

Clinical Pearls

- Biosimilars e.g. BASAGLAR, SEMGLEE, KIRSTY have cost saving advantages when an insulin analogue is desired with similar efficacy and safety as reference insulin.
Consider NPH or long-acting insulin analogue biosimilar (i.e. glargine) for initial treatment.
Rapid-acting analogues are user-friendly.
Concentrated products offer comfort, convenience & an eco-friendlier option for people who require large insulin doses.

Considerations for Insulin Therapy (Basal, Prandial, Premixed)

Many factors impact insulin response, with up to 30% day-to-day variability. Individualized approach, patient education, & follow-up are key.
AE: local injection site reactions e.g. pruritis, rash, dermatitis, hematoma, pain (strategies to minimize: review injection technique, change needle or insulin product); also may cause: peripheral fluid retention, ↓K+, systemic allergy (rare)
Lipohypertrophy: thickening of subcut tissue due to repeated insulin injections at the same site; ↓ risk: rotate injection sites, do not reuse needle
Wt gain (least to greatest): basal (~2kg) < premixed insulin ≈ basal-bolus (~2-5kg)
Hypoglycemia (least to greatest): basal < premixed insulin ≈ basal-bolus; see page 55

available OTC (schedule II)
Caution: insulin is an error-prone, high alert medication and requires great attention
eGFR <45mL/min (often need ↓ insulin); acute illness (↑testing see pg 56, may require ↑/↓ insulin dose, Patient Tools: RxFiles SADMANS Handout or SK Health Sick Day Management; frail, older adult (start low, go slow), cognitive impairment, poor vision/dexterity
DI: ↑hypoglycemia may ↓insulin dose; secretagogue (SUs, repaglinide), GLP1 agonists, SGLT2 inhibitors.
Other meds that may require blood glucose & hypo/hyperglycemia monitoring M: steroids, DPP4 inhibitors, ABX (FQ, sulfamethoxazole), atypical antipsychotics, HCV/HIV drugs, SSRIs, EtOH.
TZDs (C) fluid retention); β-blockers (mask hypoglycemia sx except sweating).
Mixing Insulins: less common, NPH with some prandial insulins. C with all long-acting analogues.

Other Diabetes Charts: Insulin Initiation, Titration, & Follow Up pg 51-52; Insulin Pen Devices pg 50; Hypoglycemia Monitoring pg 55; Perspectives on Glycemic Targets pg 47; & Insulin Landmark Trials online.

Table with 4 columns: Generic/TRADE, Cost (per 1500 units), Comments (see page 51-52 for initiating & titrating insulin), Evidence Summary / Pharmacokinetics (PK) / Formulations

BASAL Insulin LONG-ACTING: ↓ hepatic gluconeogenesis → lowers fasting & nocturnal blood glucose; ✓ T1DM & T2DM: adults, all basal children HUMULIN N; ✓ T1DM: ≥2yr, LEVEMIR >2yr, TRESIBA >6yr, LANTUS, BASAGLAR, SEMGLEE ≥6yr, TOUJEO

Table listing Intermediate-Acting insulins: Insulin NPH, HumuLIN N, NovoLIN ge NPH, HYPURIN NPH. Includes descriptions, prices, and clinical notes.

T2DM: initial insulin option; avoid if ↑ hypoglycemia risk (pg 51 & link)
advantages: may delay need for lunch prandial dose if NPH dosed BID (NPH am peak provides some lunch coverage); lower cost option; can mix (see above); & good option for steroid-induced ↑BG if not already on background basal insulin (NPH peak matches steroid-induced ↑BG, pg 52)
disadvantages: PK profile non-physiologic; inconvenient (must re-suspend); more erratic actions → BG inconsistent/variable & less smooth titration; insulin stacking & ↑hypoglycemia (peak: NPH overlaps with prandial)
CI: IV/IM (increase hypoglycemia risk), or use with an insulin pump
Administration: subcut once daily HS or BID; may titrate q1-2 days
prior to injection must re-suspend – roll between palms 10x & invert 180° 10x; inadequate re-suspension affects insulin absorption

T2DM Evidence Summary: What is the evidence of long-acting insulin analogues compared to NPH? Some advocate for a prominent role while others do not.
Mortality, macrovascular, microvascular, & quality of life outcomes are mostly unstudied.
Similar A1c lowering among long-acting analogues & NPH.
Long-acting analogues may reduce hypoglycemia; however, overall clinical benefit remains uncertain due to the following:

- RCTs were unblinded with surrogate outcomes & very low quality/certainty evidence.
There was no difference in severe hypoglycemia btwn insulin glargine & detemir vs NPH, but ↓ overall (NNT=12/6-12mos) & nocturnal (NNT=7/6-12mos).
Conflicting retrospective cohort data: one found no difference in hypoglycemia-related emergency department visits/hospitalizations.
Another, ↓ risk in those ≥65yrs with glargine/detemir aHR=0.7.
Newer analogues may have ↓ AEs vs older analogues, but the absolute benefit is usually small e.g. insulin degludec TRESIBA had less severe hypoglycemia (4.9% vs 6.6%, NNT=59/~2yrs) & nocturnal hypoglycemia (1% vs 1.9%, NNT=112/~2yrs) vs insulin glargine 100units/mL LANTUS, BASAGLAR.
DEVOTE 1 RCT (n~1600), no difference TRESIBA vs TOUJEO.

Table listing Long-Acting Insulin Analogues: Insulin glargine, BASAGLAR, SEMGLEE, LANTUS, TOUJEO, SOLIQUA 100/33. Includes descriptions, prices, and clinical notes.

T2DM: initial insulin option; esp ↑ hypoglycemia risk (pg 51, & link)
CI: mixing with other insulins, IV/IM, or use with an insulin pump
AE: ? ↑ cancer risk: non-conclusive, based on observational data
BASAGLAR, SEMGLEE are biosimilars for LANTUS; these glargine 100units/mL products have similar PK, A1c, & AE rates.
Admin (100 units/mL): subcut once daily AM/HS, may titrate q1-2 days BID dosing: consider when >50 units/d or action does not last 24h
Concentrated insulin glargine 300units/mL (TOUJEO).
reserve TOUJEO for those requiring > 20units of basal insulin/day, & hypoglycemia from other long-acting analogues e.g. LANTUS, BASAGLAR;
not bioequivalent to insulin glargine 100 units/mL LANTUS, BASAGLAR; (high concentration delays onset & lengthens duration of action)
advantages: comfort (↓ injection volume), convenience & eco-friendlier
SoloStar (450units/1.5mL pen) & DoubleStar (900units/3mL pen)
Admin (300 units/mL): subcut once daily, may titrate every 3-4 days

Bottom line (T2DM): in those who require basal insulin, NPH is a reasonable option. Based on low quality evidence, there is no clear difference in A1c between basal insulins. Long-acting analogues may reduce hypoglycemia risk vs NPH, but absolute difference is small (see perspectives for ways to reduce hypoglycemia risk beyond switching insulin). Also consider convenience, cost, & formulary status.

Table with 4 columns: Pharmacokinetics Profile, Onset, Peak, Duration. Lists various insulin products and their characteristics.

Table listing Long-Acting Insulin Analogues: Insulin detemir, LEVEMIR, Insulin degludec, TRESIBA, XULTOPHY 100/3.6. Includes descriptions, prices, and clinical notes.

T2DM: for pts with hypoglycemia on NPH or ↑ hypoglycemia risk (pg 51 & link)
CI: mixing with other insulins, IV/IM, or use with an insulin pump
Administration: subcut once daily AM/HS, may titrate every 1-2 days
BID may be required due to pharmacokinetics (duration 16-24hr)
T2DM: for pts with hypoglycemia on long-acting analogues e.g. LANTUS, BASAGLAR
CI: mixing with other insulins, IV/IM, insulin pump.
Admin (100, 200 units/mL): subcut once daily, may titrate weekly
long duration of action may provide benefit for shift workers or those who struggle with adherence
Concentrated insulin degludec 200units/mL (TRESIBA):
good option for those requiring large insulin doses
advantages: comfort (↓ injection volume), convenience (eg pen ↑ by 2 unit increments), eco-friendlier (600units vs 300units total/prefilled pen)

Table with 4 columns: Formulations, Prefilled Pen, Cartridge, Vial. Lists various insulin products and their packaging options.

Biosimilar (eg BASAGLAR, SEMGLEE): similar to the reference drug (previously authorized eg LANTUS) & has "no clinically meaningful difference in terms of safety, purity, & potency." Usually less \$, most require new Rx (not interchangeable but evolving).

