURPASS clinical trials.. The co-agonist can be modified by attaching a polyethylene glycol (PEG) or a 16-carbon acyl chain to extend half-life (allowing weekly dosing). The PEGylated co-agonist was investigated in 44 people with T2DM. After 6 weeks, a dose-dependent decrease in HbA1c compared to placebo was observed. The co-agonist was well tolerated with mild to moderate GI side effects and no hypoglycaemic events [29].. The clinical efficacy, safety and tolerability of tirzepatide has been reported in phase 1 and phase 2 clinical trials (Table 2).. A phase 1 proof-of-concept clinical trial was conducted in 53 people with T2DM, comprising five groups: two fixed dose groups (tirzepatide 0.5 mg and 5.0 mg) and two dose-titration groups (tirzepatide 0.5/5/10/10 mg and 0.5/5/10/15 mg) and a placebo group. The study had 4 weeks treatment followed by 4 weeks safety follow-up. Baseline characteristics of

study participants were mean age 56.8 ± 6.9 years, 53% male, 77% White, 13% Asian, 8% Black, BMI 31.2 ± 4.0 kg/m2 and HbA1c 8.4 ± 0.8% (all values in mean ± SD).. A similar phase 1 placebo-controlled, randomised study of tirzepatide was conducted in 48 Japanese people with T2DM. The treatment arm of the Japanese study consisted of one fixed (5 mg) dose group and two dose-titration groups (2.5 mg for 2 weeks, 5 mg for 2 weeks and 10 mg for 4 weeks; and 5 mg for 2 weeks, 10 mg for 4 weeks and 15 mg for 2 weeks). The study had a treatment exposure of 8 weeks with a 4-weeks safety follow-up. Baseline characteristics were mean age 57.4 ± 8.8 years, 47% male, BMI 25.4 ± 3.2 kg/m2 and HbA1c 8.0 ± 0.8%.. Since tirzepatide is a dual GIP/GLP-1 agonist, the side effect profile is comparable to that of a GLP-1 receptor agonist. The most frequently observed side effects were related to the gastrointestinal (GI) system and nausea, diarrhoea and vomiting were the most common adverse events. The incidence of GI adverse events was 23.1% for 1 mg, 32.7% for 5 mg, 51.0% for 10 mg and 66.0% for 15 mg, demonstrating a dose-dependent behaviour (versus 42.6% for dulaglutide and 9.8% for placebo). The second most common adverse effect was reduced appetite, the incidence ranging from 3.8% to 18.9% in tirzepatide-treated groups.. The SURPASS clinical trial programme aimed to assess the efficacy and safety of tirzepatide as a treatment to improve glycaemic control in people with T2DM (Table 3) [34–42]. The SURPASS phase 3 clinical trials include six global, two Japanese and one Asia–Pacific studies. These trials include anti-hyperglycaemic therapy-naïve patients (patients treated with diet and lifestyle alone) as well as patients on various oral anti-hyperglycaemic agents (metformin, sulfonylurea, pioglitazone, SGLT2 inhibitor and/or insulin).. Tirzepatide has demonstrated greater HbA1c reduction (− 2.4% with 15 mg tirzepatide) and superior weight loss (− 11.3 kg with tirzepatide 15 mg) with comparable adverse effects versus the GLP-1 RA dulaglutide in phase 2 trials. Of note, semaglutide, currently regarded as the most potent GLP-1 RA, demonstrated 1.5–1.8% HbA1c reduction and 4.5–6.5 kg weight reduction [1]. It is not possible to compare the efficacy of tirzepatide and semaglutide with available data from phase 2 trials; however, the SURPASS-2 trial will directly compare the efficacy and safety of tirzepatide versus semaglutide with the potential for superiority of tirzepatide, particularly with respect to weight reduction.. None of the SURPASS trials are designed to compare tirzepatide against SGLT2 inhibitors. Further study comparing tirzepatide against SGLT2 inhibitors would be of use in clinical decision-making. Since the 2008 publication of FDA guidance on anti-hyperglycaemic therapy, medications for diabetes should not only be efficacious in reduction in HbA1c but should also have favourable CV outcomes (at least no negative CV impact). The SURPASS-CVOT trial will provide long-term data on the CV safety as well as efficacy of tirzepatide.. SYNERGY-NASH is a randomized, double-blind, placebo-controlled phase 2 study comparing the efficacy and safety of tirzepatide in patients with non-alcoholic steatohepatitis (NASH) [50].. Tirzepatide, a dual GIP/GLP-1 receptor agonist, is a new incretin-based therapy for type 2 diabetes. The degree of HbA1c reduction and weight reduction observed in pre-clinical, phase 1 and 2 clinical trials has not previously been observed in diabetes clinical trials. The comprehensive phase 3 SURPASS clinical trial programme will confirm comparable efficacy, safety and cardiovascular outcomes of tirzepatide in the management of T2DM diabetes. The SURPASS trials will also provide insight into understanding of incretin hormones, particularly the role of GIP in energy metabolism. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/31441246/ Paragraphs: By providing blood glucose (BG) concentration measurements in an almost continuous-time fashion for several consecutive days, wearable minimally-invasive continuous glucose monitoring (CGM) sensors are revolutionizing diabetes management, and are becoming an increasingly adopted technology especially for diabetic individuals requiring insulin administrations. Indeed, by providing glucose real-time insights of BG dynamics and trend, and being equipped with visual and acoustic alarms for hypo- and hyperglycemia, CGM devices have been proved to improve safety and effectiveness of diabetes therapy, reduce hypoglycemia incidence and duration, and decrease glycemic variability.. Among the many glucose-sensing mechanisms tested to guarantee all the necessary requirements for long-term use of biosensor in free-living conditions, i.e., biocompatibility, lifetime, safety, sensitivity, and specificity, the most popular technique used for continuous glucose monitoring (CGM) systems relies on the glucose oxidation reaction [1]. Specifically, CGM devices based on this principle use a glucose-oxidase-doped platinum electrode deposited on a needle inserted in the subcutaneous tissue to ignite and catalyze glucose oxidation.. These improvements led to the regulatory approval of CGM nonadjunctive use, i.e.,

the use of CGM readings to make treatment decisions without confirmatory fingersticks, whose safety and effectiveness have been proved by simulations [8] and a randomized non-inferiority clinical trial [33]. From 2014 to 2015, three CGM sensors received the nonadjunctive label in Europe: the FreeStyle Navigator II, the FreeStyle Libre and the Dexcom G5 Mobile. The approval of nonadjunctive use by the FDA came a couple of years later: the Dexcom G5 Mobile obtained the approval in 2016, followed by the FreeStyle Libre in 2017 and the Dexcom G6 in 2018.. Several clinical trials were performed to assess the safety and effectiveness of basal insulin suspension algorithms both in clinic under controlled conditions [69,70,71,72] and at home under real-life conditions [67,73,74,75]. Evidences from these trials supported the effectiveness of these algorithms in reducing hypoglycemia, at the expenses of a slight increase in hyperglycemia. Nevertheless, the use of basal insulin suspension was not associated with a significant increase of HbA1c or occurrence of ketoacidosis.. For an exhaustive review of algorithms for basal insulin suspension/attenuation, their implementation in commercial devices and clinical evidence of their effectiveness and safety, we refer the reader to [76].. While research in AP is progressively increasing the safety and effectiveness of such devices, also exploring bi-hormonal systems allowing controlled delivery of both insulin and glucagon [89], patients have shown an increased interest for the AP technology. This gave rise to the OpenAPS community, a community of patients highly interested in directly improving diabetes technologies, who have designed their own open source AP system, also called do-it-yourself closed-loop system. Although no clinical trial has ever assessed the safety and effectiveness of such open source systems, OpenAPS users self-reported an improvement in HbA1c, time in range, glycemic variability and quality of life, while perceiving the OpenAPS system as safe [90,91]. URL:
https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/33964002/ Paragraphs: In an extensive phase III clinical program including patients from across the disease spectrum, treatment with oral semaglutide resulted in effective glycemic control, reductions in body weight, and decreases in systolic blood pressure when used as monotherapy or in combination with other glucose-lowering therapies. Studies showed that oral semaglutide was well tolerated, with a safety profile consistent with the GLP-1RA drug class. The risk of hypoglycemia was low, and the most common adverse events were gastrointestinal, with nausea and diarrhea generally being the most frequently reported manifestations.. Cardiovascular (CV) safety was shown to be noninferior to placebo and observations suggest that the CV profile of oral semaglutide is likely to be similar to that of subcutaneous semaglutide. The evolution of the GLP-1RA class to include an oral agent could facilitate the use of these agents earlier in the diabetes treatment cascade owing to wider acceptance from patients and healthcare professionals.. To help provide insights into the potential role of oral semaglutide in current T2D management, this article aims to discuss the pharmacology of oral semaglutide, review the current clinical evidence on the efficacy and safety of this agent from the extensive phase III PIONEER clinical trial program in patients with T2D, and describe findings from initial cost-effectiveness studies.. Hemodialysis did not appear to affect the pharmacokinetics of oral semaglutide or SNAC [36]. The pharmacokinetics, safety, and tolerability of oral semaglutide were also studied in patients (N = 56) with varying degrees of hepatic impairment (normal function, mild, moderate, and severe) over ten doses [37]. This study was important as there had been no previous reported data on the possible effects of hepatic impairment on the pharmacokinetics of SNAC, which is metabolized via β-oxidation and glucuronidation and is highly bound to albumin.. Based on the findings of this phase II study, the efficacy and safety of three doses of oral semaglutide (3, 7, and 14 mg) were investigated in the Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) phase III clinical trial program, which included eight multinational studies (PIONEER 1–8) [44–53] and two Japan-specific studies (PIONEER 9 and 10) [54, 55]. Individuals recruited for this program were patients with T2D from across a broad range of disease durations and background therapies, and representative of many patients typically encountered in clinical practice (Table 2).. In patients with moderate renal impairment, body-weight reductions were observed with oral semaglutide (14 mg) compared with placebo (ETD − 2.5 kg at 26 weeks; $p < 0.001$) [50]. Although there was no statistical comparison of bodyweight changes with treatment in the CV safety trial, by the end of that study in patients at high CV risk, body weight had decreased by 4.2 kg with oral semaglutide and by 0.8 kg with placebo [51].. Safety and tolerability findings for oral semaglutide in the PIONEER studies are summarized in Table 4, and are broadly consistent with the known safety and tolerability

