The Future of Diabetes

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Disclosures

Consultant:	Neurimmune AG
Employee:	None
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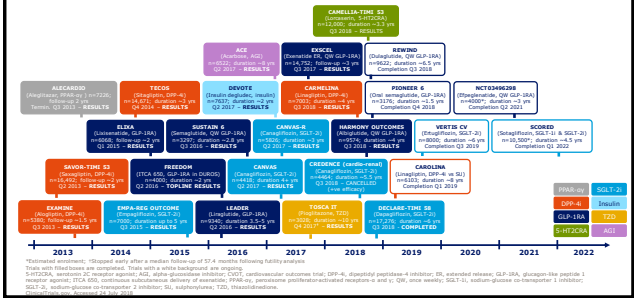
Overview

- Update on type 2 diabetes management based on multiple high impact papers over the last 3 years
  - SGLT2 inhibitors
  - GLP-1 receptor agonists
- ADA-EASD Management of Type 2 Diabetes, 2018
- Type 1 diabetes innovation
- Future of diabetes care

Contemporary CVOTs in diabetes and obesity



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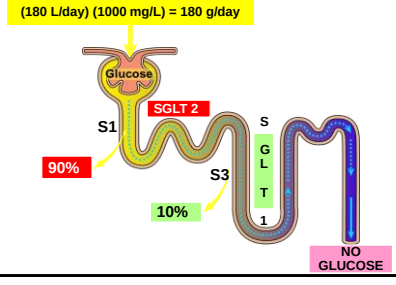
Renal Handling of Glucose



Summary of Observed Efficacy of SGLT2 Inhibitors

- **Similar to other oral antihyperglycemic agents in A1C reduction**
  - **Reduces both FPG and PPG**
  - **Certainly equivalent efficacy to metformin, sulfonylurea and DPP-4 inhibitors**
- **Modest weight loss**
  - **~3 kg at 26 weeks vs placebo; slightly greater weight loss at 52 weeks**
- **Modest blood pressure reduction**
  - **2-7 mm Hg vs placebo**
- **No intrinsic increased risk of hypoglycemia**
- **Multiple safety concerns:**

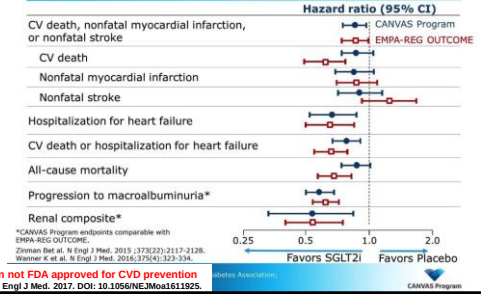
Hasan FM, Alsahli M, Gerich JE. Diabetes Res Clin Pract. 2014 Jun;104(3):297-322. Tahrani AA, Barnett AH, Bailey CJ. Lancet Diabetes Endocrinol. 2013 Oct;1(2):140-51.

Safety Concerns Raised with SGLT2 inhibitors

	Cana-gliflozin	Dapa-gliflozin	Empa-gliflozin	Ertu-gliflozin
Hypotension	C	D	E	E
Ketoacidosis	C	D	E	E
Acute kidney injury	C	D	E	E
Hyperkalemia	C	-	-	-
Urosepsis	C	D	E	E
Hypoglycemia	C	D	E	E
Genital mycotic infection	C	D	E	E
Bone fractures	C	-	-	-
Increased LDL	C	D	E	E
Amputations	C	-	-	E
Bladder cancer	-	D	-	-
Macrovascular outcomes	-	D	-	-
Do not start with eGFR less than	45	60	45	60
Stop with eGFR	45	30-60	45	30-60

Package inserts, accessed April 24, 2018

Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME



Canagliflozin not FDA approved for CVD prevention

Neal B, et al. N Engl J Med. 2017. DOI: 10.1056/NEJMoa1611925.