Generic/TRADE *		Cost (per 1500 units) 🇨🇦	Comments (see page 51-52 for initiating & titrating insulin)	Evidence Summary / Pharmacokinetics (PK) / Formulations																				
PRANDIAL (MEALTIME): lowers post-prandial or post-meal blood glucose; ✓ T1DM & T2DM: adults, all prandial ≥ 2yrs, FIASP, TRURAPI children HUMULIN R with basal insulin; ✓ T1DM: ≥ 2yrs, NOVORAPID ≥ 3yrs, HUMALOG, ADMELOG ≥ 6 yrs APIDRA																								
Rapid-Acting Insulin Analogues	Insulin glulisine APIDRA 100units/mL	APIDRA prefilled pen, cartridge \$68 vial \$55	<ul style="list-style-type: none"> • T2DM: 1st line for most people on basal insulin & requiring prandial insulin <ul style="list-style-type: none"> ○ PK profile is more physiologic than regular insulin → more user-friendly, minimizes need for snacks between meals to avoid lows • Admin: subcut 0-15mins before, or within 15mins of consuming carbohydrates/food/meal; if a meal is skipped, skip prandial insulin dose <ul style="list-style-type: none"> ○ if gastroparesis, inject after meal due to delayed gastric emptying ○ may also be used in an insulin pump exceptions: HUMALOG 200units/mL ○ insulin lispro HUMALOG, ADMELOG & aspart FIASP may give IV DKA, but not preferred • ADMELOG is a biosimilar for HUMALOG; TRURAPI & KIRSTY are biosimilars for NOVORAPID. Biosimilar = similar PK, A1c, AEs to originator. • Not biosimilar: FIASP & NOVORAPID; LYUMJEV & HUMALOG. Contain additives. FIASP: nicotinamide, arginine; LYUMJEV: citrate/treprostinil. <ul style="list-style-type: none"> ○ quicker onset but ?clinical benefit, may help ↓ PPBG ○ similar A1c & AE (hypoglycemia, Wt) between FIASP & NOVORAPID ONSET 2 ○ CI: do not mix FIASP with other insulins • Concentrated insulin lispro 200units/mL (HumaLOG): <ul style="list-style-type: none"> ○ reserve for those requiring >20 units/day of rapid-acting insulin ○ advantages: comfort (↓ injection volume), convenience & eco-friendlier (600units vs 300units total/prefilled pen) 🌿 ○ CI: mixing with other insulins, IV, or use with an insulin pump 	<p>T2DM Evidence Summary: <i>What is the evidence of rapid-acting analogues vs short-acting insulin?</i> Some advocate for a prominent role while others do not... Cochrane '18, CADTH '11, Mannucci '09, Singh '09</p> <ul style="list-style-type: none"> • No difference in mortality; macrovascular/microvascular outcomes are not studied. Cochrane '18 (mod) • It appears there is no difference in A1c; guidelines differ^{DC, ADA} & inconsistent results. <ul style="list-style-type: none"> ○ Cochrane review found no difference in A1c (low quality evidence, 2018). Another found ↓A1c by 0.4% (0.1-0.6%) favouring rapid-acting analogues. This review was limited by trial quality. Mannucci '09 • No difference in severe hypoglycemia between classes; • Results were inconsistent among other hypoglycemia outcomes. Cochrane '18 (very low quality evidence) <ul style="list-style-type: none"> ○ may prevent 1 non-severe hypoglycemia episode (symptomatic or BG <3.5mmol/L) per year (p=0.05). • There is limited real-world & long-term efficacy/safety data with FIASP and ENTUZITY. <p>Bottom line: based on low quality evidence, there is no clear difference in A1c or hypoglycemia between classes. Consider convenience, cost, & formulary status when selecting a prandial insulin. Rapid-acting analogues often offer greater convenience for most patients (vs regular insulin).</p>																				
	Insulin lispro HumaLOG 100, 200units/mL	HumaLOG prefilled pen 100units/mL \$82 200units/mL \$77 cartridge \$86 vial \$65																						
	ADMELOG biosimilar 100units/mL	ADMELOG prefilled pen, cartridge \$60 vial \$47																						
	Insulin aspart NOVORAPID 100units/mL	NOVORAPID vial ▲ ▼ \$60 cartridge x ▼ \$77																						
	TRURAPI CDN '20 biosimilar 100units/mL	TRURAPI prefilled pen, cartridge \$60																						
	KIRSTY CDN '22 biosimilar 100units/mL	KIRSTY prefilled pen \$57 FIASP x [⊗] vial \$62; prefilled pen \$83; cartridge \$80																						
FIASP 100units/mL																								
Short-Acting	Insulin regular HumuLIN R 100units/mL	HumuLIN R cartridge \$66 vial \$53	<ul style="list-style-type: none"> • 1st line for IV infusions^{DC(B,2)} e.g. to treat diabetic ketoacidosis, ↑K⁺ • disadvantages: PK non physiologic (delayed onset makes use prior to meals inconvenient but 1 RCT n=100 found no difference if taken at meal Muller '13), & long duration may lead to ↓BG & need to snack • Admin: subcut daily-TID 30-45 minutes prior to meal(s) • Rarely used: HYPURIN II R porcine 100 units/mL vial \$173 on SPDP, ⊙ 	<table border="1"> <thead> <tr> <th>Pharmacokinetics Profile: approximations</th> <th>Onset</th> <th>Peak</th> <th>Duration</th> </tr> </thead> <tbody> <tr> <td>Insulin glulisine APIDRA Insulin aspart NOVORAPID TRURAPI, KIRSTY Insulin lispro HUMALOG 100, 200units/mL ADMELOG</td> <td>10-15mins</td> <td>60-90mins</td> <td>3.5-6hrs</td> </tr> <tr> <td>Insulin aspart FIASP Insulin lispro LYUMJEV</td> <td>5-15mins</td> <td>30-90mins</td> <td>3-5hrs</td> </tr> <tr> <td>Regular insulin HUMULIN R, NOVOLIN ge TORONTO</td> <td>30-60mins</td> <td>2-3hrs</td> <td>5-10hrs</td> </tr> <tr> <td>Regular insulin ENTUZITY</td> <td>15-60mins</td> <td>4-8hrs</td> <td>17-24hrs</td> </tr> </tbody> </table>	Pharmacokinetics Profile: approximations	Onset	Peak	Duration	Insulin glulisine APIDRA Insulin aspart NOVORAPID TRURAPI, KIRSTY Insulin lispro HUMALOG 100, 200units/mL ADMELOG	10-15mins	60-90mins	3.5-6hrs	Insulin aspart FIASP Insulin lispro LYUMJEV	5-15mins	30-90mins	3-5hrs	Regular insulin HUMULIN R, NOVOLIN ge TORONTO	30-60mins	2-3hrs	5-10hrs	Regular insulin ENTUZITY	15-60mins	4-8hrs	17-24hrs
	Pharmacokinetics Profile: approximations	Onset			Peak	Duration																		
	Insulin glulisine APIDRA Insulin aspart NOVORAPID TRURAPI, KIRSTY Insulin lispro HUMALOG 100, 200units/mL ADMELOG	10-15mins			60-90mins	3.5-6hrs																		
	Insulin aspart FIASP Insulin lispro LYUMJEV	5-15mins			30-90mins	3-5hrs																		
Regular insulin HUMULIN R, NOVOLIN ge TORONTO	30-60mins	2-3hrs	5-10hrs																					
Regular insulin ENTUZITY	15-60mins	4-8hrs	17-24hrs																					
NovoLIN ge TORONTO 100units/mL	NovoLIN ge TORONTO cartridge \$61 vial \$50																							
Insulin regular ENTUZITY 500units/mL	ENTUZITY prefilled pen \$60																							
insulin delivered in 5 unit increments prime pen with 5 units Caution: potential for dose confusion/errors ^{ISMP'19}	USA 🇺🇸: U-500 unit (to be used with U-500 insulin syringes only)																							
Premixed Insulin (cloudy): contains a mixture of prandial insulin (insulin regular or rapid-acting insulin analogue) and basal insulin (intermediate insulin); ✓ T1DM & T2DM adults, children HUMULIN 30/70																								
Insulin regular / NPH	Insulin regular / NPH 100units/mL	NovoLIN 40/60, 50/50 cartridge \$61	<ul style="list-style-type: none"> • T2DM: consider in those who do not require intensive glycemic control & have a consistent lifestyle (e.g. institutionalized, frail, older adult), & in those who prefer to administer no more than 2 injections per day • CI: mixing with other insulins, IV/IM, or use with an insulin pump • advantages: convenience (only 2 injections per day) • disadvantages: not for insulin naïve people, variability in peak effect, difficult to achieve tight glycemic control (especially post-prandial control), limited flexibility in adjusting doses due to product's fixed ratio, and inconvenient (requires re-suspending prior to injection) • Administration: subcut daily-TID (usually BID); do not give HS (↑hypoglycemia) <ul style="list-style-type: none"> ○ prior to injection must re-suspend – roll between palms 10x & invert 180° 10x; inadequate re-suspension affects insulin absorption ○ Insulin regular/NPH premix: inject ~30 minutes prior to meal ○ Insulin lispro/lispro protamine, Insulin aspart/aspart protamine: inject 0-15mins before, or within 20mins of starting meal(s) 	<p>T2DM Evidence Summary: <i>What is the evidence of pre-mixed vs basal-bolus insulin?</i> Wang '15, 4-T Study</p> <ul style="list-style-type: none"> • A1c & hypoglycemia are similar with premixed vs basal-bolus insulin. Compared to basal insulin, premixed has greater ↓A1c (~0.3%) & ↑ overall hypoglycemia (NNT=18) & Wt gain (~3kg). 																				
	NovoLIN ge 50/50 (50%/50%) cartridge \$61	NovoLIN 30/70 cartridge \$61																						
	NovoLIN ge 40/60 (40%/60%) vial \$50	HumuLIN 30/70 vial \$53 cartridge \$66																						
Insulin lispro / lispro protamine	Insulin lispro / lispro protamine 100units/mL	HumaLOG Mix 50, HumaLOG Mix 25 prefilled pen x ▼ \$85 cartridge x ▼ \$86	<table border="1"> <thead> <tr> <th>Pharmacokinetics Profile: approximations</th> <th>Onset</th> <th>Peak</th> <th>Duration</th> </tr> </thead> <tbody> <tr> <td>Insulin regular / NPH</td> <td>30-60 mins</td> <td>2-12hr possible biphasic</td> <td>14-18hr up to 24hr</td> </tr> <tr> <td>Insulin lispro / lispro protamine x ▼ *</td> <td>10-15mins</td> <td>2-4hrs</td> <td>14-24hrs</td> </tr> <tr> <td>Insulin aspart / aspart protamine x ⊗ *</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Pharmacokinetics Profile: approximations	Onset	Peak	Duration	Insulin regular / NPH	30-60 mins	2-12hr possible biphasic	14-18hr up to 24hr	Insulin lispro / lispro protamine x ▼ *	10-15mins	2-4hrs	14-24hrs	Insulin aspart / aspart protamine x ⊗ *								
	Pharmacokinetics Profile: approximations	Onset		Peak	Duration																			
	Insulin regular / NPH	30-60 mins		2-12hr possible biphasic	14-18hr up to 24hr																			
Insulin lispro / lispro protamine x ▼ *	10-15mins	2-4hrs	14-24hrs																					
Insulin aspart / aspart protamine x ⊗ *																								
HumaLOG Mix 50 (50%/50%) cartridge \$86																								
HumaLOG Mix 25 (25%/75%)																								
Insulin aspart / aspart protamine	Insulin aspart / aspart protamine 100units/mL	NOVOMIX 30 cartridge x ⊗ \$75	<p>Formulations: see Pens pg 50</p> <table border="1"> <thead> <tr> <th>Prefilled Pen (disposable pen)</th> <th>Cartridge (reusable pen) 🌿</th> <th>Vial</th> </tr> </thead> <tbody> <tr> <td>Insulin regular / NPH NOVOLIN ge 50/50,40/60 NOVOLIN ge 30/70, HUMULIN 30/70</td> <td>----</td> <td>✓ see Pens pg 50 ✓ see Pens pg 50</td> <td>-- ✓</td> </tr> <tr> <td>Insulin lispro / lispro protamine HUMALOG Mix 50, HUMALOG Mix 25 x ▼ *</td> <td>KwikPen max = 60 units/injection</td> <td>HumaPen Savvio; max = 60 units/injection HumaPen Luxura HD; max=30units/injection</td> <td>--</td> </tr> <tr> <td>Insulin aspart / aspart protamine NOVOMIX 30 x ⊗ *</td> <td>----</td> <td>NovoPen 4 or 5; max = 60 units/injection NovoPen Echo; max = 30 units/injection</td> <td>--</td> </tr> </tbody> </table>	Prefilled Pen (disposable pen)	Cartridge (reusable pen) 🌿	Vial	Insulin regular / NPH NOVOLIN ge 50/50,40/60 NOVOLIN ge 30/70, HUMULIN 30/70	----	✓ see Pens pg 50 ✓ see Pens pg 50	-- ✓	Insulin lispro / lispro protamine HUMALOG Mix 50, HUMALOG Mix 25 x ▼ *	KwikPen max = 60 units/injection	HumaPen Savvio; max = 60 units/injection HumaPen Luxura HD; max=30units/injection	--	Insulin aspart / aspart protamine NOVOMIX 30 x ⊗ *	----	NovoPen 4 or 5; max = 60 units/injection NovoPen Echo; max = 30 units/injection	--						
	Prefilled Pen (disposable pen)	Cartridge (reusable pen) 🌿		Vial																				
Insulin regular / NPH NOVOLIN ge 50/50,40/60 NOVOLIN ge 30/70, HUMULIN 30/70	----	✓ see Pens pg 50 ✓ see Pens pg 50	-- ✓																					
Insulin lispro / lispro protamine HUMALOG Mix 50, HUMALOG Mix 25 x ▼ *	KwikPen max = 60 units/injection	HumaPen Savvio; max = 60 units/injection HumaPen Luxura HD; max=30units/injection	--																					
Insulin aspart / aspart protamine NOVOMIX 30 x ⊗ *	----	NovoPen 4 or 5; max = 60 units/injection NovoPen Echo; max = 30 units/injection	--																					
NOVOMIX 30 (30%/70%)																								

Hybrid Closed-Loop Insulin Systems: MiniMed 670G & 770G, Control-IQ. **Not in Canada:** **AFREZZA** inhaled **DI**; **D/C:** HumuLIN 20/80; HumuLIN L & U; NovoLIN ge Ultralente & Lente; NovoLIN 10/90 & 20/80; Iletin II Lente Pork; EXUBERA (inhaled). **Investigational:** insulin icodice (basal) once wkly.

ABBREVIATIONS: ⬇️=↓ dose for renal dysfx \$=total cost in SK (1500units = 50 units x 30 days) ⚡=Exception Drug Status in SK x =Non-formulary in SK ⊕=prior approval for NIHB ⊗=not covered by NIHB ✓=Health Canada Indication * = refrigerate **A1c**=glycosylated hemoglobin **BG**=blood glucose **DPP4**=dipeptidyl peptidase-4 **eGFR**=estimated glomerular filtration rate **FBG**=fasting blood glucose **GLP1**=glucagon-like peptide-1 **inj**=injection **NPH**=neutral protamine Hagedorn **subcut**=subcutaneous **SGLT2**=sodium-glucose cotransporter-2

Insulin: Drug Comparison Chart, Online Extras

Complete ABBREVIATIONS: ⚡=↓ dose for renal dysfx ₤=total cost in SK (1500units = 50 units x 30 days) ⚖=Exception Drug Status in SK ✕ =Non-formulary in SK ⚡=prior approval for NIHB ⊗=not covered by NIHB ✓=Health Canada Indication
 ※=refrigerate **A1c**=glycosylated hemoglobin **ABX**=antibiotic **AE(s)**=adverse effect(s) **BID**=twice daily **BG**=blood glucose **DKA**=diabetic ketoacidosis **DPP4**=dipeptidyl peptidase-4 **dysfx**=dysfunction **eGFR**=estimated glomerular filtration rate
FBG=fasting blood glucose **FQ**=fluoroquinolone **GLP1**=glucagon-like peptide-1 **hr(s)**=hour(s) **HCV**=hepatitis C virus **HS**=bedtime **IM**=intramuscular **IV**=intravenous **kg**=kilogram **mo(s)**=month(s) **NPH**=neutral protamine Hagedorn
PK=pharmacokinetics **PPBG**=postprandial (2hr) blood glucose **RCT**=randomized controlled trial **subcut**=subcutaneous **SGLT2**=sodium-glucose cotransporter-2 **SSRI**=selective serotonin reuptake inhibitor **SU**=sulfonylurea **T1DM**=type 1 diabetes mellitus **T2DM**=type 2 diabetes mellitus **TID**=three times daily **TZD**=thiazolidinediones **Wt**=weight **yr(s)**=year(s)

ac=before meals **am**=morning **CDN**=Canadian **CI**=confidence interval **CI**=contraindicated **d**=day **D/C**=discontinued **DI**=drug interaction **EtOH**=alcohol **FDA**=approved Food & Drug Admin
fx=function **HIV**=human immunodeficiency virus **HR**=heart rate or hazard ratio **hr(s)**=hour(s) **inj**=injection **K+**=potassium **M**=monitor **min(s)**=minute(s) **mL**=milliliters **n**=number
NNT=number needed to treat **pg**=page **pm**=evening **Rx**=prescription **SK**=Saskatchewan **sx**=symptoms **USA**=United States **vs**=versus

Acknowledgments: Tessa Laubscher (CCFP, College of Medicine, U of S, Saskatoon); **Reviewed by:** Devanshi Parekh, Terra Arnason, Debbie Bunka, Loren Regier, Alex Crawley, Julia Bareham, Monica Lawrence, Kerry Mansell, Stephanie Zimmer, Tahirih McAleer.
Originally Prepared by: M Jin PharmD, CDE; L. Regier BSP, BA; B. Jensen BSP; S Downey BSP

DISCLAIMER: The content of this newsletter represents the research, experience and opinions of the authors and not those of the Board or Administration of U of S, Neither the authors nor U of S nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information. Any use of the newsletter will imply acknowledgment of this disclaimer and release any responsibility of U of S, its employees, servants or agents. Readers are encouraged to confirm the information contained herein with other sources. Additional information and references online at www.RxFiles.ca

Copyright– RxFiles, University of Saskatchewan (U of S) www.RxFiles.ca

AFREZZA inhaled insulin: not in Canada rapid-acting insulin for adults with T1 and T2DM; no A1C difference from regular/NPH regimens but patients may prefer this route of administration; \$\$\$

- CI:** COPD, asthma, smoking if within prev 6 months, ketoacidosis; long-term safety ?cancer
- AE:** cough, hypoglycemia, throat pain, **bronchospasm**, ?↓pulmonary fx tests short term, ?anti-insulin antibodies
- Administration:** 8, 12 units (dry powder) given 20min ac

Mixing Insulins : NPH with insulin regular except ENTUZITY or rapid-acting analogues except HUMALOG 200units/mL, FIASP;
 insulin vial & syringe preferred (although some use cartridge & syringe); **CI:** all long-acting analogues

BASAGLAR	53
Detemir	53
Diabetes	53
Glargine	53
HUMULIN L, N, Reg, U	53
HYPURIN	53
Insulin	53
LANTUS	53
LEVEMIR	53
NOVOLIN	53
REZVOGLAR	53
RYZODEG	53
SEMGLEE	53
SOLIQUA	53
TOUJEO	53
TRESIBA	53
Type 1 Diabetes Mellitus	53
Type 2 Diabetes Mellitus	53
XULTOPHY	53
ADMELOG	54
AFREZZA	54
APIDRA	54
Aspart	54
Degludec	54
Diabetes	54
ENTUZITY	54
EXUBERA	54
FIASP	54
Glulisine	54
HUMALOG	54
HUMULIN L, N, Reg, U	54
Insulin	54
KIRSTY	54
Lispro	54
LYUMJEV	54
NOVOLIN	54
NOVOMIX	54
NOVORAPID	54

TRURAPI	54
Type 1 Diabetes Mellitus	54
Type 2 Diabetes Mellitus	54

References for Insulin Comparison Chart:

Other References:

- DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA. 2003 May 7;289(17):2254-64.
- Drug Information Handbook 10TH edition. Lacy CF et al (editors). American Pharmaceutical Association. Lexi-Comp Inc, Hudson Ohio, 2002-2003 edition.
- Boctor, MA. Diabetes Mellitus in Therapeutic Choices (3rd edition). Gray, Jean (editor). Canadian Pharmacists Association. Web-com Ltd, Ottawa, ON, 2000.
- Micromedex 2020.
- Yki-Jarvinen H, Ryysy L, Nikkila K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized controlled trial. (FINFAT STUDY) Ann Intern Med 1999;130:389-96.
- Meltzer S, Leiter L, Daneman D. et al 1998 Clinical practice guidelines for the management of diabetes in **Canada**. CMAJ **1998**;159 (8 Suppl).
- Hermann LS. Optimizing therapy for insulin-treated Type 2 Diabetes Mellitus. Drugs & Aging 2000;17(4):283-94.
- Insulin glargine (Lantus), a new long-acting insulin. Med Lett Drugs Ther. 2001 Aug 6;43(1110):65-6.
- Insulin aspart, a new rapid-acting insulin. Med Lett Drugs Ther. 2001 Oct 15;43(1115):89-90.
- American Diabetes Association: Clinical Practice Recommendations 2003, Diabetes Care 2003 26:Supplement 1
- Writing Team For The Diabetes Control And Complications Trial/Epidemiology Of Diabetes Interventions And Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA. 2003 Oct 22;290(16):2159-67.
- Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977-986.
- Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (**UKPDS**) Group. Lancet. 1998 Sep 12;352(9131):837-53.
- Yki-Jarvinen H, Ryysy L, Nikkila K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med. 1999 Mar 2;130(5):389-96.
- Wright A, Burden AC, Paisey RB, Cull CA, Holman RR; U.K. Prospective Diabetes Study Group. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (**UKPDS 57**). Diabetes Care. 2002 Feb;25(2):330-6.
- Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995 May;28(2):103-17.
- Rosenstock J, Schwartz SL, Clark CM Jr, et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (**HOE 901**) and NPH insulin. Diabetes Care. 2001 Apr;24(4):631-6.
- New Drugs: Lantus (insulin glargine injection). in Pharmacists Letter Mar 2005;21(3):210319.
- Mayfield JA, White RD. Insulin therapy for type 2 diabetes: rescue, augmentation, and replacement of beta-cell function. Am Fam Physician. 2004 Aug 1;70(3):489-500. Erratum in: Am Fam Physician. 2004 Dec 1;70(11):2079-80.
- Harjutsalo V, Podar T, Tuomilehto J. Cumulative incidence of type 1 diabetes in 10,168 siblings of Finnish young-onset type 1 diabetic patients. Diabetes 2005; 54:563-69.
- Hirsch IB. Insulin analogues. N Engl J Med. 2005 Jan 13;352(2):174-83.
- Treatment Guidelines:** Drugs for Diabetes. **The Medical Letter:** August, **2005;** (3) pp. 57-62.
- Rosenstock J, Zinman B, Murphy LJ, et al. **Inhaled insulin** improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2005 Oct 18;143(8):549-58. 24. Comparison of insulins Pharmacist's Letter/Prescriber's Letter 2006;22(2):220217
- van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, et al. Intensive insulin therapy in the **critically ill patients**. N Engl J Med. 2001 Nov 8;345(19):1359-67.
- Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the **medical ICU**. N Engl J Med. 2006 Feb 2;354(5):449-61
- Nathan DM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (**DCCT/EDIC**) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005 Dec 22;353(25):2643-53.
- Van den Berghe G, Schoonheydt K, Bex P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology. 2005;64:1348-53.
- Fiallo-Scharer R, Horner B, McFann K, Walravens P, Chase HP. **Mixing rapid-acting** insulin analogues with insulin **glargine** in children with type 1 diabetes mellitus. J Pediatr. 2006 Apr;148(4):481-4.
- Garg S, Rosenstock J, et al. Efficacy & safety of preprandial human **insulin inhalation** powder versus injectable insulin in pts with type 1 diabetes. Diabetologia. 2006 May;49(5):891-9. Epub 2006 Feb 28.
- Barnett AH, et al. An open, randomized, parallel-group study to compare the efficacy and safety profile of **inhaled human insulin (Exubera) with metformin** as adjunctive therapy in patients with type 2 diabetes poorly controlled on a sulfonylurea. Diabetes Care. 2006 Jun;29(6):1282-7.
- Hermansen K, et al. A 26-week, randomized, parallel, treat-to-target trial **comparing insulin detemir with NPH** insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care. 2006 Jun;29(6):1269-74.
- Siebenhofer A, et al. **Short acting insulin analogues versus regular** human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD003287.
- Cheung NW, Wong VW, McLean M. The hyperglycemia: intensive insulin infusion in infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care. 2006 Apr;29(4):765-70.
- Inhaled insulin (**Exubera**). Med Lett Drugs Ther. 2006 Jul 17;48(1239):57-8.
- Pearson ER, et al. Neonatal Diabetes International Collaborative Group. Switching **from insulin to oral sulfonylureas** in pts with diabetes due to Kir6.2 mutations. N Engl J Med. 2006 Aug 3;355(5):467-77.
- Babenko AP, et al. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl J Med. 2006 Aug 3;355(5):456-66.
- Mooradian AD, Bernbaum M, Albert SG. Narrative review: a rational approach to starting insulin therapy. Ann Intern Med. 2006 Jul 18;145(2):125-34.
- Health Canada Insulin Products update Sept/06 http://www.hc-sc.gc.ca/iyh-vsv/alt_formats/cmcd-dcmc/pdf/insulin_e.pdf .
- Ballani P, Tran MT, Navar MD, Davidson MB. Clinical experience with **U-500 regular insulin** in obese, markedly insulin-resistant type 2 diabetic patients. Diabetes Care. 2006 Nov;29(11):2504-5.
- Ceglia L, Lau J, Pittas AG. Meta-analysis: efficacy and safety of **inhaled insulin** therapy in adults with diabetes mellitus. Ann Intern Med. 2006 Nov 7;145(9):665-75.
- Budnitz DS, et al. National surveillance of emergency department visits for outpatient **adverse drug events**. JAMA. 2006 Oct 18;296(15):1858-66.
- Dunn C, Curran MP. **Inhaled human insulin** (Exubera): a review of its use in adult patients with diabetes mellitus. Drugs. 2006;66(7):1013-32.
- Shapiro AM, et al. International trial of the **Edmonton protocol for islet transplantation**. N Engl J Med. 2006 Sep 28;355(13):1318-30.

45. Barnett AH, et al. An open, randomized, parallel-group study to compare the efficacy and safety profile of **inhaled human insulin** (Exubera) with glibenclamide as adjunctive therapy in patients with type 2 diabetes poorly controlled on metformin. *Diabetes Care*. 2006 Aug;29(8):1818-25.
46. Cheung NW, et al. The Hyperglycemia: **Intensive Insulin Infusion in Infarction (HI-5)** study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care*. 2006 Apr;29(4):765-70.
47. Martin CL, et al. **DCCT/EDIC** Research Group. **Neuropathy** among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care*. 2006 Feb;29(2):340-4.
48. Skyler JS, Jovanovic L, Klioze S, Reis J, Duggan W; Inhaled Human Insulin Type 1 Diabetes Study Group. Two-year safety and efficacy of inhaled human insulin (**Exubera**) in adult patients with type 1 diabetes. *Diabetes Care*. 2007 Mar;30(3):579-85.
49. McMahon GT, Arky RA. **Inhaled insulin** for diabetes mellitus. *N Engl J Med*. 2007 Feb 1;356(5):497-502.
50. Taylor R, Davison JM. **Type 1 diabetes and pregnancy**. *BMJ*. 2007 Apr 7;334(7596):742-5.
51. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group; (**DCCT/EDIC**) Jacobson AM, Musen G, Ryan CM, et al. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med*. 2007 May 3;356(18):1842-52.
52. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):CD005613.
53. Gandhi GY, Nuttall GA, Abel MD, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. *Ann Intern Med*. 2007 Feb 20;146(4):233-43.
54. Pharmacist's Letter. Treatment of Diabetes in women who are **pregnant**. Sept 2007.
55. Bryden KS, et al. Eating habits, body weight, and insulin misuse. A longitudinal study of teenagers and young adults with type 1 diabetes. *Diabetes Care*. 1999 Dec;22(12):1956-60.
56. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, et al.; the **4-T Study** Group. Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. (4T) *N Engl J Med*. 2007 Sep 21; [Epub ahead of print] Holman, Rury R., Farmer, Andrew J., Davies, Melanie J., et al. the 4-T Study Group, **Three-Year** Efficacy of Complex Insulin Regimens in Type 2 Diabetes. *N Engl J Med* 2009 0: NEJMoa0905479.
57. Pharmacists Letter. Exubera. Oct 2007.
58. Norris JM, Yin X, Lamb MM, Barriga K, et al. **Omega-3** polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes. *JAMA*. 2007 Sep 26;298(12):1420-8.
59. Weston C, Walker L, Birkhead J; National Audit of Myocardial Infarction Project, National Institute for Clinical Outcomes Research. Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an **acute coronary syndrome**. *Heart*. 2007 Dec;93(12):1542-6. Epub 2007 May 13
60. Datta S, Qaadir A, Villanueva G, Baldwin D. Once-daily insulin glargine versus 6-hour sliding scale regular insulin for control of hyperglycemia after a bariatric surgical procedure: a randomized clinical trial. *Endocr Pract* 2007;13(3):225-31.
61. Yeldandi RR, Lurie A, Baldwin D. Comparison of once-daily glargine insulin with twice-daily NPH/regular insulin for control of hyperglycemia in inpatients after cardiovascular surgery. *Diabetes Technology & Therapeutics* 2006;8(6):609-16.
62. Hofman PL, Lawton SA, Peart JM, et al. An angled insertion technique using 6-mm needles markedly reduces the risk of intramuscular injections in children and adolescents. *Diabetic Medicine* 2007;74(12):1400-1405.
63. Goebel-Fabbri AE, Fikkan J, et al. **Insulin restriction and associated morbidity and mortality** in women with type 1 diabetes. *Diabetes Care*. 2008 Mar;31(3):415-9. Epub 2007 Dec 10.
64. Hassan K, Rodriguez LM, Johnson SE, et al. A randomized, controlled trial comparing twice-a-day insulin glargine mixed with rapid-acting insulin analogs versus standard neutral protamine Hagedorn (NPH) therapy in newly diagnosed type 1 diabetes. *Pediatrics*. 2008 Mar;121(3):e466-72. Epub 2008 Feb 25.
65. Coustan DR. Pharmacological management of **gestational diabetes**: an overview. *Diabetes Care*. 2007 Jul;30 Suppl 2:S206-8. Review. Erratum in: *Diabetes Care*. 2007 Dec;30(12):3154.
66. Bretzel RG, Nuber U, Landgraf W, et al. **Once-daily basal insulin glargine** versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (**APOLLO**): an open randomised controlled trial. *Lancet*. 2008 Mar 29;371(9618):1073-84.
67. Lopez X, Castells M, Ricker A, Velazquez EF, Mun E, Goldfine AB. **Human insulin analog--induced lipatrophy**. *Diabetes Care*. 2008 Mar;31(3):442-4. Epub 2007 Dec 27.
68. Cope JU, Morrison AE, Samuels-Reid J. Adolescent use of **insulin** and patient-controlled analgesia **pump** technology: a 10-year Food and Drug Administration retrospective study of adverse events. *Pediatrics*. 2008 May;121(5):e1133-8.
69. Guideline Development Group. Management of diabetes from **preconception to the postnatal** period: summary of NICE guidance. *BMJ*. 2008 Mar 29;336(7646):714-7.
70. Crowther CA, Hiller JE, Moss JR, et al. Australian Carbohydrate Intolerance Study in Pregnant Women (**ACHOIS**) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med*. 2005 Jun 16;352(24):2477-86. Epub 2005 Jun 12.
71. Rowan JA, Hague WM, Gao W, Battin MR, et al; **MiG** Trial Investigators. **Metformin versus insulin** for the treatment of gestational diabetes. *N Engl J Med*. 2008 May 8;358(19):2003-15.
72. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of **glyburide and insulin** in women with gestational diabetes mellitus. *N Engl J Med*. 2000 Oct 19;343(16):1134-8.
73. Gangemi A, Salehi P, Hatipoglu B, Martellotto J, Barbaro B, Kuechle JB, Qi M, Wang Y, Pallan P, Owens C, Bui J, West D, Kaplan B, Benedetti E, Oberholzer J. **Islet transplantation** for brittle type 1 diabetes: the UIC protocol. *Am J Transplant*. 2008 Jun;8(6):1250-61. Epub 2008 Apr 29.
74. Vardi M, Jacobson E, Nini A, Bitterman H. Intermediate acting versus long acting insulin for type 1 diabetes mellitus. *Cochrane Database Syst Rev*. 2008 Jul 16;(3):CD006297
75. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, et al. A randomised, 52-week, treat-to-target trial comparing **insulin detemir with insulin glargine** when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia*. 2008 Jan 16; [Epub ahead of print]
76. Soylemez Wiener R, Wiener DC, Larson RJ. Benefits and risks of **tight glucose control in critically ill** adults: a meta-analysis. *JAMA*. 2008 Aug 27;300(8):933-44.
77. de Boer IH, Kestenbaum B, Rue TC, et al. Diabetes Control and Complications Trial (**DCCT**)/Epidemiology of Diabetes Interventions and Complications (**EDIC**) Study Research Group. Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. *Arch Intern Med*. 2008 Sep 22;168(17):1867-73.
78. Qayyum R, Bolen S, Maruthur N, et al. Systematic Review: Comparative Effectiveness and Safety of Premixed Insulin Analogues in Type 2 Diabetes. *Ann Intern Med*. 2008 Sep 15. [Epub ahead of print]
79. Murphy HR, Rayman G, Lewis K, et al; Effectiveness of **continuous glucose monitoring** in pregnant women with diabetes: randomised clinical trial. *BMJ*. 2008 Sep 25;337:a1680. doi: 10.1136/bmj.a1680. Continuous glucose monitoring during pregnancy is associated with improved glycaemic control in the third trimester, lower birth weight, and reduced risk of macrosomia.
80. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, et al. **Continuous glucose monitoring** and intensive treatment of type 1 diabetes. *N Engl J Med*. 2008 Oct 2;359(14):1464-76. Epub 2008 Sep 8.
81. Weng J et al. Effect of **intensive insulin** therapy on β -cell function and glycaemic control in patients with **newly diagnosed** type 2 diabetes: A multicentre randomised parallel-group trial. *Lancet* 2008 May 24; 371:1753.
82. Chen HS, Wu TE, Jap TS, Hsiao LC, Lee SH, Lin HD. Beneficial effects of insulin on glycaemic control and beta-cell function in **newly diagnosed** type 2 diabetes with severe hyperglycemia after short-term **intensive insulin** therapy. *Diabetes Care*. 2008 Oct;31(10):1927-32. Epub 2008 Jun 12. n=50. A 6-month course of insulin therapy, compared with OAD treatment, could more effectively achieve adequate glycaemic control and significant improvement of beta-cell function in new-onset type 2 diabetic patients with severe hyperglycemia.
83. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycaemia in type 2 diabetes mellitus: a **consensus algorithm** for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association (**ADA**) and the European Association for the Study of Diabetes. *Diabetologia*. 2008 Oct 22. <http://care.diabetesjournals.org/misc/MedicalManagementofHyperglycemia.pdf>
84. Ludvigsson J, Faresjo M, Hjorth M, et al. **GAD treatment** and insulin secretion in recent-onset type 1 diabetes. *N Engl J Med*. 2008 Oct 30;359(18):1909-20. Epub 2008 Oct 8.
85. Arabi YM, Dabbagh OC, Tamim HM, et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical **critically ill patients**. *Crit Care Med*. 2008 Dec;36(12):3190-7. Intensive insulin therapy was not associated with improved survival among medical surgical intensive care unit patients and was associated with increased occurrence of hypoglycemia. Based on these results, we do not advocate universal application of intensive insulin therapy in intensive care unit patients.
86. Esposito K, Ciotola M, Maiorino MI, et al. Addition of neutral protamine lispro insulin or insulin glargine to oral type 2 diabetes regimens for patients with suboptimal glycaemic control: a randomized trial. *Ann Intern Med*. 2008 Oct 21;149(8):531-9. Similar glycaemic control occurred with the addition of NPL or glargine insulin to oral regimens in patients with poorly controlled type 2 diabetes. Hypoglycemia was similar in the 2 groups, but sample size limited the ability to make a definite safety assessment.