profile of a GLP-1RA. Overall, the doses of oral semaglutide investigated in the PIONEER trials were generally well tolerated, with AEs typically reported in similar proportions of patients in the oral semaglutide, placebo, and active-comparator groups across all of the studies [46–50, 52–55]. Serious AEs (SAEs) were generally reported in similar proportions of patients in the oral semaglutide, placebo, and active-comparator groups across studies. As CV disease is the leading cause of death among patients with T2D, establishing the CV safety of new glucose-lowering therapies is of prime importance and required by regulatory authorities. PIONEER 6 was an event-driven CV outcomes trial conducted to establish the CV safety of oral semaglutide (14 mg) compared with placebo in patients considered at high CV risk [51]. Patients were followed up for a median of 15.9 months. Observations for key CV endpoints are summarized in Table 5. The primary composite endpoint of major adverse CV events (MACE) was reported in 3.8% of patients in the oral semaglutide group versus 4.8% in the placebo group [hazard ratio (HR) 0.79; 95% CI 0.57–1.11].. In patients with T2D and moderate renal impairment (PIONEER 5), no unexpected safety concerns were observed for oral semaglutide [50] (Table 4). Pharmacokinetic studies in patients with renal impairment (mild, moderate, or severe, or ESRD) and hepatic impairment (mild, moderate, or severe) indicated no impact of such impairment on either oral semaglutide pharmacokinetics or safety [36, 37].. The impact of age at baseline on the efficacy and safety of oral semaglutide was also examined in an exploratory analysis, and this showed that there were greater effects of oral semaglutide versus comparators on HbA1c and body weight in patients with T2D regardless of age group (< 45, ≥ 45–< 65, or ≥ 65 years). For the < 65 and ≥ 65 age groups, the safety profile of oral semaglutide was in line with that of other GLP-1RAs. In general, there was a higher discontinuation rate with oral semaglutide in older patients, although this was also true for many comparators [67].. The potential impact of background therapy in the PIONEER trials is an important consideration. An exploratory subgroup analysis of five PIONEER trials (3–5, 7, and 8) assessed the potential impact of different background medications (metformin, SU, SGLT2i, insulin, or combinations) on the efficacy and safety of oral semaglutide and comparators [71]. Reductions in HbA1c and body weight were greater for oral semaglutide versus comparators (except liraglutide 1.8 mg, which gave similar reductions in HbA1c), regardless of background medication.. [72]. An exploratory sub-analysis of the PIONEER 8 study evaluated the impact of background insulin (basal, premixed, or basal-bolus) with or without metformin on the efficacy and safety of oral semaglutide. Reductions in both HbA1c and body weight were similar across all background insulin groups. Most of the hypoglycemic episodes (six out of nine) were observed in the basal-bolus insulin subgroup. Fewer patients had severe or symptomatic blood glucose-confirmed hypoglycemia with oral semaglutide compared with placebo (basal: 10.4–15.8% vs. 20.0%; premix: 18.8–22.2% vs. 34.4%) except in the basal-bolus subgroup (39.7–50.7% vs. 37.5%). The safety and tolerability of the GLP-1RA class is well established [3, 63], with evidence available from a large number of clinical trials and from routine use in daily clinical practice. It is widely accepted that the most frequently encountered AEs with GLP-1RAs are gastrointestinal disorders, in particular nausea, vomiting, and diarrhea [3, 83]. In the PIONEER trials, oral semaglutide was shown to be well tolerated, including in patients with renal impairment or at high CV risk [50, 51], and the safety and tolerability profile was consistent with the GLP-1RA class. Initially, the majority of patients favored the use of a once-daily oral versus a once-weekly injectable GLP-1RA (76.5% vs. 23.5%). However, when patients were then presented with a video detailing the dosing conditions required with oral semaglutide and those with once-weekly injectable dulaglutide, 52.5% indicated a preference for oral semaglutide [90]. This study assessed patient preferences based only on the dosing conditions, but a wide range of treatment-related factors may be considered when selecting a GLP-1RA, including the expected efficacy and safety.

Marketing Experience: URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/27885969/ Paragraphs: P209 - A worldwide multicentre evaluation of acute kidney injury in septic and non-septic critically ill patients: the intensive care over nations (icon) audit. Methods: Between June and October 2015, we disseminated an online questionnaire, available in 10 languages, to medical doctors and nurses working in ICUs through national and international ICU societies. We investigated clinical practices related to central line (CL) insertion, maintenance and measurement of CLABSI-related data. Countries were categorized as high, middle, or low income according to World Bank definitions. We computed

weighted estimates (% and standard error, SE) for countries providing at least 10 complete responses.. Introduction: Multi-drug resistant (MDR) Bacteria are a worldwide threat especially for intensive care unit's patients (ICU). In Gram Negative Bacilli, the emergence and spread of Extended-spectrum Beta-lactamase (ESBL) and carbapenemase-producing bacteria (CPB) is one of the common causes of morbidity and mortality associated with ICU-acquired infections (ICU AI).. Introduction: The prevalence of carbapenems resistant bacteria has increased since the first case reported, becoming a worldwide serious concern. This problem specially affects the intensive care units (ICUs).. 1. World Health Organization. Disease outbreak news (MERS-CoV) [http://www.who.int/csr/don/archive/disease/coronavirus_infections/en/]. Last accessed October 1, 2015.. 2. Mulier S, Penninckx F, Verwaest C, et al. Factors affecting mortality in generalized postoperative peritonitis: multivariate analysis in 96 patients. World J Surg 2003;27:379–384. Conclusions: One century after phages discovery, Phagoburn is the first mutlicentric control randomized trial ever done in the world about phage therapy in humans. Results will be available in 2016. Phages could be an old but innovative way in the war against antimicrobial resistance. Antimicrobial resistance could be the leading cause of mortality in 2050.. Introductions: Neurocysticercosis (NCC) is the most common parasitic disease of the central nervous system. Every newly diagnosed patient with NCC has probably been infected by someone harboring tapeworm in patient's immediate environment. On the basis of an incorrect assumption that human NCC does not occur in countries in which law prohibit swine breeding and consumption of pork, the disease is has been considered nonexistent in Arab world.. Introductions: In the developing world about 1.2 % of deliveries are associated with postpartum haemorrhage (PPH) and when PPH occurred about 3 % of women died.. 1. Besen BA. World J Crit Care Med 2015;. 4:116–129.. Introduction: AKI is characterised by an abrupt loss of kidney function. Due to its worldwide increasing prevalence and mortality, the disease has become an important health care challenge to be treated in intensive care units (ICU)1,2]. AKI causes are numerous,~10 % of cases are postrenal obstruction with urineaccumulation. Ultrasound(US) is the procedure of choice diagnosing this cause of AKI and hence choosing the best therapy. A survey in UK revealed more than 40 % ICUs do not contact a nephrologist within 48 h in AKI.. Introduction: Acute Kidney Injury (AKI) is a serious complication in hospitalized patients, particularly in the critically ill, in whom AKI is independently associated with poor prognosis and outcome. Sepsis is the most important cause of AKI and its pathogenesis is clearly distinct from non-septic AKI. Here, we compared the clinical course and outcome in septic and non-septic critically ill patients worldwide.. Introduction: Although there are differences in criteria of live-kidney transplantation in organ transplantation programmes in the World, it is still performed widespread. Even though there are developments in tissue matching and immunesupressive protocols, graft loss is still an important problem after live-kidney transplantations because of acute and chronic allograft nephropathy. We aimed to assess the survival rates of patients and grafts after live-kidney transplantation.. -Audit on preoperative fasting of elective surgical patients in an African academic medical center. World J Surg 2014. This data shows that our unit has been unable to consistently apply targeted temperature management in "real world practice" according to evidence based guidelines, however this has not resulted in adverse outcomes for our patient population.. Aneurismal subarachnoid haemorrhage (aSAH) is a significant cause of morbidity and mortality throughout the world. The primary goal of the treatment is the occlusion of the ruptured aneurysm preventing a rebleeding. To reduce the rate of this adverse event current guidelines recommend that surgical clipping or endovascular coiling should be performed as early as feasible. However, this strategy may be associated with several disadvantages and timing of procedure remains controversial. The aim of this study was to evaluate the effect of timing of invasive treatment for aSAH on clinical outcomes.. 74 patients (47 %) experienced 98 septic episodes: incidence was low (31 %) in less severe (World Federation of Neurosurgeons grade (WFNS) 1 to 3) and higher in more severe aSAH (WFNS 4-5 78 %, $p < 0.001$). Diagnosis was made at 4 ± 1 days from admission. VAP (79 %) and urinary tract infections (10 %) were the most prevalent infection. 1 patients had septic shock. Most common pathogens were Haemophilus influenzae, Escherichia coli and Pseudomonas aeruginosa, accounting for 37 % of infections, while multidrug resistant bacteria were less than 5 %.. The majority of chest pain complaints are not due to (ACS). Non-cardiac chest pain is the second most common reason presentation to the ED and accounts for approximately 2 to 5

percent of all visits worldwide. Unnecessary and inappropriate requests for serum troponin should be reduced. The reduction in these requests eases the workload, cuts test and labor costs. Reducing unnecessary testing can lead to shortening stay times also beneficial for patients.. Our TTM system had three big appeals. First, it showed time data per examination or per intervention in real time. It helped to share patient Ls flow within medical staff. It would prevent to mistake. Second, this time data was being compared with a world standard time period based quality indicators such as door to balloon time in real time. It was also alerted if that time ran past the time limit. Moreover, we can analyze the relationship between diseases and time data because TTM has capability as database.. Latrodectus is a genus of spider, which is the widely known black widow. It is characterised by neurotoxic venom. It has a worldwide distribution. The purpose of this study is to describe patients' presentation, clinical manifestations and management course of patients with envenomations by black widow spiders in southern region of Saudi Arabia.. This study investigated the incidence and location of chronic pain in patients discharged from ICU and classified the analgesics prescribed according to the World Health Organization analgesic. 2. World Health Organization. Cancer pain relief, with a guide to opioid availability. 2nd edition. Geneva: WHO, 1996. Sedation is routine in UK emergency departments (EDs); to maintain and improve our quality of care, and compare local practice with national and international standards, a standardised and sensitive tool is needed to detect and report adverse events (AE). The World SIVA International Sedation Taskforce tool [1] incorporates physiological thresholds, clinical interventions, and overall outcome to grade AE as minimal to sentinel. We incorporated this tool into our sedation documentation, and report its effect on the detection and documentation of AEs.. Introduction: Burnout is a rapid resurgent worldwide problem; intensive care unit (ICU) practitioners are particularly at risk. Leader-empowering behavior could reduce the encountered job tension and enhancement of work effectiveness [1]. We aim to assess the role of empowerment on ICU practitioners' burnout.. In recent studies researchers suggested that false optimism is associated with medical activism or a strong need for control over death, which is prevalent in the western world.. or ignorance or some emotional anesthesia present in us. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/28642701/ Paragraphs: Methods: A descriptive analysis was undertaken of the investment and development strategies of the top 25 pharmaceutical companies according to 2015 worldwide prescription drug sales. Strategies were documented by collecting data on manufacturing plans, development programs, acquisition and collaboration agreements, the portfolio and pipeline of biosimilar, originator and next-generation biopharmaceutical products. Data were extracted from publicly available sources.. Totaling US$ 228 billion in global sales in 2016 (Troein, 2017), biopharmaceutical medicines represent a growing share of the global pharmaceutical market. With many of these biopharmaceutical products facing loss of patent protection and other exclusivity rights, also non-innovator versions of these molecules, biosimilars, may now enter the market, resulting in a shift of market shares (IMS Health, 2016), revision of strategies of companies and attraction of new players to the biopharmaceutical market.. A descriptive analysis was undertaken of the investment and development strategies of the top 25 pharmaceutical companies according to 2015 worldwide prescription drug sales (Evaluate Pharma, 2016; Pharm Exec, 2016). Identification of various investment and development strategies was based on previous research (Meuwissen, 2016). Identified strategies were further documented by collecting data on manufacturing plans, development programs, acquisition and collaboration agreements, the portfolio and pipeline of biosimilar, originator and next-generation biopharmaceutical products of these companies.. The last column provides information on collaborations between companies, this includes also co-marketing of products. Categories are not mutually exclusive, for example, next-generation biopharmaceuticals can also be classified as originator biopharmaceuticals. Furthermore, examples provided in Table 1 are not exhaustive.. Top 25 pharmaceutical companies ranked by 2015 worldwide prescription drug sales and examples of their investment and development strategies in the global biopharmaceutical market as of December 2016.. Almost every company in the top 25 invests in originator biopharmaceuticals and in biotechnology in general, but only half of them develops next-generation biopharmaceuticals. Furthermore, only half of them invest in development and marketing of biosimilars. Six companies [6, 7, 10, 18, 20, 23] (numbers between square brackets indicate the position of the company in Table 1) only have originator biopharmaceuticals, and no next-generation biopharmaceuticals or biosimilars. Eight