87. Hollander P, Cooper J, Bregenhøj J, Pedersen CB. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing **insulin detemir with insulin glargine** in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. Clin Ther. 2008 Nov;30(11):1976-87. When used as indicated as part of a basal-bolus regimen in patients with T2DM who had previously received other insulin and/or OAD regimens, detemir was noninferior to glargine in its effects on overall glycemic control. Both basal insulins were associated with clinically relevant reductions in hyperglycemia. Both were well tolerated, with no significant difference in the frequency of hypoglycemia or AEs.
88. Pharmacist's Letter. **How Much Insulin is Too Much?** Jan 2009.
89. Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart. Diabet Med. 2006 Aug;23(8):879-86.
90. Ashwell SG, Gebbie J, Home PD. Optimal timing of injection of once-daily insulin glargine in people with Type 1 diabetes using insulin lispro at meal-times. Diabet Med. 2006 Jan;23(1):46-52.
91. Lund SS, Tarnow L, Astrup AS, et al. Effect of adjunct **metformin** treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomized study. PLoS ONE. 2008;3(10):e3363. Epub 2008 Oct 9.
92. NeedleAid Ensures: injection at the proper angle & depth & shields the needle. Useful for visually impaired. <http://www.needleaid.com/>
93. Hirsch IB. **Sliding scale** insulin--time to stop sliding. JAMA. 2009 Jan 14;301(2):213-4.
94. Singh SR, Ahmad F, Lal A, et al. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ 2009;180(4):385-97. Online at: <http://www.cmaj.ca/cgi/reprint/180/4/385> Rapid-and long-acting insulin analogues offer little benefit relative to conventional insulins in terms of glycemic control or reduced hypoglycemia. Long-term, high-quality studies are needed to determine whether insulin analogues reduce the risk of long-term complications of diabetes.
95. Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. CMAJ 2009;180(4):400-7. <http://www.cmaj.ca/cgi/reprint/180/4/400>. The cost-effectiveness of insulin analogues depends on the type of insulin analogue and whether the patient receiving the treatment has type 1 or type 2 diabetes. With the exception of rapid-acting insulin analogues in type 1 diabetes, routine use of insulin analogues, especially long-acting analogues in type 2 diabetes, is unlikely to represent an efficient use of finite health care resources.
96. Siebenhofer-Kroitzsch A, Horvath K, Plank J. Insulin analogues: too much noise about small benefits. CMAJ. 2009 Feb 17;180(4):369-70. <http://www.cmaj.ca/cgi/reprint/180/4/369>
97. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, et al. **Early insulin therapy in very-low-birth-weight infants**. N Engl J Med. 2008 Oct 30;359(18):1873-84.
98. **NICE-SUGAR** Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, et al. **Intensive** versus conventional glucose control in **critically ill** patients. N Engl J Med. 2009 Mar 26;360(13):1283-97. Epub 2009 Mar 24. In this large, international, randomized trial, we found that intensive glucose control **increased mortality** among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter. Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009 Apr 14;180(8):821-7. Epub 2009 Mar 24.
99. Montori VM, Fernández-Balsells M. **Glycemic Control** in Type 2 Diabetes: **Time for an Evidence-Based About-Face?**. Ann Intern Med. 2009 Apr 20.
100. Ray KK, Seshasai SR, et al. Effect of **intensive control of glucose on cardiovascular outcomes** and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. Lancet 2009; 373: 1765-72.
101. Perez, Norma, Moisan, Jocelyne, Sirois, Caroline, Poirier, Paul, Gregoire, Jean-Pierre. **Initiation of insulin** therapy in elderly patients taking oral antidiabetes drugs. CMAJ 2009 180: 1310-1316.
102. Glargine & cancer: FDA Jul/09 : Early Communication About Safety of Lantus (insulin glargine): <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm169722.htm> ; <http://www.diabetologia-journal.org/cancer.html> ; Related links: <http://www.medscape.com/viewarticle/705198?src=mp&spon=34&uac=93517FV> ; <http://www.nationalpost.com/life/health/story.html?id=4578946f-1f50-426e-b92a-bc0f7dd86eed> ; http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2009/2009_115-eng.php ; <http://www.endo-society.org/advocacy/policy/upload/Statement-for-Patients-on-Insulin-Glargine.pdf>
- Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia. 2009 Jul 2. [Epub ahead of print]
- Hemkens LG, Grouven U, Bender R, Günster C, Gutschmidt S, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia. 2009 Jun 30. [Epub ahead of print]
- Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdóttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. Diabetologia. 2009 Jul 9. [Epub ahead of print]
- Ruiter R, Vissler LE, van Herk-Sukel MP, et al. Risk of cancer in patients on insulin glargine and other insulin analogues in comparison with those on human insulin: from a large population-based follow-up study. Diabetologia. 2011 Sep 29.
- Wu JW, Azoulay L, Majdan A, et al. Long-Term Use of **Long-Acting Insulin Analogs and Breast Cancer** Incidence in Women With Type 2 Diabetes. J Clin Oncol. 2017 Sep 27;JCO2017734491.
103. Pérez N, Moisan J, Sirois C, Poirier P, Grégoire JP. **Initiation of insulin** therapy in elderly patients taking oral antidiabetes drugs. CMAJ. 2009 Jun 23;180(13):1310-6
104. Bolli GB, Kerr D, Thomas R, et al. Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes: a randomized open parallel multicenter study. Diabetes Care. 2009 Jul;32(7):1170-6. Epub 2009 Apr 23. In unselected people with type 1 diabetes naive to CSII or insulin glargine, glycemic control is no better with the more expensive CSII therapy compared with glargine-based MDI therapy.
105. Lingvay I, Legendre JL, Kaloyanova PF, et al. **Insulin-Based versus Triple Oral Therapy** for Newly-Diagnosed Type 2 Diabetes: Which is Better? Diabetes Care. 2009 Jul 10. [Epub ahead of print] When compared with a clinically equivalent treatment regimen, insulin-based therapy is effective, did not cause greater weight gain or hypoglycemia, nor decrease compliance, treatment satisfaction, or QoL. Insulin is safe, well-accepted, and effective for ongoing treatment of patients with newly-diagnosed type 2 diabetes.
106. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G. Insulin **Glargine Safety in Pregnancy**: a Transplacental Transfer Study. Diabetes Care. 2009 Oct 6. [Epub ahead of print]
107. Dejgaard A, Lynggaard H, Råstam J, Krogsgaard Thomsen M. No evidence of increased risk of **malignancies** in patients with diabetes treated with insulin **detemir**: a meta-analysis. Diabetologia. 2009 Oct 17.
108. Van den Berghe G, Mesotten D, Vanhorebeek I. Intensive insulin therapy in the intensive care unit. CMAJ. 2009 Apr 14;180(8):799-800. Epub 2009 Mar 24.
109. Pescovitz MD, Greenbaum CJ, et al. Type 1 Diabetes TrialNet Anti-CD20 Study Group. **Rituximab**, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med. 2009 Nov 26;361(22):2143-52.
110. Wilson Jennifer F. **In the Clinic: Diabetic Ketoacidosis**. Ann Intern Med January 5, 2010 152:ITC1-1; doi:10.1059/0003-4819-152-1-201001050-01001.
111. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (**CSII**) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD005103.
112. Hernández-Díaz S, Adami HO. Diabetes therapy and **cancer risk**: causal effects and other plausible explanations. Diabetologia. 2010 Feb 23.
113. Hovorka R, Allen JM, Elleri D, et al. Manual **closed-loop insulin delivery** in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet. 2010 Feb 27;375(9716):743-51.
114. Egí M et al. **Hypoglycemia** and outcome in critically ill patients. Mayo Clin Proc 2010 Mar; 85:217.
115. Barton AL, Gilbertson HR, Donath SM and Cameron FJ. Is bedtime **supper** necessary for older children with diabetes using **glargine insulin** in multiple daily injection regimens?. Diabet Med. 2010 Feb;27:238-41.
116. Gibney MA, Arce CH, et al. Skin & subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for **needle length** recommendations. Curr Med Res Opin.2010Jun;26(6):1519-30.
117. Nguyen TM, Renukuntla VS, Heptulla RA. **Mixing Insulin Aspart With Detemir** Does Not Affect Glucose Excursion In Children With Type 1 Diabetes Mellitus. Diabetes Care. 2010 May 26.
118. Giovannucci, Edward, Harlan, David M., Archer, Michael C., et al. **Diabetes and Cancer**: A Consensus Report. CA Cancer J Clin 2010 0: caac.20078.
119. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet. 2010 Feb 27;375(9716):743-51.
120. Rosenstock Julio, Lorber Daniel L, Gnudi Luigi, et al., Prandial inhaled insulin plus basal insulin glargine versus twice daily biapart insulin for type 2 diabetes: a multicentre randomised trial, The Lancet, Volume 375, Issue 9733, 26 June 2010-2 July 2010, Pages 2244-2253
121. Bergenstal, Richard M., Tamborlane, William V., Ahmann, Andrew, et al. the **STAR 3** Study Group, Effectiveness of **Sensor-Augmented Insulin-Pump** Therapy in Type 1 Diabetes. N Engl J Med 2010 0: NEJMoa1002853.
122. Miser William F., Arakaki R, Jiang H et al., Randomized, open-label, parallel-group evaluations of **basal-bolus therapy versus** insulin lispro **premixed** therapy in patients with type 2 diabetes mellitus failing to achieve control with starter insulin treatment and continuing oral antihyperglycemic drugs: A noninferiority intensification substudy of the DURABLE trial, Clinical Therapeutics, Volume 32, Issue 5, May 2010, Pages 896-908.
123. Hofman PL, Behrendorf Derraik JG, et al. Defining the ideal injection techniques when using **5-mm needles** in children and adults. Diabetes Care. 2010 Jun 28.
124. Campbell PT, Deka A, Jacobs EJ, et al. Prospective study reveals associations between **colorectal cancer** and type 2 diabetes mellitus or insulin use in men. Gastroenterology. 2010 Oct;139(4):1138-46.

125. Grimaldi-Bensouda L, Marty M, Pollak M, et al. The international study of insulin and cancer (**ISICA**). *Lancet*. 2010 Sep 4;376(9743):769-70.
126. Zhao YT, Weng CL, Chen ML, et al. Comparison of **glucose-insulin-potassium and insulin-glucose** as adjunctive therapy in acute myocardial infarction: a contemporary meta-analysis of randomised controlled trials. *Heart*. 2010 Oct;96(20):1622-6. Current evidence suggests that GIK with insulin does not reduce mortality in patients with AMI. However, studies of glycaemia are inconclusive & it remains possible that glycaemic control is beneficial.
127. Knip Mikael, Virtanen Suvii M, Seppä Karri, et al. for the Finnish TRIGR Study Group. **Dietary Intervention** in Infancy and Later Signs of Beta-Cell Autoimmunity. *N Engl J Med* 2010; 363:1900-1908.
128. Frid A, Hirsch L, Gaspar R, et al. Scientific Advisory Board for the Third Injection Technique Workshop. **New injection recommendations** for patients with diabetes. *Diabetes Metab*. 2010 Sep;36 Suppl 1:S3-18.
129. Pharmacist's Letter. **Insulin Pump Therapy**. Dec 2010.
130. Dhulkotia JS, Ola B, Fraser R, et al. **Oral hypoglycemic agents vs insulin in management of gestational diabetes**: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2010 Nov;203(5):457.e1-9.
131. Pollex E, Moretti ME, Koren G, et al. Safety of Insulin **Glargine Use in Pregnancy**: A Systematic Review and Meta-Analysis (January). *Ann Pharmacother*. 2011 Jan 4.
132. Kansagara Devan, Fu Rongwei, Freeman Michele, et al. **Intensive Insulin Therapy in Hospitalized Patients**: A Systematic Review. *Ann Intern Med* February 15, 2011 154:268-282.
133. Qaseem Amir, Humphrey Linda L., Chou Roger, et al. and for the Clinical Guidelines Committee of the American College of Physicians. Use of **Intensive Insulin Therapy for the Management of Glycemic Control in Hospitalized Patients**: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med* February 15, 2011 154:260-267.
134. Zinman Bernard, Fulch e Greg r, Rao Paturi V. **Insulin degludec**, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial. *The Lancet*, Early Online Publication, 10 March 2011. doi:10.1016/S0140-6736(10)62305-7
135. Morgan CL, Evans M, Toft AD, et al. Clinical Effectiveness of Biphasic Insulin **Aspart 30:70** Vs Biphasic Human Insulin 30 in UK General Clinical Practice: A Retrospective Database Study. *Clin Ther*. 2011 Jan;33(1):27-35.
136. Hovorka R, Kumareswaran K, Harris J, Allen JM, Elleri D, Xing D, et al. **Overnight closed loop insulin delivery (artificial pancreas)** in adults with type 1 diabetes: crossover randomised controlled studies. *BMJ* 2011;342:1855.
137. Buse JB, Wolfenbutter BH, Herman WH, et al. **DURABLE** of Basal versus Lispro mix 75/25 insulin Efficacy (DURABLE) Trial: Comparing the durability of lispro mix 75/25 and glargine. *Diabetes Care*. 2011 Feb;34(2):249-55.
138. Hamaty M. **Insulin treatment for type 2 diabetes**: When to start, which to use *Cleveland Clinic Journal of Medicine* 2011; 78(5):332-342; doi:10.3949/ccjm.78a.10051.
139. Korownyk C, Ivers N, Allan GM. Strategies for **initiating insulin** in type 2 diabetes. *Can Fam Physician*. 2011 May;57(5):562.
140. Umpierrez GE, Hor T, Smiley D, et al. Comparison of inpatient insulin regimens with **detemir plus aspart versus neutral protamine Hagedorn plus regular** in medical patients with type 2 diabetes. (*DEAN*) *J Clin Endocrinol Metab* 2009; 94:564–569.
141. Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care* 2011; 34:256–261.
142. Umpierrez GE, Smiley D, Zisman A, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care* 2007; 30:2181–2186.
143. Umpierrez GE, How to manage type 2 diabetes in **medical and surgical patients in the hospital**. *Cleveland Clinic Journal of Medicine* 2011; 78(6):379-384; doi:10.3949/ccjm.78gr.11001.
144. Rogal SS, Ukomadu C, Levy BD, Loscalzo J. Clinical problem-solving. A sweet source of abdominal pain. (Glycogenic hepatopathy) *N Engl J Med*. 2011 May 5;364(18):1762-7.
145. Ajay Varanasi, Natalie Bellini, Deepti Rawal, et al. **Liraglutide** as Additional Treatment in Type 1 Diabetes *Eur J Endocrinol* 2011 EJE-11-0330.
146. Levin Philip A., Zhang Quanwu, Mersey James H., et al. Glycemic Control With Insulin **Glargine Plus Insulin Glulisine Versus Premixed Insulin Analogues** in Real-World Practices: A Cost-Effectiveness Study With a Randomized Pragmatic Trial Design, Clinical Therapeutics, In Press, Corrected Proof, Available online 30 June 2011.
147. Pickup John C, Freeman Suzanne C, Sutton Alex J. Glycaemic control in type 1 diabetes during real time **continuous glucose monitoring** compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ* 2011;343:doi:10.1136/bmj.d3805 (7 July 2011)
148. Zachariah S, Sheldon B, Shojaae-Moradie F, et al. **Insulin detemir reduces weight gain** as a result of reduced food intake in patients with type 1 diabetes. *Diabetes Care*. 2011 Jul;34(7):1487-91.
149. Petznick A. **Insulin management** of type 2 diabetes mellitus. *Am Fam Physician*. 2011 Jul 15;84(2):183-90.
150. Cohen D. The prickly problem of **access to insulin**. *BMJ*. 2011 Sep 14;343:d5782. doi: 10.1136/bmj.d5782.
151. Blair JC, Peak M, Gregory JW. What is the best way to deliver subcutaneous **insulin to infants, children, and young people** with type 1 diabetes mellitus? *BMJ*. 2011 Sep 2;343:d5221.
152. Ruiter R, Visser LE, van Herk-Sukel MP, et al. Risk of **cancer in patients on insulin glargine and other insulin analogues** in comparison with those on human insulin: results from a large population-based follow-up study. *Diabetologia*. 2011 Sep 29.
153. Rascati KL, Richards KM, Lopez D, et al. **Progression to Insulin** for Patients with Diabetes Mellitus Using the Texas Medicaid Database. *Clin Ther*. 2011 Nov 17.
154. Bellolio MF, Gilmore RM, Stead LG. **Insulin** for glycaemic control in acute **ischaemic stroke**. *Cochrane Database Syst Rev*. 2011;(9): CD005346. Starting intravenous insulin within the first 24 hours of acute ischemic stroke to maintain normoglycemia does not reduce death or dependency but increases the risk for hypoglycemia.
155. Gray CS, Hildreth AJ, Sandercock PA, et al; GIST Trialists Collaboration. **Glucose-potassium-insulin infusions** in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol*. 2007;6:397-406.
156. Tibaldi JM. Intensifying insulin therapy in type 2 diabetes mellitus: dosing options for **insulin analogue premixes**. *Clin Ther*. 2011 Nov;33(11):1630-42.
157. Rascati KL et al. **Progression to insulin** for patients with diabetes mellitus using the Texas medicaid database. *Clin Ther*. 2011 Dec;33(12):2016-20. (slower progression with metformin/TZD than sulfonylurea/TZD)
158. Lee P, Chang A, Blaum C, Vlainic A, Gao L, Halter J. Comparison of safety and efficacy of **insulin glargine and neutral protamine hagedorn** insulin in older adults with type 2 diabetes mellitus: results from a pooled analysis. *J Am Geriatr Soc*. 2012 Jan;60(1):51-9.
159. Ng KW, Allen ML, Desai A et al. **Cardioprotective effects of insulin**: how intensive insulin therapy may benefit cardiac surgery patients. *Circulation*. 2012 Feb 7;125(5):721-8.
160. Heller S, Buse J, Fisher M, et al, on behalf of the **BEGIN Basal-Bolus Type 1** Trial Investigators. **Insulin degludec**, an ultra-longacting basal insulin, **versus insulin glargine** in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012; 379: 1489–97.
161. Garber AJ, King AB, Del Prato S, et al, on behalf of the NN1250–3582 (BEGIN BB T2D) Trial Investigators. **Insulin degludec**, an ultra-longacting basal insulin, **versus insulin glargine** in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012; 379: 1498–507.
162. Lau AN, Tang T, Halapy H, Thorpe K, Yu CH. **Initiating insulin** in patients with type 2 diabetes. *CMAJ*. 2012 Apr 2.
163. Pickup JC. **Insulin-pump** therapy for type 1 diabetes mellitus. *N Engl J Med*. 2012 Apr 26;366(17):1616-24.
164. Donner T, Muñoz M. **Update on insulin** therapy for type 2 diabetes. *J Clin Endocrinol Metab*. 2012 May;97(5):1405-13.
165. Lasserson D, Fox R, Farmer A. **Late onset type 1 diabetes**. *BMJ*. 2012 Apr 30;344:e2827.
166. Mauras N, Beck R, Xing D, et al. A randomized clinical trial to assess the efficacy and safety of **real-time continuous glucose monitoring** in the management of type 1 diabetes in young children aged 4 to <10 years. *Diabetes Care*. 2012 Feb;35(2):204-10.
167. Aschner PJ, Chan J, Owens DR, et al, **EASIE** investigators. **Insulin glargine versus sitagliptin** in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised, open-label trial. *Lancet* 2012; online June 9.
168. **ORIGIN** Trial Investigators. Basal insulin (glargine) and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012 Jun 11; [e-pub ahead of print].
169. Chang CH, Lin JW, Wu LC, Lai MS, Chuang LM. Oral Insulin Secretagogues, Insulin, and **Cancer Risk** in Type 2 Diabetes Mellitus. *J Clin Endocrinol Metab*. 2012 May 4.
170. Baldwin D, Zander J, Munoz C, et al. A Randomized Trial of Two Weight-Based Doses of **Insulin Glargine and Glulisine** in Hospitalized Subjects With Type 2 Diabetes and **Renal Insufficiency**. *Diabetes Care*. 2012 Jun 14.
171. Rosso C, Corvol JC, Pires C, et al. Intensive Versus Subcutaneous Insulin in Patients With **Hyperacute Stroke**: Results From the Randomized **INSULINFARCT** Trial. *Stroke*. 2012 Jun 14.
172. Mathiesen ER, Hod M, Ivanisevic M, et al. Maternal Efficacy and Safety Outcomes in a Randomized, Controlled Trial Comparing **Insulin Detemir With NPH** Insulin in 310 **Pregnant** Women With T1DM. *Diabetes Care*. 2012 Jul 30.

173. Yeh HC, Brown TT, et al. Comparative Effectiveness and Safety of Methods of **Insulin Delivery and Glucose Monitoring** for Diabetes Mellitus: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2012 Jul 10;E-508.
174. Rosso C, Corvol JC, Pires C, et al. **Intensive Versus Subcutaneous Insulin** in Patients With **Hyperacute Stroke**: Results From the Randomized INSULINFARCT Trial. *Stroke.* 2012 Sep;43(9):2343-9.
175. Gale EA. **Newer insulins** in type 2 diabetes. *BMJ.* 2012 Sep 11;345:e4611.
176. Testa MA et al. Comparative effectiveness of **basal-bolus versus premix** analog insulin on glycemic variability and patient-centered outcomes during insulin intensification in type 1 and type 2 diabetes: A randomized, controlled, crossover trial. *J Clin Endocrinol Metab* 2012 Oct; 97:3504.
177. Cornish A, Chase HP. Navigating **Airport Security** with an Insulin Pump and/or Sensor. *Diabetes Technol Ther.* 2012 Nov;14(11):984-5.
178. Freemantle N, Meneghini L, Christensen T, et al. **Insulin degludec** improves health-related quality of life (SF-36((R))) compared with insulin glargine in people with Type 2 diabetes starting on basal insulin: a meta-analysis of phase 3a trials. *Diabet Med.* 2013 Feb;30(2):226-32.
179. Thalange N, Bereket A, Larsen J, et al. Insulin analogues (**detemir vs NPH**) in children with Type 1 diabetes: a 52-week randomized clinical trial. *Diabet Med.* 2013 Feb;30(2):216-25.
180. Fox CS. **Weighty Matters**: Balancing Weight Gain with Cardiovascular Risk among Patients with Type 1 Diabetes Mellitus on Intensive **Insulin** Therapy. *Circulation.* 2013 Jan 15;127(2):157-9.
181. Zinman B, Philis-Tsimikas A, Cariou B, et al; NN1250-3579 (BEGIN Once Long) Trial Investigators. **Insulin degludec versus insulin glargine** in insulin-naïve patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care.* 2012 Dec;35(12):2464-71.
182. Muller N, Frank T, Kloos C, et al. Randomized Crossover Study to Examine the Necessity of an **Injection-to-Meal Interval** in Patients With Type 2 Diabetes Mellitus and Human Insulin. *Diabetes Care.* 2013 Jan 22.
183. Haidar A, Legault L, et al. Glucose-responsive insulin and glucagon delivery (dual-hormone **artificial pancreas**) in adults with type 1 diabetes: a randomized crossover controlled trial. *CMAJ.* 2013 Mar 5;185(4):297-305.
184. Phillip M, Battelino T, Atlas E, et al. Nocturnal glucose control with an **artificial pancreas** at a diabetes camp. *N Engl J Med.* 2013 Feb 28;368(9):824-33.
185. Balena R, Hensley IE, Miller S, et al. Combination therapy with **GLP-1 receptor agonists and basal insulin**: a systematic review of the literature. *Diabetes Obes Metab.* 2012 Oct 15.
186. Currie CJ et al. **Mortality and other important diabetes-related outcomes** with insulin vs other antihyperglycemic therapies in type 2 diabetes. *J Clin Endocrinol Metab* 2013; 98: 668-77.
187. Wang L, Wei W, Miao R, et al with **insulin glargine** or neutral protamine Hagedorn insulin: a comparative retrospective database study. *BMJ Open.* 2013 Apr 30;3(4).
188. Meneghini L, Kesavadev J, Demissie M, et al. Once-daily initiation of **basal insulin as add-on to metformin**: a 26-week, randomized, treat-to-target trial comparing **insulin detemir with insulin glargine** in patients with type 2 diabetes. *Diabetes Obes Metab.* 2013 Feb 19.
189. Bergenstal RM, Klonoff DC, Garg SK, et al; the ASPIRE In-Home Study Group. **Threshold-Based Insulin-Pump** Interruption for Reduction of Hypoglycemia. *N Engl J Med.* 2013 Jun 22.
190. Jacobi J, Bircher N, Krinsley J, Agus M, et al. Guidelines for the use of an **insulin infusion** for the management of hyperglycemia in **critically ill patients**. *Crit Care Med.* 2012 Dec;40(12):3251-76.
191. Dailey GE, Gao L, Aurand L, et al. Impact of diabetes duration on **hypoglycaemia** in patients with type 2 diabetes treated with insulin **glargine or NPH** insulin. *Diabetes Obes Metab.* 2013 May 17.
192. Ly TT, Nicholas JA, et al. Effect of **sensor-augmented insulin pump** therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA.* 2013;310(12):1240-1247.
193. Grimaldi-Bensouda L, Cameron D, Marty M, et al. Risk of **breast cancer by individual insulin use** - an international multicenter study. *Diabetes Care.* 2013 Aug 15.
194. Ziegler R, Cavan DA, Cranston I, et al. Use of an **Insulin Bolus Advisor** Improves Glycemic Control in Multiple Daily Insulin Injection (MDI) Therapy Patients With Suboptimal Glycemic Control: First results from the ABACUS trial. *Diabetes Care.* 2013 Jul 30.
195. Sturmer T, Marquis MA, Zhou H, et al. **Cancer** Incidence Among Those Initiating Insulin Therapy With **Glargine Versus Human NPH** Insulin. *Diabetes Care.* 2013 Jul 22.
196. Spaulonci CP, Bernardes LS, Trindade TC, et al. Randomized trial of **metformin vs insulin in the management of gestational** diabetes. *Am J Obstet Gynecol.* 2013 Jul;209(1):34.e1-34.e7.
197. Geller AI, Shehab N, Lovegrove MC, et al. National estimates of **insulin-related hypoglycaemia** and errors leading to emergency department visits and hospitalizations [online March 10, 2014]. *JAMA Intern Med.* 2013.
198. Wallace JP, Wallace JL, McFarland MS. Comparing dosing of **Basal insulin analogues detemir and glargine**: is it really unit-per-unit and dose-per-dose? *Ann Pharmacother.* 2014 Mar;48(3):361-8.
199. Habel LA, Danforth KN, Quesenberry CP, et al. Cohort study of insulin **glargine and risk of breast, prostate, and colorectal cancer** among patients with diabetes. *Diabetes Care.* 2013 Dec;36(12):3953-60.
200. Mathieu C, Rodbard HW, Cariou B, et al. A comparison of adding **liraglutide** versus a single daily dose of **insulin aspart to insulin degludec** in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). *Diabetes Obes Metab.* 2014 Jan 20.
201. Bordeleau L, Yakubovich N, Dagenais GR, et al. for the ORIGIN Trial Investigators. The Association of **Basal Insulin Glargine and/or n-3 Fatty Acids With Incident Cancers** in Patients With Dysglycemia. *Diabetes Care.* 2014 Feb 26.
202. Pawaskar M, Tuttle KR, et al. Observational Study of Kidney Function and Albuminuria in Patients With Type 2 Diabetes Treated With **Exenatide BID Versus Insulin Glargine**. *Ann Pharmacother.* 2014 May;48(5):571-6.
203. Lane W, Weinrib S, Rappaport J, et al. The effect of addition of **liraglutide to high-dose intensive insulin** therapy: a randomized prospective trial. *Diabetes Obes Metab.* 2014 Mar 3.
204. Bu W, Song L, Zhao D, et al. **Insulin therapy and the risk of colorectal cancer** in patients with type 2 diabetes: a meta-analysis of observational studies. *British Journal of Clinical Pharmacology.* 2014.
205. The **ORIGIN** trial investigators, Gilbert RE, Mann JF, Hanefeld M, Spinas G, et al. **Basal insulin glargine** and microvascular outcomes in dysglycaemic individuals: results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial. *Diabetologia.* 2014 Apr 26.
206. Fulcher GR, Christiansen JS, Bantwal G, et al. Comparison of Insulin **Degludec/Insulin Aspart and Biphasic Insulin Aspart 30** in Uncontrolled, Insulin-Treated Type 2 Diabetes: A Phase 3a, Randomized, Treat-to-Target Trial. *Diabetes Care.* 2014 May 9.
207. Wallia A, MolitchME. **Insulin therapy** for type 2 diabetes mellitus. *JAMA.* doi:10.1001/jama.2014.5951.
208. Cukierman-Yaffe T, Bosch J, Diaz R, et al. for the **ORIGIN** Investigators. Effects of **basal insulin glargine and omega-3 fatty acid on cognitive** decline and probable cognitive impairment in people with dysglycaemia: a substudy of the ORIGIN trial. *Lancet Diabetes Endocrinol.* 2014 May 30. pii: S2213-8587(14)70062-2.
209. Jin J. **Starting Insulin Treatment** for Diabetes. *JAMA.* 2014 Jun 11;311(22):2347.
210. Reznik Y, Cohen O, Aronson R, et al, for the **OpT2mise** Study Group. **Insulin pump treatment compared with multiple daily injections** for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. *Lancet* 2014; online July 3.
211. Rosenstock J, Fonseca VA, Gross JL, et al; for the Harmony-6 Study Group. Advancing Basal Insulin Replacement in Type 2 Diabetes Inadequately Controlled With Insulin **Glargine Plus Oral Agents**: A Comparison of Adding **Albiglutide**, a Weekly GLP-1 Receptor Agonist, Versus Thrice-Daily Prandial Insulin **Lispro**. *Diabetes Care.* 2014 Jun 4.
212. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient Glycemic Control with a **Bionic Pancreas** in Type 1 Diabetes. *N Engl J Med.* 2014 Jun 15.
213. Tinahones FJ, Gross JL, Onaca A, et al. **Insulin lispro low mixture twice daily versus basal insulin glargine once daily and prandial insulin lispro** once daily in patients with type 2 diabetes requiring insulin intensification: a randomized phase IV trial. *Diabetes Obes Metab.* 2014 Apr 11.
214. Reznik Y, Cohen O, Aronson R, et al; for the **OpT2mise** Study Group. **Insulin pump treatment compared with multiple daily injections** for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. *Lancet.* 2014 Jul 2.
215. Davies MJ, Gross JL, Ono Y, et al.; on behalf of the BEGIN BB T1 study group. Efficacy and safety of **insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart** in type 1 diabetes: a 26-week randomized, open-label, treat-to-target non-inferiority trial. *Diabetes Obes Metab.* 2014 Apr 7.
216. Riddle MC, Bolli GB, Ziemien M, et al. New Insulin **Glargine 300 Units/mL Versus Glargine 100** Units/mL in People With Type 2 Diabetes Using Basal and Mealtime Insulin: Glucose Control and Hypoglycemia in a 6-Month Randomized Controlled Trial (EDITION 1). *Diabetes Care.* 2014 Jul 30. pii: DC_140991.
217. Santos Cavaioia T, Edelman S. **Inhaled Insulin**: A Breath of Fresh Air? A Review of Inhaled Insulin. *Clin Ther.* 2014 Jul 17.
218. Li X, Du T, Li W, et al. Efficacy and Safety of **Weight-Based Insulin Glargine Dose** Titration Regimen Compared With Glucose Level- and Current Dose-Based Regimens in Hospitalized Patients With Type 2 Diabetes: A Randomized, Controlled Study. *Clin Ther.* 2014 Jul 22.