companies [1, 4, 5, 9, 11, 13, 15, 22] invest in next-generation biopharmaceuticals and also in biosimilars.. Collaboration between companies is a common strategy for developing and marketing biopharmaceuticals. All but one company in the list, Gilead [6], are collaborating with other companies or are engaged in co-marketing. Seven companies use all six investment and development strategies [1, 4, 5, 11, 13, 15, 22].. If new originator molecules are not ready to follow up, revenue is lost. Big pharmaceutical companies that solely invest in innovation are companies like Roche, GSK, AbbVie, and J&J.; AbbVie owns with Humira® one of the highest selling medicines in the world, with global sales in 2016 of US$ 16.1 billion (AbbVie, 2017). While facing loss of exclusivity rights in US in December 2016 and in Europe in 2018 (GaBI Online-Generics and Biosimilars Initiative, 2015), a key challenge will be to retain market share with new biopharmaceutical products.. When companies not established as biotechnological companies (e.g., traditional, big pharmaceutical companies) wish to enter the biopharmaceutical market, they would need the right infrastructure and knowledge. This can be achieved via acquisition of biotechnological companies. In this way, they can link their image and marketing to the experience and knowledge biotechnological companies have in developing biopharmaceutical medicines. For instance, the acquisition of Genentech by Roche, or MedImmune by AstraZeneca.. Collaboration between companies has been a common strategy for marketing pharmaceuticals for decennia, and is also used for biopharmaceuticals. In this way, the combined experience of companies can be used in synergy to compete on the market. Companies can work together with biotechnological companies from emerging countries in order to obtain a place on the local market. For smaller biotechnological companies, collaboration with a large, reputable pharmaceutical company can help to increase trust in their product by physicians and patients.. Examples of this strategy with respect to biosimilars are the arrangements made by new market entrants, such as Celltrion and Samsung Bioepis, with more established companies. Celltrion is collaborating with Hospira (Pfizer) in different regions in the world, and with Mundipharma and Orion in Europe. Likewise, Samsung Bioepis has a co-investment strategy with US biotech originator company Biogen, and with Merck US.. It is interesting to note that in the top 10 five companies (50%) and in the top 25 eleven companies (44%) currently have not entered in the development or marketing of biosimilars. It suggests that companies deliberately choose whether or not to enter the biosimilar market.. In this respect, it should be noted that now that patents of new classes of biopharmaceutical products (e.g., mAbs in oncology) expire, many companies revise their strategy. For instance, Amgen will, as an innovator with originator medicines and next-generation products, focus on the development of biosimilars of monoclonal antibodies. Amgen will use its experience as an innovator to compete with other biosimilar developers. Table 1 only provides a qualitative overview of the investment and development strategies used by different players in the biopharmaceutical market and does not give quantitative information like sales figures and amounts invested.. A common strategy to market biopharmaceutical medicines is collaboration between companies, whether or not from different regions in the world. These collaborations can as well be used to gain access in regions the company has less experience with. With patents expiring for some of the highest selling monoclonal antibodies, this snapshot highlights the interest of companies to invest in the development of these molecules and/or enter into collaborations to create access to these molecules.

Benefits/Risks: URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/35690958/ Paragraphs: Adult patients with diabetes or newly recognized hyperglycemia account for over 30% of noncritically ill hospitalized patients. These patients are at increased risk for adverse clinical outcomes in the absence of defined approaches to glycemic management.. In adults with insulin-treated diabetes hospitalized for noncritical illness who are at high risk of hypoglycemia, we suggest the use of real-time continuous glucose monitoring (CGM) with confirmatory bedside point-of-care blood glucose (POC-BG) monitoring for adjustments in insulin dosing rather than point-of-care blood glucose (POC-BG) testing alone in hospital settings where resources and training are available. (2⊕⊕■■). In adults with insulin-treated diabetes hospitalized for noncritical illness who are at high risk of hypoglycemia, we suggest the use of real-time CGM with confirmatory bedside POC-BG monitoring for adjustments in insulin dosing rather than POC-BG testing alone in hospital settings where resources and training are available. (2⊕⊕OO). Panel members placed a high value on the moderate benefits that may occur with CGM use, including

early detection and avoidance of hypoglycemia, and less on the trivial undesired effects. The majority of patients included in studies comparing CGM with POC-BG had type 2 diabetes (T2D).The baseline risk of hypoglycemia may be similar in insulin-treated patients with T2D to what occurs with type 1 diabetes (T1D), suggesting that hospitalized patients with T1D would derive similar benefits with CGM use (21).. Many of the studies investigating CGM in the inpatient setting represent externally funded research studies, which could lead to concern about potential equity issues for hospitals without described resources and barriers to safe implementation of CGM. However, several reported studies included minority populations in underserved areas, many of whom had chronic kidney disease stages 3 to 5, demonstrating the feasibility of CGM in high-risk populations (15, 17). Overall, the panel determined that the feasibility of introducing CGM for noncritically ill patients at high risk for hypoglycemia will vary by institution, and if implemented, a protocol for guiding the process is necessary for success (Table 2) (23, 24).. The accuracy of CGM devices when compared to POC-BG measures in the inpatient setting has been demonstrated as moderate to good in several RCT and non-RCT studies in the inpatient setting (12, 19, 20). The lower accuracy of CGM for BG < 70 mg/dL (<3.9 mmol/L) raises some concern for overtreating low BG; however, the benefit of avoiding significant hypoglycemia outweighs this concern. The lower accuracy at higher BG levels supports recommendations to confirm results with POC-BG prior to making insulin adjustments.. The panel agreed that based on low-certainty evidence for a higher detection rate of hypoglycemia, lower percentage time spent with hypoglycemia and hyperglycemia, and lower mean BG (moderate level of certainty) with the use of CGM in patients at high risk for hypoglycemia, CGM use is preferred over POC-BG testing alone.. Hyperglycemia occurs in 56% to 86% of hospitalized patients receiving supraphysiologic doses of GCs (25, 26). GC-associated hyperglycemia, independent of preexisting diabetes, is associated with increased risk of mortality, cardiovascular events, and infections (27). The optimal insulin regimen for preventing GC-associated hyperglycemia and maintaining glycemic measures in hospitalized patients is not known.. The systematic review identified 2 non-RCTs to address this question (11, 42, 43). These studies, performed predominantly in patients with T1D, suggest that in select patients insulin pump use is safe with no increased risk of hypoglycemia or diabetic ketoacidosis. The number of hypoglycemic or hyperglycemic events per patient may not be different between those continuing CSII compared and those discontinuing CSII during hospitalization (42, 43). One study showed a lower percentage of BG measurements < 40 mg/dL (2.2 mmol/L; 0.5% vs 1.0%), and BG measurements > 300 mg/dL (16.7 mmol/L), >350 mg/dL (19.4 mmol/L), and > 400 mg/dL (22.2 mmol/L; 11% vs 18%) in “pump on” vs “pump off’ cases (43).. The panel agreed that the evidence suggests little difference in benefits and harms of continued use of insulin pump therapy compared to SC injections in the hospital setting. Continued use of insulin pump therapy may be acceptable for patients who are able to self-manage these devices adequately, and a protocol needs to be in place guiding the inpatient use of this form of insulin delivery.. The systematic review identified 4 RCTs and 6 non-RCTs to address this question (11, 45-54). Evidence from RCTs shows that providing inpatient diabetes education as part of a comprehensive diabetes discharge-planning program likely reduces hemoglobin A1c (HbA1c) at 3 months by 1.25% (95% CI –2.08 to –0.42) and 6 months by 0.8% (95% CI –1.07 to –0.54) following discharge (moderate level of certainty) (46-48). In addition, evidence from 3 non-RCTs suggests a moderate benefit in readmission rates [RR 0.72 (95% CI: 0.60 to 0.88)] with an estimated 43 fewer hospital readmissions per 1000 patients (95% CI –61 to –18); very low level of certainty] when inpatient diabetes education was part of a comprehensive diabetes discharge-planning process (49-51).. Panel members placed high value on the moderate benefits of improved HbA1c and reduced readmissions with inpatient diabetes education provided as part of a comprehensive diabetes discharge-planning process. Providing diabetes education during a hospital stay may help socioeconomically challenged patients who do not have access to this resource as outpatients and who typically have higher hospital readmission rates (51). The panel acknowledged that although it may not be feasible for all patients with diabetes in the hospital to receive diabetes education directly from a DCES, healthcare personnel providing diabetes education should optimally have a DCES as a readily available resource.. The panel agreed that inpatient diabetes education likely lowers HbA1c postdischarge, may reduce hospital readmissions, may enhance patient satisfaction, and may improve health inequities for those who may not have access to outpatient education. Although inpatient diabetes education is associated with costs