219. Edelman SV, Liu R, Johnson J, et al. **AUTONOMY**: The First Randomized Comparing Two Patient-Driven Approaches to Initiate and **Titrate Prandial Insulin Lispro** in Type 2 Diabetes. *Diabetes Care*. 2014 Aug;37(8):2132-40.
220. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of **long acting versus intermediate acting insulin for patients with type 1 diabetes**: systematic review and network meta-analysis. *BMJ*. 2014 Oct 1;349:g5459.
221. Buse JB, Vilsbøll T, Thurman J, et al; on behalf of the NN9068-3912 (DUAL-II) Trial Investigators. Contribution of Liraglutide in the Fixed-Ratio Combination of Insulin Degludec and Liraglutide (IDegLira). *Diabetes Care*. 2014 Aug 11.
222. Gough SC, Bode B, Woo V, et al; the NN9068-3697 (DUAL-I) trial investigators. Efficacy and safety of a fixed-ratio combination of **insulin degludec and liraglutide (IDegLira)** compared with its components **given alone**: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naïve patients with type 2 diabetes. *Lancet Diabetes Endocrinol*. 2014 Sep 1.
223. Nallasamy K, Jayashree M, Singhi S, et al. **Low-Dose vs Standard Dose Insulin in Pediatric Diabetic Ketoacidosis**: A Randomized Clinical Trial. *JAMA Pediatr*. 2014 Sep 29.
224. Haidar A, Legault L, Messier V, et al. Comparison of dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy for glycaemic control in patients with type 1 diabetes: an open-label randomised controlled crossover trial. *Lancet Diabetes Endocrinol*. 2014 Nov 26.
225. Sabin MA, Magnussen CG, Juonala M, et al. **Insulin and BMI** as Predictors of Adult Type 2 Diabetes Mellitus. *Pediatrics*. 2015 Jan;135(1):e144-51.
226. Nuffer W, Trujillo JM, Ellis SL. **Technosphere Insulin (Afrezza)**: A New, Inhaled Prandial Insulin. *Ann Pharmacother*. 2015 Jan;49(1):99-106.
227. Yki-Jarvinen H, Bergenstal R, Ziemien M, et al. New **Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL** in People With Type 2 Diabetes Using Oral Agents and Basal Insulin: Glucose Control and Hypoglycemia in a 6-Month Randomized Controlled Trial (EDITION 2). *Diabetes Care*. 2014 Dec;37(12):3235-43. Gla-300 was as effective as Gla-100 and associated with a lower risk of hypoglycemia during the night and at any time of the day.
228. Buse JB, Peters A, Russell-Jones D, et al. Is **insulin the most effective injectable antihyperglycaemic therapy?** *Diabetes Obes Metab*. 2014 Oct 17.
229. Haidar A, Legault L, Messier V, et al. Comparison of dual-hormone **artificial pancreas**, single-hormone artificial pancreas, and conventional insulin pump therapy for glycaemic control in patients with type 1 diabetes: an open-label randomised controlled crossover trial. *Lancet Diabetes Endocrinol*. 2015 Jan;3(1):17-26.
230. Home PD, Bolli GB, Mathieu C, et al. Modulation of insulin dose titration using a **hypoglycaemia-sensitive algorithm**: insulin glargine versus neutral protamine Hagedorn insulin in insulin-naive people with type 2 diabetes. *Diabetes Obes Metab*. 2015 Jan;17(1):15-22.
231. Greene JA, Riggs KR. Why is there **no generic insulin**? Historical origins of a modern problem. *N Engl J Med*. 2015 Mar 19;372(12):1171-5.
232. Heinemann L, Fleming GA, Petrie JR, et al. **Insulin pump risks and benefits**: a clinical appraisal of pump safety standards, adverse event reporting and research needs. A Joint Statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. *Diabetologia*. 2015 Mar 18.
233. Bonifacio E, Ziegler A-G, Klingensmith G, et al; **Pre-POINT** Study Group. Effects of **high-dose oral insulin** on immune responses in children at **high risk for type 1 diabetes**: the Pre-POINT randomized clinical trial. *JAMA*. doi:10.1001/jama.2015.2928.
234. Zhao L, Sheng X, Zhou S, et al. **Metformin versus insulin for gestational diabetes mellitus**: a meta-analysis. *Br J Clin Pharmacol*. 2015 Apr 29.
235. Ali A, Cheng AY, Yu CH. Breaking down **barriers to initiating insulin**: Insulin prescription pad. *Can Fam Physician*. 2015 May;61(5):445-7.
236. Tran L, Zielinski A, Roach AH, et al. Pharmacologic Treatment of Type 2 **Diabetes: Injectable Medications**. *Ann Pharmacother*. 2015 Jun;49(6):700-714.
237. Wang C, Mamza J, Idris I. **Biphasic vs basal bolus insulin** regimen in Type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabet Med*. 2015 May;32(5):585-94.
238. Luo J, Avorn J, Kesselheim AS. **Trends in Medicaid Reimbursements for Insulin** From 1991 Through 2014. *JAMA Intern Med*. 2015 Aug 24.
239. Tylee T, Hirsch IB. **Costs Associated With Using Different Insulin Preparations**. *JAMA*. 2015 Aug 18;314(7):665-6.
240. Steineck I, Cederholm J, Eliasson B, et al; Swedish National Diabetes Register. **Insulin pump therapy, multiple daily injections, and cardiovascular mortality** in 18 168 people with type 1 diabetes: observational study. *BMJ*. 2015 Jun 22;350:h3234.
241. Goldman J, White JR Jr. New **Insulin Glargine 300 U/mL** for the Treatment of Type 1 and Type 2 Diabetes Mellitus. *Ann Pharmacother*. 2015 Oct;49(10):1153-61.
242. Lee YY, Lin YM, Leu WJ, et al. **Sliding-scale insulin** used for blood glucose control: a meta-analysis of randomized controlled trials. *Metabolism*. 2015 Sep;64(9):1183-92.
243. Buse JB, Rodbard HW, Trescoli Serrano C, et al.**IMAGINE 5** Investigators. Randomized Clinical Trial Comparing Basal **Insulin Peglispro and Insulin Glargine** in Patients With Type 2 Diabetes Previously Treated With Basal Insulin: IMAGINE 5. *Diabetes Care*. 2015 Nov 17.
244. Buse JB, Rodbard HW, Trescoli Serrano C, et al.**IMAGINE 5** Investigators. Randomized Clinical Trial Comparing Basal **Insulin Peglispro and Insulin Glargine** in Patients With Type 2 Diabetes Previously Treated With Basal Insulin: IMAGINE 5. *Diabetes Care*. 2015 Nov 17.
245. Roze S, Smith-Palmer J, Valentine W, et al. **Cost-effectiveness of continuous subcutaneous insulin infusion versus multiple daily injections** of insulin in Type 1 diabetes: a systematic review. *Diabet Med*. 2015 Nov;32(11):1415-24.
246. **ORIGIN** Trial Investigators. **Cardiovascular and Other Outcomes** Postintervention With **Insulin Glargine and Omega-3 Fatty Acids (ORIGINALE)**. *Diabetes Care*. 2015 Dec 17.
247. Lingvay I, Manghi FP, García-Hernández P, et al; **DUAL V Investigators**. Effect of Insulin **Glargine Up-titration vs Insulin Degludec/Liraglutide** on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes: The **DUAL V** Randomized Clinical Trial. *JAMA*. 2016 Mar 1;315(9):898-907.
248. Boghossian NS, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Outcomes of **Extremely Preterm Infants** Born to Insulin-Dependent Diabetic Mothers. *Pediatrics*. 2016 May 13.
249. Herrera KM, Rosenn BM, Foroutan J, et al. Randomized controlled trial of **insulin detemir versus NPH** for the treatment of pregnant women with diabetes. *Am J Obstet Gynecol*. 2015 Sep;213(3):426.e1-7.
250. Holden SE, Jenkins-Jones S, Currie CJ. Association between **Insulin Monotherapy versus Insulin plus Metformin** and the Risk of All-Cause Mortality and Other Serious Outcomes: A Retrospective Cohort Study. *PLoS One*. 2016 May 6;11(5):e0153594.
251. Munshi MN, Slyne C, Segal AR, et al. Simplification of Insulin Regimen in Older Adults and **Risk of Hypoglycemia**. *JAMA Intern Med*. 2016 Jun 6.
252. Zargham H, O'Brien E. **Cutaneous sarcoidosis** at insulin injection sites. *CMAJ*. 2016 Jun 14;188(9):674.
253. Frid AH, Kreugel G, Grassi G, et al. **New Insulin Delivery Recommendations**. *Mayo Clin Proc*. 2016 Sep;91(9):1231-55.
254. Peters AL, Ahmann AJ, et al. Diabetes Technology-**Continuous Subcutaneous Insulin Infusion Therapy and Continuous Glucose Monitoring in Adults: An Endocrine Society Clinical Practice Guideline**. *J Clin Endocrinol Metab*. 2016 Sep 2;jc20162534
255. Fath M, Danne T, Biester T, et al. **Faster-acting insulin aspart** provides faster onset and greater early exposure vs insulin aspart in children and adolescents with type 1 diabetes mellitus. *Pediatr Diabetes*. 2017 Feb 6.
256. Strich D, Balagour L, Shenker J, et al. **Lower Basal Insulin Dose** is Associated with Better Control in Type 1 Diabetes. *J Pediatr*. 2016 Dec 12.
257. Yuan T, Zhao W, Wang L, et al. Continuous Subcutaneous **Insulin Infusion** as an Effective Method of **Desensitization Therapy** for Diabetic Patients with **Insulin Allergy**: A 4-year Single-Center Experience. *Clin Ther*. 2016 Oct 25.
258. Russell-Jones D, et al. **Fast-Acting Insulin Aspart** Improves Glycemic Control in Basal-Bolus Treatment for Type 1 Diabetes: a 26-Week Multicenter, Active-Controlled, Treat-to-Target, Randomized, Parallel-Group Trial (Onset 1). *Diabetes Care*. 2017 Mar 29.
259. Turksøy K, Frantz N, Quinn L, et al. **Automated Insulin Delivery**-The Light at the End of the Tunnel. *J Pediatr*. 2017 Apr 7.
260. **REPOSE** Study Group. Relative effectiveness of **insulin pump treatment over multiple daily injections** and structured education during flexible intensive insulin treatment for type 1 diabetes: cluster randomised trial (REPOSE). *BMJ*. 2017 Mar 30;356:j1285
261. Baidal DA, Ricordi C, Berman DM, Alvarez et al. **Bioengineering of an Intraabdominal Endocrine Pancreas**. *N Engl J Med*. 2017 May 11;376(19):1887-1889.
262. Pickup JC, Reznik Y, Sutton AJ. Glycemic Control During **Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Insulin Injections** in Type 2 Diabetes: Individual Patient Data Meta-analysis and Meta-regression of Randomized Controlled Trials. *Diabetes Care*. 2017 May;40(5):715-722.