related to the employment and training of personnel, the panel agreed that, overall, the benefits may outweigh these costs.. The panel agreed that the evidence suggests that patients with better preoperative glucose management have better outcomes. While the majority of studies compared outcomes associated with HbA1c < 7% or ≥7 % (<53 mmol/mol vs ≥53 mmol/mol), the panel suggests a target HbA1c of >8 % (63.9 mmol/mol) as a feasible goal for identifying patients at higher risk for postoperative complications. In addition, although very limited data exist on the effect of preoperative BG levels on postoperative outcomes, the panel suggests a BG target 100 to 180 mg/dL (5.6 to 10 mmol/L) 1 to 4 hours preoperatively, which is also the recommended target for intra- and postoperative glycemic management.. Hyperglycemia frequently occurs in hospitalized patients receiving enteral nutrition and is associated with a higher risk of complications and mortality (4, 98-100). Effective management of hyperglycemia in patients on enteral nutrition decreases adverse outcomes but also increases the risk of hypoglycemia (4, 99). It has been proposed that NPH insulin, due to the shorter half-life and duration of action compared to long-acting insulin preparations, may be appropriate for patients on enteral nutrition.. The systematic review identified 5 RCTs that compared the effects of a noninsulin agent without scheduled insulin in comparison to an insulin-only approach (11, 105-109). All studies enrolled patients with established T2D. There were no RCTs in hospitalized patients comparing insulin therapy to MET, SUs, TZDs, or SGLT2is. Two RCTs comparing GLP-1RAs with insulin therapy in select patient populations found a small absolute reduction in risk of hypoglycemia [RR 0.09 (95% CI 0.01 to 0.66); adjusted RR (ARR) 100 fewer events per 1000 (95% CI −109 to −37); low-certainty evidence] and lower mean daily BG [15.1 mg/dL lower (95% CI −65.2 to 34.9 mg/dL); very low certainty].. These findings were outweighed by a nearly 6-fold increase in nausea and/or vomiting [RR 5.95 (95% CI 1.07 to 33.03); ARR 50 more per 1000 (95% CI 1 to 320); low certainty]. Several retrospective analyses identified SU use as a risk factor for hypoglycemia in the hospital, indicating more harm than benefit. Since interrupted nutrition and other hypoglycemia risk factors are common in hospitalized patients, SUs are generally not advisable for inpatient use. Theoretical concerns derived from the use of some noninsulin glucose-lowering therapies in the outpatient setting, including rare and known adverse events, were considered as being more likely to occur in the acute care setting.. Based on a metanalysis of 3 RCTs performed in individuals with established T2D prior to hospitalization, DPP4i dosed once daily compared with BBI therapy may provide no benefit on glycemic management (11). In select patients, there may be a reduced insulin requirement and lower frequency of hypoglycemic events [RR 0.27 (95% CI 0.09 to 0.84); low certainty evidence]. The incidence of hypoglycemia was reduced with use of DPP4i in several trials; however, patients with impaired renal function and those considered to be at higher risk of hypoglycemia and hyperglycemia were excluded from enrollment.. DPP4is are approved for use and considered safe in patients with any degree of kidney disease (note that dose adjustment for renal dysfunction is required for select DPP4is; eg, sitagliptin and alogliptin). Therefore, while patients with advanced kidney disease may benefit from reduced hypoglycemia, this remains unknown. Of importance, the meta-analysis excluded those studies in which the intervention was a combination of DPP4i and scheduled insulin. However, all RCTs except 1 comparing DPP4i to BBI allowed the use of correction insulin for intermittent hyperglycemia.. The panel agreed that DPP4i dosed once daily compared with BBI therapy may provide no benefit on glycemic management. However, in select patients treated with a DPP4i, there may be reduced insulin requirements and lower frequency of hypoglycemic events. Due to uncertainty of the difference in effects, cost, acceptability, and feasibility between DPP4is and insulin therapy, the panel made a conditional recommendation for using either DPP4is or insulin therapy in select adults requiring management of hyperglycemia.. The panel determined that the recommendation would not apply to patients with T1D or with significant risk of hyperglycemia.. The potential benefits, such as decreased insulin resistance, would not be expected in patients with diabetes who have insulin resistance and/or insulinopenia. There are also potential harms associated with administration of CHO-containing beverages to patients with diabetes, such as hyperglycemia with potential cancellation of scheduled procedures. In the majority of published studies, patients with diabetes were specifically excluded. Nevertheless, the practice of preoperative oral CHO administration is often used in patients with diabetes.. The systematic review identified 1 RCT and 2 non-RCTs to address this question in patients with diabetes (11, 110-112). With low to very low certainty, evidence suggests little to no differences in

hypoglycemia, mean daily BG, and hospital LOS with or without oral caloric fluids. Based on 1 study of 169 patients, the risk for hypoglycemia with CHO drinks may not be importantly increased [RR 1.33 (95% CI 0.42 to 4.21); very low level of certainty; 19 more per 1000 hypoglycemia events (95% CI –33 to 180)].. The guideline panel agreed that there may be no benefit and instead potential harm with use of preoperative caloric oral fluids in patients with diabetes. Oral CHO administration may be harmful if it causes preoperative hyperglycemia in patients with all forms of diabetes. Given the uncertainty of benefit and potential for harm, the panel made a conditional recommendation suggesting against preoperative oral caloric fluids.. In parallel to the development of the evidence summaries, the GDP members searched for and summarized research evidence for other EtD criteria, such as patients' values and preferences, feasibility, acceptability, costs/resource use, cost-effectiveness, and health equity. Research evidence summaries noted in the EtD frameworks were compiled using standardized terminology templates for clarity and consistency (133). During a series of video conferences, the GDP judged the balance of benefits and harms, in addition to the other EtD criteria, to determine the direction and strength of the recommendation (Table 4 and 5) (133-136). URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/31547562/ Paragraphs: The cut-off for PREDIMED score ≤ 6 ($p < 0.001$, area under the curve (AUC) 0.848, standard error 0.036, 95% confidence interval (CI) 0.768 to 0.909) could serve as a threshold for significantly increased risk of high value of testosterone levels. In conclusion, a novel direct association between the adherence to MD and the clinical severity of the disease was reported in women with PCOS. This association could support a therapeutic role of foods and nutrients of the Mediterranean dietary pattern in the PCOS pathogenesis likely involving their inflammatory status, IR, and hyperandrogenemia.. The ROC analysis was performed to determine the cut off values of the PREDIMED score that was predictive of the highest values of testosterone levels (above the median value 22.27 ng/dL) (Figure 2). A value of PREDIMED score of ≤ 6 ($p < 0.001$, AUC 0.848, standard error 0.036, 95% CI 0.768 to 0.909) could serve as a threshold for a significantly increased risk of high value of testosterone levels.. The ROC analysis was performed to determine the cut off values of the PREDIMED score that was predictive of highest values of testosterone levels (above the median value 22.27 ng/dL). A value of PREDIMED score of ≤ 6 ($p < 0.001$, AUC 0.848, standard error 0.036, 95% CI 0.768 to 0.909) could serve as a threshold for a significantly increased risk of high value of testosterone levels. PREDIMED, PREvención con DIetaMEDiterránea; ROC, Receiver operator characteristic; AUC, area under the curve; CI, confidence interval.. The MD is a well-established health-promoting dietary pattern. In particular, there is evidence that the adherence to the MD is inversely associated with adiposity [58], IR [59], and risk of type 2 diabetes mellitus [60] and cardiovascular disease [61]. On this basis, it was conceivable that MD might be considered to be one of the best nutritional strategies also for the management of PCOS women. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/36324146/ Paragraphs: The PubMed, EMBASE, Cochrane Library, Web of Science and Medline databases were searched until March 2022 to evaluate the association between the TyG index and cerebrovascular disease risk. A random■effects model was used to calculate the effect estimates and 95% confidence intervals (CIs).. A total of 19 cohort studies and 10 case■control/cross■sectional studies were included in our study, which included 11,944,688 participants. Compared with a low TyG index, a higher TyG index increased the risk of cerebrovascular disease (RR/HR = 1.22, 95% CI [1.14, 1.30], P< 0.001; OR = 1.15, 95% CI [1.07, 1.23], P< 0.001). Furthermore, the results of the dose-response analysis of the cohort study demonstrated that the risk of cerebrovascular disease increased by 1.19 times per 1 mg/dl increment of the TyG index (relative risk = 1.19, 95% CI. The following criteria were used to identify the eligible articles: (1) the study design was an observational study; (2) the TyG index could be obtained via laboratory examinations and cerebrovascular disease must be an outcome disease; And (3) all of the outcomes are presented as odds ratios (ORs), relative risks (RRs) or hazard ratios (HRs), along with their corresponding 95% confidence intervals (CIs), for the relationship between the TyG index and cerebrovascular disease. Furthermore, we excluded some studies, such as in vitro studies, animal experiments, duplicate literature articles, reviews, letters or conference papers.. The risk of bias for the observational literature was independently evaluated by two investigators by using the Newcastle■Ottawa scale(NOS) [21], which included three parts (selection of the patients, comparability of the case/exposure groups and controls and exposure evaluation), and a study was awarded a maximum of one star for each