263. Campbell M, Walker Mark, Ajjan Ramzi A, Ajjan Ramzi A, et al. An **additional bolus of rapid-acting insulin to normalise postprandial cardiovascular risk factors** following a high-carbohydrate high-fat meal in patients with type 1 diabetes: A randomised controlled trial. *Diab Vasc Dis Res.* 2017 Mar 1;1479164117698918.
264. Baidal DA, Ricordi C, Berman DM, Alvarez et al. **Bioengineering of an Intraabdominal Endocrine Pancreas.** *N Engl J Med.* 2017 May 11;376(19):1887-1889.
265. Pickup JC, Reznik Y, Sutton AJ. **Glycemic Control During Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Insulin Injections** in Type 2 Diabetes: Individual Patient Data Meta-analysis and Meta-regression of Randomized Controlled Trials. *Diabetes Care.* 2017 May;40(5):715-722.
266. Marso SP, McGuire DK, Zinman B, et al. Efficacy and Safety of **Degludec versus Glargine** in Type 2 Diabetes. (**DEVOTE**) *N Engl J Med.* 2017 Jun 12
267. Lane W, Bailey TS, Gerety G, et al. Effect of **insulin degludec vs insulin glargine U100** on hypoglycemia in patients with type 1 diabetes: the **SWITCH 1** randomized clinical trial. *JAMA.* doi:10.1001/jama.2017.7115
268. Wysham C, Bhargava A, Chaykin L, et al. Effect of **insulin degludec vs insulin glargine U100** on hypoglycemia in patients with type 2 diabetes: the **SWITCH 2** randomized clinical trial. *JAMA.* doi:10.1001/jama.2017.7117
269. Wu JW, Azoulay L, Majdan A, et al. Long-Term Use of **Long-Acting Insulin Analogs and Breast Cancer** Incidence in Women With Type 2 Diabetes. *J Clin Oncol.* 2017 Sep 27;JCO2017734491.
270. **ADA 2018:** American Diabetes Association. 14. **Diabetes Care in the Hospital:** Standards of Medical Care in Diabetes-2018. *Diabetes Care.* 2018 Jan;41(Suppl 1):S144-S151.
- ADA 2018:** American Diabetes Association. 13. **Management of Diabetes in Pregnancy:** Standards of Medical Care in Diabetes-2018. *Diabetes Care.* 2018 Jan;41(Suppl 1):S137-S143.
- ADA 2018:** American Diabetes Association. 12. **Children and Adolescents:** Standards of Medical Care in Diabetes-2018. *Diabetes Care.* 2018 Jan;41(Suppl 1):S126-S136.
- ADA 2018:** American Diabetes Association. 11. **Older Adults:** Standards of Medical Care in Diabetes-2018. *Diabetes Care.* 2018 Jan;41(Suppl 1):S119-S125. Jan;41(Suppl 1):S86-S104.
- ADA 2018:** American Diabetes Association. 8. **Pharmacologic Approaches to Glycemic Treatment:** Standards of Medical Care in Diabetes-2018. *Diabetes Care.* 2018 Jan;41(Suppl 1):S73-S85.
271. Anyanwagu U, Mamza J, Gordon J, et al. **Premixed vs basal-bolus insulin** regimen in Type 2 diabetes: comparison of clinical outcomes from randomized controlled trials and real-world data. *Diabet Med.* 2017 Dec;34(12):1728-1736.
272. Gerstein HC, Jung H, Rydén L, et al. Effect of Basal Insulin **Glargine** on First and Recurrent Episodes of **Heart Failure** Hospitalization: The **ORIGIN** Trial (Outcome Reduction With Initial Glargine Intervention). *Circulation.* 2018 Jan 2;137(1):88-90
273. Howard-Thompson A, Khan M, Jones M et al. Type 2 Diabetes Mellitus: **Outpatient Insulin Management.** *Am Fam Physician.* 2018;97(1):29-37.
274. Gazzina S, Alberici A, Padovani A, et al. **Myoclonic dystonia (DYT11) responsive to insulin therapy:** A case report. *Neurology.* 2017 Aug 1;89(5):517-518.
275. Gerstein HC, Jung H, Rydén L, et al; **ORIGIN** Investigators. Effect of Basal Insulin **Glargine** on First and Recurrent Episodes of **Heart Failure Hospitalization:** The **ORIGIN** Trial (Outcome Reduction With Initial Glargine Intervention). *Circulation.* 2018 Jan 2;137(1):88-90.
276. Home PD;Bergenstal RM;Bolli GB;Ziemen M;Rojeski M;. Glycaemic control and hypoglycaemia during 12 months of randomized treatment with **insulin glargine 300 U/mL versus glargine 100 U/mL** in people with type 1 diabetes (**EDITION 4**). *Diabetes Obes Metab.* 2017 Jun 29.
277. Yamada T, Kamata R, Ishinohachi K, et al. **Biosimilar vs originator insulins:** Systematic review and meta-analysis. *Diabetes Obes Metab.* 2018 Mar 14.
278. Crowley MJ, Maciejewski ML. Revisiting **NPH Insulin for Type 2 Diabetes:** Is a Step Back the Path Forward? *JAMA.* 2018 Jul 3;320(1):38-39.
279. Lipska KJ, Parker MM, Moffet HH, et al. Association of **Initiation of Basal Insulin Analogs vs Neutral Protamine Hagedorn Insulin With Hypoglycemia**-Related Emergency Department Visits or Hospital Admissions and With Glycemic Control in Patients With Type 2 Diabetes. *JAMA.* 2018 Jul 3;320(1):53-62.
280. Madenidou AV, Paschos P, Karagiannis T, et al. Comparative **Benefits and Harms of Basal Insulin Analogues for Type 2 Diabetes:** A Systematic Review and Network Meta-analysis. *Ann Intern Med.* 2018 Jul 10.
281. Blair J, McKay A, Ridyard C, et al. **Continuous subcutaneous insulin infusion versus multiple daily injections in children and young people** at diagnosis of type 1 diabetes: the **SCIPI** RCT. *Health Technol Assess.* 2018 Aug;22(42):1-112.
282. Lopez PE, Evans M, King BR, et al. A randomized comparison of **three prandial insulin dosing algorithms for children and adolescents** with Type 1 diabetes. *Diabet Med.* 2018 Jun 5.
283. Rosenstock J, Cheng A, Ritzel R, et al. More Similarities Than Differences Testing **Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL** in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head **BRIGHT** Trial. *Diabetes Care.* 2018 Oct; 41(10):2147-2154.
284. Holmes RS, Crabtree E, McDonagh MS. Comparative effectiveness and **harms of long-acting insulins for type 1 and type 2 diabetes:** A systematic review and meta-analysis. *Diabetes Obes Metab.* 2018 Dec 15.
285. Luo J, Khan NF, Manetti T, et al. Implementation of a health plan program for **switching from analogue to human insulin** and glycemic control among Medicare beneficiaries with type 2 diabetes [Jan 29, 2019]. *JAMA.* doi:10.1001/jama.2018.21364
286. Bergenstal RM, Johnson M, Passi R, et al. **Automated insulin dosing guidance** to optimize insulin management in patients with type 2 diabetes: a multicentre, randomised controlled trial. *Lancet* 2019; published online Feb 23.
287. Goldstein JN, Patel RM, Bland K, Hicks LS. **Frequency of Sale and Reasons for Purchase** of Over-the-Counter Insulin In the United States. *JAMA Intern Med.* 2019 Feb 18.
288. Paldus B, Lee MH, O'Neal DN. **Insulin pumps in general practice.** *Aust Prescr.* 2018 Dec;41(6):186-190
289. Blonde L, Rosenstock J, Del Prato S, et al. Switching to **iGlarLixi Versus Continuing Daily or Weekly GLP-1 RA** in Type 2 Diabetes Inadequately Controlled by GLP-1 RA and Oral Antihyperglycemic Therapy: The **LixiLan-G** Randomized Clinical Trial. *Diabetes Care.* 2019 Sep 17.
290. Philis-Tsimikas A, Billings LK, Busch R, et al. Superior efficacy of insulin **degludec/liraglutide versus insulin glargine U100** as add-on to sodium-glucose co-transporter-2 inhibitor therapy: A randomized clinical trial in people with uncontrolled type 2 diabetes. *Diabetes Obes Metab.* 2019 Feb 13.
291. Health Canada Jun/19: is advising patients and health care providers that certain older **Medtronic MiniMed 508 and MiniMed Paradigm insulin pumps** distributed between 2010 and 2015
292. Feldman WB, Rome BN, Lehmann LS, Kesselheim AS. Estimation of **Medicare Part D Spending on Insulin** for Patients With Diabetes Using Negotiated Prices and a Defined Formulary. *JAMA Intern Med.* 2020 Feb 3. doi:10.1001/jamainternmed.2019.7018.
293. Lee TY, Kuo S, Yang CY, Ou HT. **Cost-effectiveness of long-acting insulin analogues versus intermediate/long-acting human insulin** for type 1 diabetes: a population-based cohort following over 10 years. *Br J Clin Pharmacol.* 2019 Nov 29. doi: 10.1111/bcp.14188.
294. Neugebauer R, Schroeder EB, Reynolds K, et al. Comparison of **Mortality and Major Cardiovascular Events** Among Adults With Type 2 Diabetes Using Human vs Analogue Insulins. *JAMA Netw Open.* 2020 Jan 3;3(1):e1918554
295. **National Institute for Health and Care Excellence (NICE).** Type 2 diabetes in adults: management. (NICE guideline) 2015. www.nice.org.uk/guidance/ng28
296. Garber AJ, Handelsman Y, Grunberger G, et al. **CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY (AAACE/ACE) ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2020 EXECUTIVE SUMMARY.** *Endocr Pract.* 2020;26(1):107-139. doi:10.4158/CS-2019-0472 **CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – 2020 EXECUTIVE SUMMARY**
297. Rosenstock J, Hollander P, Bhargava A, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the **ELEMENT 2** study). *Diabetes Obes Metab.* 2015;17(8):734-741. doi:10.1111/dom.12482.
298. Clinical Study Report. **ABEO.** Data on file. Eli Lilly and Company.
299. Ritzel et al. Patient-level **meta-analysis of the EDITION 1, 2 and 3 studies:** glycaemic control and hypoglycaemia with new **insulin glargine 300 U/ml versus glargine 100 U/ml** in people with type 2 diabetes. *Diabetes Obes Metab* 2015;17:859–67.
300. Meneghini L, et al (BEGIN FLEX) TrialInvestigators. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. *Diabetes Care.* 2013 Apr;36(4):858-64.
301. **CADTH:** Long-Acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of Clinical Outcomes. 2008.
302. Tools For Practice Alberta College of Family Physicians. Allan et al. The Long and Short of Long Acting Insulin Analogues (versus NPH). Original 2010. **Updated 2018.**
303. Derwahl et al. Efficacy and Safety of Biosimilar SAR342434 Insulin Lispro in Adults with Type 2 Diabetes, Also Using Insulin Glargine: **SORELLA 2** Study. *Diabetes Technol Ther.* 2018 Jan;20(1):49-58.

304. Bowring et al. Faster versus insulin aspart as part of a basal-bolus regimen in inadequately controlled type 2 diabetes: the onset 2 trial. *Diabetes Care* 2017; 40:951.
305. **Mannucci** E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: A meta-analysis. *Diabetes Obes Metab* 2009;11:53–9
306. Fullerton B, et al. Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus. **Cochrane Database of Systematic Reviews** 2018, Issue 12. Art. No.: CD013228.
307. Holman et al. 4-T Study Group. Addition of **biphasic, prandial, or basal insulin** to oral therapy in type 2 diabetes. *N Engl J Med.* 2007 Oct 25;357(17):1716-30.
308. Wang C, Mamza J, Idris I. **Biphasic vs basal bolus insulin** regimen in Type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabet Med.* 2015;32(5):585-594. doi:10.1111/dme.12694
309. CPS product monographs 2020 (e-CPS accessed Apr, 2020); *Product information leaflets.*
310. Craft S, Raman R, Chow TW, et al. Safety, Efficacy, and Feasibility of **Intranasal Insulin** for the Treatment of Mild Cognitive Impairment and Alzheimer Disease Dementia: A Randomized Clinical Trial. *JAMA Neurol.* 2020;e201840.
311. Ji L, Wan H, Wen B, et al. **Higher versus standard starting dose of insulin glargine** 100 U/mL in overweight or obese Chinese patients with type 2 diabetes: Results of a multicentre, open-label, randomized controlled trial (BEYOND VII). *Diabetes Obes Metab.* 2020 Jan 15. doi: 10.1111/dom.13967.
312. Lane WS, Favaro E, Rathor N, et al. A Randomized Trial Evaluating the Efficacy and Safety of **Fast-Acting Insulin Aspart Compared With Insulin Aspart**, Both in Combination With **Insulin Degludec** With or Without Metformin, in Adults With Type 2 Diabetes (Onset 9). *Diabetes Care.* 2020 Mar 24. doi: 10.2337/dc19-2232
313. Watada H, Takami A, Spranger R, et al. Efficacy and Safety of 1:1 Fixed-Ratio Combination of **Insulin Glargine and Lixisenatide Versus Lixisenatide** in Japanese Patients With Type 2 Diabetes Inadequately Controlled on Oral Antidiabetic Drugs: The LixiLan JP-O1 Randomized Clinical Trial. *Diabetes Care.* 2020 Apr 15. doi: 10.2337/dc19-2452
314. Chua KP, Lee JM, Conti RM. Potential Change in Insulin **Out-of-Pocket Spending Under Cost-Sharing Caps** Among Pediatric Patients With Type 1 Diabetes. *JAMA Pediatr.* 2020;10.1001/jamapediatrics.2020.1065.
315. Danne T, Matsuhisa M, Sussebach C, et al. Lower Risk for Severe Hypoglycaemia with **Insulin Glargine 300 U/mL vs Glargine 100 U/mL** in Participants with Type 1 Diabetes: a Meta-Analysis of 6-Month Phase 3 Clinical Trials. *Diabetes Obes Metab.* 2020;10.1111/dom.14109.
316. Danne T, Tamborlane WV, Malievsky OA, et al. Efficacy and Safety of Insulin **Glargine 300 Units/mL (Gla-300) Versus Insulin Glargine 100 Units/mL (Gla-100)** in Children and Adolescents (6-17 years) With Type 1 Diabetes: Results of the EDITION JUNIOR Randomized Controlled Trial. *Diabetes Care.* 2020;43(7):1512-1519
317. Morea N, Retnakaran R, Vidal J, et al. **iGlarLixi** effectively reduces residual hyperglycaemia in patients with type 2 diabetes on basal insulin: A post hoc analysis from the LixiLan-L study. *Diabetes Obes Metab.* 2020;10.1111/dom.14077.
318. Rayman G, Lumb AN, Kennon B, et al. **Dexamethasone therapy in COVID-19 patients:** implications and guidance for the management of blood glucose in people with and without diabetes. *Diabet Med.* 2020;10.1111/dme.14378.
319. Home P, Blonde L, Kalra S, et al A. Insulin **glargine/lixisenatide fixed-ratio combination (iGlarLixi)** compared with premix or addition of meal-time insulin to basal insulin in people with type 2 diabetes: A systematic review and Bayesian network meta-analysis. *Diabetes Obes Metab.* 2020 Jul 22. doi: 10.1111/dom.14148
320. Home PD, Aroda VR, Blonde L, et al. Efficacy and safety of **iGlarLixi versus iDegLira** in adults with type 2 diabetes inadequately controlled by glucagon-like peptide-1 receptor agonists: a systematic literature review and indirect treatment comparison. *Diabetes Obes Metab.* 2020 Jul 6. doi: 10.1111/dom.14136
321. Klaff L, Cao D, Dellva MA, et al. **Ultra rapid lispro** improves postprandial glucose control compared with lispro in patients with type 1 diabetes: Results from the 26-week PRONTO-T1D study. *Diabetes Obes Metab.* 2020;10.1111/dom.14100.
322. Meneghini LF, Sullivan SD, Oster G, et al. A pragmatic randomized clinical trial of **insulin glargine 300 U/mL vs first-generation basal insulin analogues** in insulin-naïve adults with type 2 diabetes: 6-month outcomes of the ACHIEVE Control study. *Diabetes Obes Metab.* 2020 Jul 30. doi: 10.1111/dom.14152
323. Rosenstock J, Bajaj HS, Janež A, et al; NN1436-4383 Investigators. **Once-Weekly Insulin** for Type 2 Diabetes without Previous Insulin Treatment. *N Engl J Med.* 2020 Sep 22. doi: 10.1056/NEJMoa2022474.
324. Terauchi Y, Nakama T, Spranger R, et al. Efficacy and safety of insulin **glargine/lixisenatide fixed-ratio combination (iGlarLixi 1:1)** in Japanese patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs: A randomized, 26-week, open-label, multicenter study: The LixiLan JP-O2 Randomized Clinical Trial. *Diabetes Obes Metab.* 2020 Apr 14. doi: 10.1111/dom.14036
325. Pdf Chen J, Fan L, Peng X, et al. Patient-reported outcomes in a study of **human regular U-500 insulin** delivered by continuous subcutaneous insulin infusion or multiple daily injections in patients with type 2 diabetes. *Diabetes Obes Metab.* 2020 Sep 7. doi: 10.1111/dom.14191
326. Kaneto H, Takami A, Spranger R, et al. **Efficacy and safety of insulin glargine/lixisenatide** fixed-ratio combination (iGlarLixi) in Japanese patients with type 2 diabetes mellitus inadequately controlled on basal insulin and oral antidiabetic drugs: The LixiLan JP-L Randomized Clinical Trial. *Diabetes Obes Metab.* 2020 Feb 19. doi: 10.1111/dom.14005.
327. Rayner CK, Wu T, Aroda VR, et al. **Gastrointestinal adverse events with insulin glargine/lixisenatide** fixed-ratio combination versus glucagon-like peptide-1 receptor agonists in people with type 2 diabetes mellitus: A network meta-analysis. *Diabetes Obes Metab.* 2020 Sep 29. doi: 10.1111/dom.14202
328. Semlitsch T, Engler J, Siebenhofer A, et al. **(Ultra-)long-acting insulin analogues versus NPH** insulin (human isophane insulin) for adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2020 Nov 9;11:CD005613
329. Aso Y, Takada Y, Tomotsune K, et al. Comparison of insulin **degludec (IDeg)/insulin Aspart (IAsp)** co-formulation therapy twice-daily with free combination of GLP-1 receptor agonist **liraglutide plus insulin degludec** in Tochigi: IDEAL Trial. *Int J Clin Pract.* 2020 Oct 25:e13734
330. Bradley MC, Chillarige Y, Lee H, et al. Severe Hypoglycemia Risk With Long-Acting Insulin Analogs vs Neutral Protamine **Hagedorn Insulin**. *JAMA Intern Med.* 2021 Mar 1. doi: 10.1001/jamainternmed.2020.9176
331. Kaufmann B, Boulle P, Berthou F, et al. **Heat-stability study of various insulin types** in tropical temperature conditions: New insights towards improving diabetes care. *PLoS One.* 2021 Feb 3;16(2):e0245372
332. Pal R, Banerjee M, Bhadada SK. Glycaemic efficacy and safety of mealtime **faster-acting insulin aspart** administered by injection as compared to insulin aspart in people with diabetes mellitus: A meta-analysis of randomized controlled trials. *Diabet Med.* 2021 Mar;38(3):e14515
333. Rados DV, Falcetta MRR, Pinto LC, et al. All-cause mortality and cardiovascular **safety of basal insulin treatment** in patients with type 2 diabetes mellitus: A systematic review with meta-analysis and trial sequential analysis. *Diabetes Res Clin Pract.* 2021 Feb 4;173:108688
334. Trish E, Kaiser K, Joyce G. Association of **Out-of-Pocket Spending With Insulin Adherence** in Medicare Part D. *JAMA Netw Open.* 2021 Jan 4;4(1):e2033988
335. Coffer S, Schlichting L, Cunningham JM. **Insulin Pump Treatment** for the Hospitalized Patient. *JAMA Intern Med.* 2021 Mar 15. doi: 10.1001/jamainternmed.2021.0106
336. Hemmingsen B, Metzendorf MI, Richter B. **(Ultra-)long-acting insulin** analogues for people with type 1 diabetes mellitus. *Cochrane Database Syst Rev.* 2021 Mar 4;3:CD013498
337. Tricco AC, Ashoor HM, Antony J, et al. Comparative Efficacy and Safety of **Ultra-Long-Acting, Long-Acting, Intermediate-Acting, and Biosimilar Insulins** for Type 1 Diabetes Mellitus: a Systematic Review and Network Meta-Analysis. *J Gen Intern Med.* 2021 Mar 19. doi: 10.1007/s11606-021-06642-7
338. Bajaj HS, Bergenstal RM, Christoffersen A, et al. Switching to **Once-Weekly Insulin Icodec Versus Once-Daily Insulin Glargine U100** in Type 2 Diabetes Inadequately Controlled on Daily Basal Insulin: A Phase 2 Randomized Controlled Trial. *Diabetes Care.* 2021 Apr 19:dc202877.
339. Giugliano D, Longo M, Caruso P, et al. Feasibility of Simplification From a **Basal-Bolus Insulin Regimen to a Fixed-Ratio Formulation** of Basal Insulin Plus a GLP-1RA or to Basal Insulin Plus an SGLT2 Inhibitor: BEYOND, a Randomized, Pragmatic Trial. *Diabetes Care.* 2021 Apr 21:dc202623.
340. Lingvay I, Buse JB, Franek E, et al. A Randomized, Open-Label Comparison of Once-Weekly Insulin **Icodec Titration Strategies Versus Once-Daily Insulin Glargine U100**. *Diabetes Care.* 2021 Apr 19:dc202878
341. Najmi U, Haque WZ, Ansari U, et al. **Inpatient Insulin Pen** Implementation, Waste, and Potential Cost Savings: A Community Hospital Experience. *J Diabetes Sci Technol.* 2021 Apr 12:19322968211002514
342. Feng W, Chen W, Jiang S, et al. Efficacy and safety of **LY2963016 insulin glargine versus insulin glargine (Lantus)** in Chinese adults with type 2 diabetes: A phase III, randomized, open-label, controlled trial. *Diabetes Obes Metab.* 2021 Mar 30. doi: 10.1111/dom.14392.
343. Ferreira JP, Lamiral Z, McMurray JJV, et al. Impact of **Insulin Treatment on the Effect of Eplerenone**: Insights From the EMPHASIS-HF Trial. *Circ Heart Fail.* 2021 Jun;14(6):e008075.
344. Mehta R, Goldenberg R, Katselnik D, Kuritzky L. Practical guidance on the **initiation, titration, and switching of basal insulins**: a narrative review for primary care. *Ann Med.* 2021 Dec;53(1):998-1009
345. Avgerinos I, Papanastasiou G, Karagiannis T, et al. **Ultra-rapid-acting insulins** for adults with diabetes: A systematic review and meta-analysis. *Diabetes Obes Metab.* 2021 Jun 9. doi: 10.1111/dom.14461

346. Giugliano D, Longo M, Caruso P, et al. Feasibility of Simplification From a **Basal-Bolus Insulin Regimen to a Fixed-Ratio Formulation** of Basal Insulin Plus a GLP-1RA or to Basal Insulin Plus an SGLT2 Inhibitor: BEYOND, a Randomized, Pragmatic Trial. *Diabetes Care*. 2021 Apr 21;44(6):1353–60
347. Goldenberg RM, Aroda VR, Billings LK, et al. Effect of **insulin degludec versus insulin glargine U100** on time in range: SWITCH PRO, a crossover study of basal insulin-treated adults with type 2 diabetes and risk factors for hypoglycaemia. *Diabetes Obes Metab*. 2021 Jul 28. doi: 10.1111/dom.14504
348. Lee MH, Paldus B, Vogrin S, et al. **Fast-Acting Insulin Aspart Versus Insulin Aspart** Using a Second-Generation Hybrid Closed-Loop System in Adults With Type 1 Diabetes: A Randomized, Open-Label, Crossover Trial. *Diabetes Care*. 2021 Aug 6;dc210814.
349. Nam YH, Brensing CM, Bilker WB, et al. Association Between Serious Hypoglycemia and Calcium-Channel Blockers Used Concomitantly With **Insulin Secretagogues**. *JAMA Netw Open*. 2021 Sep 1;4(9):e2124443
350. Pei Y, Agner BR, Luo B, et al. DUAL II China: Superior HbA1c reductions and weight loss with **insulin degludec/liraglutide (IDegLira) versus insulin degludec** in a randomized trial of Chinese people with type 2 diabetes inadequately controlled on basal insulin. *Diabetes Obes Metab*. 2021 Aug 13. doi: 10.1111/dom.14522.
351. Rosenstock J, Emral R, Sauque-Reyna L, et al; SoliMix Trial Investigators. Advancing Therapy in Suboptimally Controlled Basal Insulin-Treated Type 2 Diabetes: Clinical **Outcomes With iGlarLixi Versus Premix BIAsp 30** in the SoliMix Randomized Controlled Trial. *Diabetes Care*. 2021 Jun 28;dc210393
352. Shah VN, Akturk HK, Joseph H, et al. A randomized controlled trial of transition from **insulin pump to multiple daily injections using insulin degludec**. *Diabetes Obes Metab*. 2021 Aug;23(8):1936-1941
353. Vaduganathan M, Inzucchi SE, Sattar N, et al. Effects of **Empagliflozin on Insulin Initiation or Intensification** in Patients with Type 2 Diabetes and Cardiovascular Disease: Findings from the EMPA-REG OUTCOME® Trial. *Diabetes Obes Metab*. 2021 Aug 31. doi: 10.1111/dom.14535
354. Del Prato S, Kahn SE, Pavo I, et al; SURPASS-4 Investigators. **Tirzepatide versus insulin glargine** in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet*. 2021 Oct 18:S0140-6736(21)02188-7.
355. Schroeder EB, Neugebauer R, Reynolds K, et al. Association of **Cardiovascular Outcomes and Mortality** With Sustained Long-Acting Insulin Only vs Long-Acting Plus Short-Acting Insulin Treatment. *JAMA Netw Open*. 2021 Sep 1;4(9):e2126605
356. Van Nuys K, Ribero R, Ryan M, Sood N. Estimation of the Share of **Net Expenditures on Insulin** Captured by US Manufacturers, Wholesalers, Pharmacy Benefit Managers, Pharmacies, and Health Plans From 2014 to 2018. *JAMA Health Forum*. 2021;2(11):e213409. doi:10.1001/jamahealthforum.2021.3409
357. Dahl D, Onishi Y, Norwood P, et al. Effect of **Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine** on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial. *JAMA*. 2022 Feb 8;327(6):534-545.
358. Pedersen-Bjergaard U, Agesen RM, Brøsen JMB, et al. Comparison of **treatment with insulin degludec and glargine U100** in patients with type 1 diabetes prone to nocturnal severe hypoglycaemia: The HypoDeg randomized, controlled, open-label, crossover trial. *Diabetes Obes Metab*. 2021 Oct 12. doi: 10.1111/dom.14574.
359. Rao P, Jiang SF, Kipnis P, et al. Evaluation of Outcomes Following Hospital-Wide Implementation of a **Subcutaneous Insulin Protocol for Diabetic Ketoacidosis**. *JAMA Netw Open*. 2022 Apr 1;5(4):e226417
360. Bali IA, Al-Jelaifi MR, AlRuthia Y, et al. Estimated Cost-**effectiveness of Subcutaneous Insulin Aspart** in the Management of Mild Diabetic Ketoacidosis Among Children. *JAMA Netw Open*. 2022 Sep 1;5(9):e2230043.
361. Hramiak I, Gerstein HC, Leiter LA, et al. Comparing a daily versus weekly titration algorithm in people with type 2 diabetes **switching from basal insulin to iGlarLixi in the LixiLan ONE CAN randomized trial**. *Diabetes Obes Metab*. 2022 Jun 7. doi: 10.1111/dom.14787.
362. Kellerer M, Kaltoft MS, Lawson J, et al. Effect of **once-weekly semaglutide versus thrice-daily insulin aspart**, both as add-on to metformin and optimized insulin glargine treatment in participants with type 2 diabetes (SUSTAIN 11): A randomized, open-label, multinational, phase 3b trial. *Diabetes Obes Metab*. 2022 May 11. doi: 10.1111/dom.14765.
363. Pharmacist's Letter Canada. Help Patients Manage Diabetes Meds During a Fast. September 2021, No. 370905.
364. Basal insulin formulations for the Management of T2DM. CADTH. March 2021. Available from: [Basal Insulin Formulations for the Management of Type 2 Diabetes \(cadth.ca\)](https://www.cadth.ca/basal-insulin-formulations-for-the-management-of-type-2-diabetes).
365. Li M, Yuan J, Lu K. Estimates of **Insulin Out-of-Pocket Cap-Associated Prescription Satisfaction, Adherence, and Affordability** Among Medicare Beneficiaries. *JAMA Netw Open*. 2023 Jan 3;6(1):e2251208.
366. Mathiesen ER, Alibegovic AC, Corcoy R, et al; EXPECT study group. **Insulin degludec versus insulin detemir**, both in combination with insulin aspart, in the treatment of pregnant women with type 1 diabetes (EXPECT): an open-label, multinational, randomised, controlled, non-inferiority trial. *Lancet Diabetes Endocrinol*. 2023 Jan 6:S2213-8587(22)00307-2
367. McGovern AP, Hirwa KD, Wong AK, et al. **Patient-led rapid titration of basal insulin** in gestational diabetes is associated with improved glycaemic control and lower birthweight. *Diabet Med*. 2022 Oct;39(10):e14926.
368. Pasqua MR, Jafar A, Kobayati A, et al. **Low-Dose Empagliflozin as Adjunct to Hybrid Closed-Loop Insulin Therapy** in Adults With Suboptimally Controlled Type 1 Diabetes: A Randomized Crossover Controlled Trial. *Diabetes Care*. 2022 Nov 4;dc220490.
369. Bue-Valleskey JM, Kazda CM, Ma C, et al. Once-Weekly **Basal Insulin Fc Demonstrated Similar Glycemic Control to Once-Daily Insulin Degludec** in Insulin-Naive Patients With Type 2 Diabetes: A Phase 2 Randomized Control Trial. *Diabetes Care*. 2023 Mar 21;dc222396.
370. Fang M, Selvin E. **Cost-Related Insulin Rationing** in US Adults Younger Than 65 Years With Diabetes. *JAMA*. 2023 Mar 29:e235747.
371. Joshi SR, Singh G, Marwah A, et al. Comparative clinical efficacy and safety of **insulin glargine 300 U/ml (Toujeo) versus insulin glargine 100 U/ml** in type 2 diabetes and type 1 diabetes: A systematic literature review and meta-analysis. *Diabetes Obes Metab*. 2023 Feb 6. doi: 10.1111/dom.15007.
372. Kazda CM, Bue-Valleskey JM, Chien J, et al. **Novel Once-Weekly Basal Insulin Fc** Achieved Similar Glycemic Control With a Safety Profile Comparable to Insulin Degludec in Patients With Type 1 Diabetes. *Diabetes Care*. 2023 Mar 15;dc222395.
373. Anderson KE, Xuan A, Anderson GF, Socal MP. Estimating **Changes in Medicare Part D and Commercial Insurer Insulin Spending** Amid Planned State-Led Biosimilar Insulin Production in California. *JAMA Intern Med*. 2023 May 8:e230373.
374. Mathieu C, Ásbjörnsdóttir B, Bajaj HS, et al. **Switching to once-weekly insulin icodex versus once-daily insulin glargine U100** in individuals with basal-bolus insulin-treated type 2 diabetes (ONWARDS 4): a phase 3a, randomised, open-label, multicentre, treat-to-target, non-inferiority trial. *Lancet*. 2023 May 5:S0140-6736(23)00520-2.
375. Phillis-Tsimikas A, Asong M, Franek E, et al. **Switching to once-weekly insulin icodex versus once-daily insulin degludec** in individuals with basal insulin-treated type 2 diabetes (ONWARDS 2): a phase 3a, randomised, open label, multicentre, treat-to-target trial. *Lancet Diabetes Endocrinol*. 2023 May 3:S2213-8587(23)00093-1.
376. Dickson S, Gabriel N, Gellad WF, Hernandez I. Estimated Changes in **Insulin Prices and Discounts** After Entry of New Insulin Products, 2012-2019. *JAMA Health Forum*. 2023 Jun 2;4(6):e231430.
377. Heerspink HJL, Sattar N, Pavo I, et al. Effects of **Tirzepatide Versus Insulin Glargine** on Cystatin C-Based Kidney Function: A SURPASS-4 Post Hoc Analysis. *Diabetes Care*. 2023 Jun 2;dc230261.
378. Larose S, Filliter C, Platt RW, et al. Long-acting insulin analogues and the **risk of diabetic retinopathy** among patients with type 2 diabetes: A population-based cohort study. *Diabetes Obes Metab*. 2023 May 11. doi: 10.1111/dom.15106.
379. Lingvay I, Asong M, Desouza C, et al. **Once-Weekly Insulin Icodex vs Once-Daily Insulin Degludec** in Adults With Insulin-Naive Type 2 Diabetes: The ONWARDS 3 Randomized Clinical Trial. *JAMA*. 2023 Jun 24. doi: 10.1001/jama.2023.11313.
380. Ritzel R, Ghosh S, Emral R, et al. Comparative efficacy and safety of **Gla-300 versus IDegAsp** in insulin-naïve people with type 2 diabetes mellitus uncontrolled on oral anti-diabetics. *Diabetes Obes Metab*. 2023 Jun 13. doi: 10.1111/dom.15121.
381. Rosenstock J, Bain SC, Gowda A, et al; ONWARDS 1 Trial Investigators. **Weekly Icodex versus Daily Glargine U100** in Type 2 Diabetes without Previous Insulin. *N Engl J Med*. 2023 Jun 24. doi: 10.1056/NEJMoa2303208.

FDA Nov/19: Medtronic is recalling the specified insulin pumps due to potential cybersecurity risks. (MiniMed Insulin Pumps)