numbered item within the selection and outcome categories. A maximum of two stars was given for comparability. Moreover, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to classify the quality of evidence for the observational studies [22].. The included trials were classified as high quality, moderate quality, low quality or very low quality based on the risk of bias, inconsistency, indirectness, imprecision and publication bias.. In total, our study evaluated 4,405 relevant articles that were initially screened from electronic databases, but only 28 articles met our inclusion criteria, which contained a total of 11,944,688 participants. These 28 studies, involving nineteen cohort studies [10, 19, 27–43] and ten case■control/cross■sectional studies [16, 18, 38, 44–50] (with one of the articles including both cohort and cross■sectional portions), investigated the risk of cerebrovascular disease in populations with different TyG index.. The specific details are presented in Table 1. The risk of bias within the included studies was assessed via the NOS (Table 1, Tabl S2 and Table S3). Simultaneously, the GRADE system was utilized to classify the quality of the included evidence. The quality of the evidence in the cohort study was considered to be high (Table 2). In case■control/cross■sectional studies, the quality of the evidence was considered to be moderate because the dose■response relationship remains unclear, due to limited number of studies (Table 3).. Abbreviations: CI, confidence interval; RR/HR, relative risk/hazard ratio. a Results for cerebrovascular diseases risk of subjects with higher levels of triglyceride glucose index compared with lower triglyceride glucose index. b Upgraded by one level due to all the results of the included studies were almost consistent (subjects with high triglyceride glucose index had high risk of cerebrovascular diseases). c Upgraded by one level due to a dose■response relationship between cerebrovascular disease and triglyceride glucose index (The higher triglyceride glucose index, the higher risk of cerebrovascular diseases). Nineteen cohort studies with 11,644,261 subjects were included in the study. The detailed characteristics of the participants are presented in Table 1. A higher TyG index increased the risk of cerebrovascular disease compared to a lower TyG index group (RR/HR = 1.22, 95% CI [1.14, 1.30], P< 0.001, Fig. 2). No publication bias was found via the Egger's test and funnel plot (coefficient = 0.08, t = 0.14, P = 0.89, Fig. 3).. Forest plot of the risk of cerebrovascular disease in subjects with a high TyG index vs. a low TyG index (cohort studies; RR/HR, relative risk/hazard ratio; CI, confidence interval). Funnel plot for the effect estimates of the TyG index (cohort studies; ln RR/HR = ln (relative risk/hazard ratio); se, standard error). [1.25, 1.55], P< 0.001). However, a similar relationship was not found in the unclassified group. Moreover, in the subgroup analyses of region, a higher TyG index increased the risk of cerebrovascular disease in the Asia group (RR/HR = 1.22, 95% CI [1.13,1.30], P< 0.001) but not in Europe. We also performed subgroup analyses based on age, sex and diabetes, and all of the results indicated that cerebrovascular disease was related to TyG index. The details of these results are shown in Table 4. Furthermore, the results of the dose■response analysis demonstrated that a linear relationship was existed and the risk of cerebrovascular disease increased by 1.19 times per 1 mg/dl increment of the TyG index via a random-effects model (relative risk = 1.19, 95% CI. RR/HR, relative risk/hazard ratio; CI, confidence interval. A total of 10 case■control/cross■sectional studies (including 305,808 samples) were included in our study, which investigated whether the risk of cerebrovascular disease was related to the TyG index. The detailed description and breakdown is shown in Table 1. The results indicated that the TyG index was higher in people with cerebrovascular disease. Moreover, the risk of cerebrovascular disease in the case group was 1.15 times that of the control group (OR = 1.15, 95% CI [1.07, 1.23], P< 0.001, Fig. 5).. Forest plot of the risk of cerebrovascular disease in populations with a high TyG index vs. control groups (case-control/cross-sectional studies; OR, odds ratio; CI, confidence interval). (OR = 1.20, 95% CI [1.05,1.37], P = 0.006). However, the relationship was not observed in the other subgroups. Furthermore, the studies indicated that a high TyG index had a higher cerebrovascular disease risk than controls in the Asia subgroup (OR = 1.13, 95% CI [1.05,1.22], P = 0.001). The specific results are shown in Table 5.. Additionally, IR can aggravate the effects of dyslipidaemia, diabetes, smoking and other factors on cerebrovascular disease and lead to the development of cerebrovascular disease [47]. Many studies have demonstrated that the TyG index is the indicator with the most potential for IR [14, 51]. Furthermore, the TyG index has also been proven to directly correlate with some traditional cerebrovascular risk factors and indicators, such as dyslipidaemia, diabetes, smoking, TG, LDL-C and hs-CRP [38, 59].. As the principal clinical type of cerebrovascular disease, stroke has elicited an

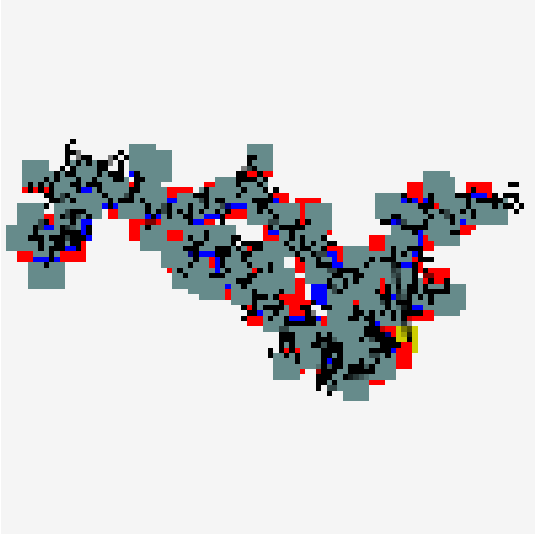
increasing burden to the global health care system [3]. A subgroup analysis of our cohort study showed that subjects with a high TyG index had a 1.39-fold higher risk of developing stroke than those patients with a low TyG index, which was consistent with the studies of Zhao Y and Wang A et al. [10, 33]. Similar results were found in the carotid artery disease group. A possible mechanism has been previously mentioned.. Our research demonstrated that the risk of cerebrovascular disease in people younger than 60-years-old with a high TyG index was higher than that in people over 60-years-old. In recent years, it has been reported that incidences of obesity, hyperlipidaemia, hyperglycaemia, IR and other diseases have gradually been affecting younger individuals due to excessive intake of energy-intensive foods and a sedentary lifestyle [65, 66], which leads to higher levels of TyG in young people. The elderly population possesses more risk factors associated with cerebrovascular disease due to their increasing age, such as hypertension, metabolic disorders, degree of arterial stiffness and other vascular diseases [67, 68].. These factors may mask the influence of the TyG index on cerebrovascular disease. In contrast, in young people, the role of the TyG index on cerebrovascular disease was highlighted after excluding these risk factors. In addition, the administration of certain medications can also conceal this relationship [18].. In conclusion, our meta-analysis found that TyG index is related to cerebrovascular disease. When considering the limitations of this meta-analysis, more data and basic research are needed to verify the relationship between the TyG index and cerebrovascular disease. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/30944112/ Paragraphs: 294 participants were randomised and 293 included in intention to treat analyses (CSI, n=144; MDI, n=149). At 12 months, mean HbA1c was comparable with clinically unimportant differences between CSII and MDI participants (60.9 mmol/mol v 58.5 mmol/mol, mean difference 2.4 mmol/mol (95% confidence interval −0.4 to 5.3), P=0.09). Achievement of HbA1c lower than 58 mmol/mol was low among the two groups (66/143 (46%) CSII participants v 78/142 (55%) MDI participants; relative risk 0.84 (95% confidence interval 0.67 to 1.06)).. During the first year following type 1 diabetes diagnosis, no clinical benefit of CSII over MDI was identified in children and young people in the UK setting, and treatment with either regimen was suboptimal in achieving HbA1c thresholds. CSII was not cost effective.. Type 1 diabetes is a common, chronic disease of childhood, affecting about 26 000 infants, children, and young people in the United Kingdom.1 Treatment requires administration of subcutaneous insulin in doses calculated according to carbohydrate consumption, physical activity, and blood glucose measurements. During childhood and adolescence, poor glycaemic control is associated with impaired memory,2 poorer cognitive outcomes,3 an increased risk of depression,4 and poor growth.5 In the longer term, vascular complications lead to blindness, renal failure, premature heart disease, stroke, and amputation.6. The risk of developing complications is related to glycaemic control, and is lower in patients treated with intensive regimens on insulin treatment: multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII).7 There is no cure for type 1 diabetes, so optimal treatment is essential to enable the best possible quality of life and the effective use of healthcare resources while minimising the risk of complications.. A meta-analysis of six randomised controlled trials involving 165 children reported a modest benefit of CSII treatment on glycaemic control (as measured by glycated haemoglobin (HbA1c); −0.24%, 95% confidence interval −0.41% to −0.07%)8 albeit below the threshold associated with better clinical outcomes (0.5%),7 but no difference in the risk of severe hypoglycaemia or diabetic ketoacidosis.8 However, key limitations need to be considered when interpreting these results.. In the REPOSE study, when adults with type 1 diabetes and poor glycaemic control were randomised to treatment with CSII or MDI and given equivalent education, no additional benefit from CSII was identified.11. Observational studies of national paediatric databases from the United States, UK, Germany, and Austria have reported an association between CSII treatment and superior glycaemic control12 13 with only a modest effect. CSII use is lower in patients from ethnic minorities and those with greatest socioeconomic deprivation.14 15 16 Given that glycaemic control and severe hypoglycaemia are independently related to ethnicity and deprivation,14 15 16 there is a risk of bias, inherent to observational data, in estimates of the effect of CSII in these studies.. This included the cause of type 1 diabetes, the use and administration of insulin, hyperglycaemia and correction doses of insulin, hypoglycaemia symptoms and treatment, exercise, sick day rules, carbohydrate counting, the benefits of maintaining optimal glycaemic control for long term health, and blood glucose monitoring. The number of education sessions was recorded to ensure

parity across treatment arms. All participants received training on the use of MDI regimen and the Expert glucometer, with participants randomised to CSII receiving additional training in the use of CSII.. For the primary outcome (HbA1c 12 months after randomisation), we used least squares regression adjusted for age category and centre as a random effect. Owing to the expected low incidence of events, secondary binary outcomes were presented as unadjusted relative risks. We undertook a per protocol analysis for the primary outcome to check the robustness of conclusions to major prespecified protocol deviations (table S2). Body mass index and height were standardised by use of WHO growth standards,34 35 and analysed by analysis of covariance including respective baseline measures, age group, and treatment group as covariates in the model with centre fitted as a random effect.. We conducted a safety analysis on adverse event data according to the method of insulin delivery at the time of the event. The incidence density rate was used to quantify the number of patients with at least one new case per population at risk in a given time period. The denominators were the sum of the person time in years for each treatment group (accounting for treatment switches) of the population at risk. For the cost utility analysis, we used UK Health Utilities Index Mark 2 tariffs26 to estimate utilities and used the trapezoidal rule to calculate QALYs.. The trial was powered to detect a difference in HbA1c between groups at 12 months unadjusted for baseline HbA1c values. The prognostic value of significance of HbA1c at diagnosis of type 1 diabetes was not well recognised at the time SCIPI opened to recruitment. Two exploratory analyses were considered to include HbA1c measured at baseline as a continuous explanatory variable (table S5). These results did not alter the SCIPI study conclusions for CSII compared with MDI at 12 months (adjusted mean difference 2.9 mmol/mol, 95% confidence interval −0.02 to 5.9), but did suggest the importance of early baseline values for 12 month measurements (HbA1c level baseline coefficient estimate 0.07; standard error 0.03, 95% confidence interval 0.01 to 0.13).. A second exploratory analysis considered the effect of deprivation (table S7). Although we saw an association between higher HbA1c values at baseline and at 12 months with greater deprivation, the conclusions remained unaltered (adjusted mean differences in HbA1c at 12 months between treatment groups (CSII-MDI) were 2.9 mmol/mol (95% confidence interval −0.02 to 5.9) and 2.2 mmol/mol (−0.7 to 5.0), respectively).. Eight episodes of severe hypoglycaemia (CSII=6, MDI=2) and two episodes of diabetic ketoacidosis (CSII=2, MDI=0) were reported. Safety dataset reports events were categorised according to the treatment the participant received at the time of the adverse event, and took into account temporary or permanent switches in the method of insulin delivery. The total number of events experienced and the number of participants experiencing at least one event were provided, along with the incidence density rate (defined as the number of patients with at least one new adverse event per population at risk in a given time period).. The intention-to-treat analysis included all participants in the group that they were randomised to while the per protocol analysis excluded participants with major protocol deviations, which included switching method of insulin delivery. This difference allows some consideration of the effect, and although both analyses were not significant, the conclusions are robust. In addition, to account for participants who switched method of insulin delivery, the safety population analysed participants in the group to the method of insulin delivery at the time of the safety event.. Glycaemic control is poorer in the UK than other European and North America country, where CSII is used more commonly,11 leading to speculation that increased use of CSII could improve glycaemic control. The relative inexperience of NHS practitioners in CSII treatment could have obscured the potential benefits of this treatment. However, study sites were selected on the availability of a core set of trained and experienced staff. We saw no evidence of a treatment effect over time, and block randomisation ensured balance between treatment arms.. Many adverse events were reported in the study cohort, which is consistent with the background population of patients with childhood type 1 diabetes treated with CSII. The NPDA reports that CSII treatment increased the risk of being admitted to hospital for diabetic ketoacidosis by 23%, and of being admitted to hospital for reasons other than diabetic ketoacidosis or hypoglycaemia by 27%. CSII treatment did not confer benefit or increased risk from admission with hypoglycaemia.41. The speed of technological developments outpaces the time required to deliver a clinical trial. It could be argued that the findings of the SCIPI trial are outdated: technology has advanced, clinical teams have greater experience of CSII, and improved education programmes and psychological support equips patients and their families to manage this treatmemt more successfully with fewer adverse events. However,

observational data from the most mature CSII services report benefits in HbA1c below thresholds thought to be clinically meaningful,9 13 taking no account of the effect of deprivation or ethnicity on clinical outcomes.. Many patient advocacy groups and healthcare professionals are of the strong opinion that treatment with CSII is beneficial and further research should focus on determining what these perceived benefits are and on developing validated tools to measure them. Individual patients are likely to experience benefits from this treatment that are not directly associated with the outcomes measured in this study. For example, preschool children who consume carbohydrates and exercise erratically could benefit from a treatment with fewer injections and a basal insulin profile that can be modified readily.. Data sharing: We are committed to sharing anonymised individual patient data for the purpose of research for the benefit of patients with bonefide researchers. Requests for data should be sent to the Clinical Trials Research Centre, University of Liverpool. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/32247823/ Paragraphs: We identified 6 independent genetic variants associated with liver cT1 that reached the GWAS significance threshold ($p < 5 \times 10\text{-}8$). Four of the variants (rs759359281 in SLC30A10, rs13107325 in SLC39A8, rs58542926 in TM6SF2, rs738409 in PNPLA3) were also associated with elevated aminotransferases and had variable effects on liver fat and other metabolic traits. Insulin resistance, type 2 diabetes, non-alcoholic fatty liver and body mass index were causally associated with elevated cT1, whilst favourable adiposity (instrumented by variants associated with higher adiposity but lower risk of cardiometabolic disease and lower liver fat) was found to be protective.. The association between 2 metal ion transporters and cT1 indicates an important new mechanism in steatohepatitis. Future studies are needed to determine whether interventions targeting the identified transporters might prevent liver disease in at-risk individuals.. It is important to identify which individuals are at risk of developing the more inflammatory phenotype, steatohepatitis (a condition characterised by lipotoxicity and histological necroinflammation), which is considered to be the main pathophysiological driver of liver fibrosis and subsequent disease progression.5 Steatohepatitis and fibrosis affect approximately 1 in 10 middle-aged adults, and can lead to cirrhosis, hepatocellular carcinoma and death.6. Understanding the underlying genetic susceptibility to steatohepatitis and fibrosis may provide new insights into the main pathophysiological mechanisms that contribute to chronic liver disease, helping in the identification of new drug targets. Genetic studies have so far been limited due to the phenotyping challenge. Liver biopsy is an invasive procedure with associated risks, significant sampling error and marked interobserver variance,12 while routinely available liver blood tests such as aminotransferases, despite being useful in the identification of important liver disease susceptibility loci, are overall poor predictors of liver disease severity.13,14. Another challenging question is which metabolic traits cause steatohepatitis since treating causal factors can help prevent liver disease. Observational associations between steatohepatitis and other features of the metabolic syndrome might occur because they share common risk factors, rather than one causing the other. Mendelian randomisation is an established epidemiological approach that uses genetic studies to provide insight on causality.15 Mendelian randomisation uses genetic variants associated with an exposure (e.g. body mass index [BMI], LDL cholesterol, insulin resistance) to assess their causal effect on an outcome of interest (e.g. cT1, steatohepatitis).. Genetic markers of a risk factor are largely independent of confounders that may otherwise cause bias since genetic variants are randomly allocated before birth. Furthermore, the non-modifiable nature of genetic variants provides an analogy to randomised trials, in which exposure is allocated randomly and is non-modifiable by subsequent disease.16. In our GWAS of liver cT1 in individuals of European ancestry, variants in 6 independent loci (Table 2) reached genome-wide significance. Genomic inflation was low ($\lambda GC = 1.006$, Fig. S2). We observed the strongest association with a missense variant, rs13107325, located in an exon of SLC39A8 (Fig. 1B). The minor allele (T; allele frequency 7%) of rs13107325 was associated with 0.54 SD increase in cT1 ($p = 1.2 \times 10{-}133$). The mean cT1 was 692 ms in individuals with no risk allele, 727 ms in heterozygotes, and 772 ms in risk allele homozygotes (Fig. S3).. To validate these variants and further understand their role in other metabolic traits and diseases, we investigated their association with liver blood tests, MRI-determined liver iron and liver PDFF, lipids, blood pressure, BMI and cardiometabolic disease outcomes (Fig. 2, Table S3). cT1-increasing alleles at 4 variants (in SLC30A10, SLC39A8, TM6SF2, and PNPLA3) were associated with higher ALT and AST (all with p values $<2 \times 10{-}5$) and higher risk of type 2 diabetes (all with p

<0.002, except the SLC30A10 variant).. None of cT1 variants were associated with cardiovascular disease risk, whilst their effects on other metabolic traits including lipids and blood pressure were variable (Fig. 2). Among the novel identified and replicated variants (rs759359281 in SLC30A10, and rs13107325 in SLC39A8), only the latter was available in a non-UK Biobank cohort with available liver blood tests. The cT1-increasing allele in rs13107325 showed a similar direction of effect on ALT (n = 46,316, beta = 0.01, p = 0.27) and AST (n = 39,015, beta = 0.014, p = 0.0005) levels in an independent cohort (Table S4).26. Effects are in SD for continuous traits and log(OR) for disease outcomes per copy of the risk allele. A linear mixed model was used for genetic associations. Levels of significance: p <0.05. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; cT1, corrected T1; GGT, gamma-glutamyltransferase; HDL-C, HDL-cholesterol; LDL-C, LDL cholesterol; OR, odds ratio; T2DM, type 2 diabetes.. We investigated the effects of all-cause cirrhosis risk variants on cT1 values. Among 6 variants associated with all-cause cirrhosis in a recent GWAS of 5,770 cases and 572,850 controls,28 4 variants (those in or near MARC1, HSD17B13, TM6SF2 and PNPLA3) demonstrated associations with cT1 (Table 3), where alleles associated with higher risk of liver cirrhosis were also associated with higher cT1. The HFE haemochromatosis risk allele (in rs1800562) was inversely associated with cT1, however this is to be expected since cT1 measures are corrected for liver iron content.. Consistently, this association became remarkably attenuated (from beta = –0.11, p = 8×10–7 to beta = –0.055, p = 0.02) in our sensitivity analysis correcting for liver iron content. In the GWAS of all-cause cirrhosis, the effect of a1-antitrypsin risk variant (rs28929474 in SERPINA1) was very weak (p = 0.01) and present only when a recessive model was used (Table 3).28 We did not have any risk allele homozygotes in our liver cT1 cohort and therefore could not perform a recessive model of associations with cT1.. Effects of all-cause cirrhosis risk alleles on liver cT1.. We used genetic methods (Mendelian randomisation, Fig. 4) that are generally free of biases such as confounding and reverse causation to examine the potential causal effect of metabolic traits on liver cT1. We found evidence of a causal association between insulin resistance (IVW p = 0.0001), non-alcoholic fatty liver (IVW p = 0.01), type 2 diabetes (IVW p = 0.004), BMI (IVW p = 0.002) and higher cT1. We also found evidence for a protective role of favourable adiposity variants (variants associated with higher adiposity but lower risk of cardiometabolic diseases and lower ectopic fat)36 and cT1 (IVW p = 0.01) (Table S6).. It is not known which metal is involved in liver pathogenicity but there is evidence that hepatic ZIP8 regulates manganese metabolism in the liver, a metal ion that is hepatotoxic at high levels.50 Zinc and selenium also have important roles in liver cellular injury, oxidative stress and dysregulated inflammation; dietary supplementation of both has shown benefit in animal models of liver disease.51,52. We identified a further 2 missense variants that were associated with cT1 but not with elevated aminotransferases; therefore, further research is required to validate these findings and explore their potential role in liver inflammation and fibrosis. The cT1-increasing allele in rs111723834 (missense variant in PCK2, also an intronic variant in NRL) was associated with lower aminotransferases, lower risk of type 2 diabetes, and lower triglycerides. PCK2 encodes a mitochondrial enzyme that catalyses the conversion of oxaloacetate to phosphoenolpyruvate and has a key role in hepatic gluconeogenesis.. The cT1-increasing allele (rs4820268-A >G) in TMPRSS6 has previously been reported to be associated with lower plasma iron levels and lower liver iron content.21,60 It is also associated with a dysmetabolic profile including higher LDL cholesterol, higher cardiovascular disease risk and hypertension (Fig. 2). Its effect on cT1 however remained significant even after correcting for liver iron content in sensitivity analyses, making it unlikely that the association was secondary to bias resulting from iron correction when calculating cT1.. Known NAFLD and cirrhosis risk alleles in PNPLA3 and TM6SF2 were also associated with both elevated cT1 and MRI-derived PDFF in our cohort. These associations provide strong positive controls for our study and validate for the first time the association with MRI-determined liver PDFF. The risk alleles in these 2 genes were further associated with higher risk of type 2 diabetes, but with lower serum triglycerides, LDL cholesterol, and lower risk for cardiovascular disease, as previously described.63,64 In our GWAS on PDFF, alongside PNPLA3 and TM6SF2, we further identified variants in GCKR (another known NAFLD variant which we have replicated) and APOE (apolipoprotein E, a gene which encodes a major cholesterol carrier).63,65. The APOE risk allele (T) for PDFF is associated with a higher risk of diabetes, and lower risk of cardiovascular disease and elevated LDL cholesterol in

independent GWASs.66 This data provide evidence that cT1 and PDFF phenotypes share some but not all aetiopathogenic mechanisms.. Identifying causal mechanisms to steatohepatitis is crucial since interventions targeting these modifiable exposures may prevent liver disease progression. Our Mendelian randomisation study investigated 24 possible metabolic traits that may cause steatohepatitis. We provide genetic evidence that insulin resistance, non-alcoholic fatty liver and higher BMI causally increase cT1. Recent genetic studies have further identified variants associated with higher BMI but lower risk of type 2 diabetes, hypertension and heart disease.67 These “favourable adiposity” variants are also associated with higher subcutaneous-to-visceral adipose tissue ratio and may protect from disease through higher adipose storage capacity, by promoting lipid deposition in subcutaneous tissue rather than within the circulation and ectopic places.. Our study had several limitations. We did not have any independent cohort to replicate our findings. To overcome this limitation, we investigated associations between cT1 variants and ALT and AST levels both in the UK Biobank and an independent GWAS of liver enzymes.68 While MRI-derived cT1 is clinically available and is used to assess the severity of steatohepatitis, this measure is still novel, and further research is needed to determine the relative contributions of inflammation and fibrosis to cT1.10 Whilst it would be useful to have histological reference data for cT1, pathologist-interpreted liver biopsies do not lend themselves to large studies of this nature because of the risk to patients and inter-rater variance in assessment of histology.. cT1 and PDFF phenotypes share some but not all aetiopathogenic mechanisms. We identified novel associations between an MRI-derived measure of fibroinflammatory liver disease and variants in SLC30A10 and SLC39A8 that replicated with blood biomarkers of hepatocyte injury. These genes have a critical role in transporting heavy metal cofactors for a multitude of biological processes. Future studies may determine whether targeting SLC30A10 and SLC39A8 are possible therapeutic options to prevent liver disease in at-risk individuals.



Img 1: Molecule structure of insulin (Source: PubChem)