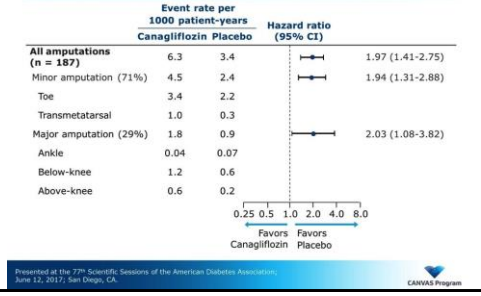
EMPA-REG (empagliflozin) Adverse events

- Genital infections
  - ~6% in men, ~10% in women (vs. 2% w placebo over 3 years)
- Otherwise, no signal for
  - UTI, complicated UTI, pyelonephritis, urosepsis
  - DKA
  - Acute kidney injury
  - Volume depletion
  - Venous thrombosis
  - Hepatic injury
  - Hypersensitivity
  - Bone fracture
  - Amputation

Zinman B, et al. *N Engl J Med.* 2015. 373(22):2117-28.

EMPA-REG OUTCOME

Highest Level of Amputation



Amputation Risk Factors - Multivariate Analysis

Risk Factor at Baseline	Hazard Ratio	95% CI
Amputation	20.9	(14.2-30.8)
Peripheral vascular disease*	3.1	(2.2-4.5)
Male	2.4	(1.6-3.5)
Neuropathy	2.1	(1.6-2.9)
HbA1c >8%	1.9	(1.4-2.6)
Canagliflozin treatment	1.8	(1.3-2.5)
Presence of CV disease	1.5	(1.0-2.3)

- Predictors of amputation risk are similar in both arms
- Canagliflozin treatment, independent of the risk factors, increased amputation risk

Predictive on univariate analysis: nephropathy, insulin use, retinopathy, loop diuretic, eGFR, diabetes duration
Factors assessed but not significantly predictive: non-loop diuretic, smoking, SBP, hemoglobin, age

* Excludes amputations

Presented at the 77th Scientific Sessions of the American Diabetes Association; June 12, 2017; San Diego, CA
CANVAS Program

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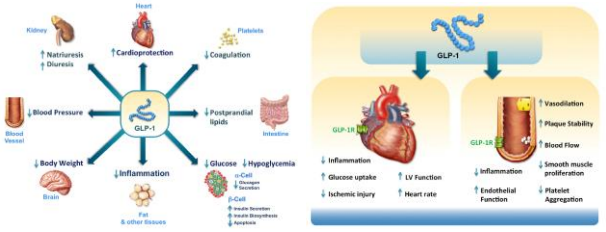
GLP-1 Has Broad Activity



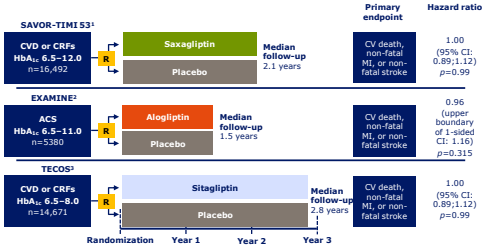
Drucker DJ, *Cell Metabolism* 2016; Epub ahead of print. DOI: http://dx.doi.org/10.1016/j.cmet.2016.06.009

Overview: GLP-1 Receptor Agonists

- **Excellent improvement in A1C**
  - **Head-to-head studies versus other classes suggest similar or greater efficacy of GLP-1 receptor agonists, even as compared to basal insulin**
- **Moderate weight loss**
  - **~2-3 kg over 6-12 months**
- **Modest improvement in blood pressure**
- **No intrinsic increased risk of hypoglycemia**
- **Adverse events largely gastrointestinal**
- **Safety concerns (renal failure, pancreatitis, medullary thyroid cancer, pancreatic cancer)**

A1C, glycosylated hemoglobin; GLP-1, glucagon-like peptide-1.

DPP-4i CV outcomes studies



ACS, acute coronary syndrome; CI, confidence interval; CRF, cardiovascular risk factor; CV, cardiovascular; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; EXAMINE, Examination of Cardiovascular Outcomes: Alogliptin vs. Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome; MI, myocardial infarction; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial-Thrombolysis in Myocardial Infarction; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin

1. Scirica *et al. N Engl J Med* 2013;369:1317–26; 2. White *et al. N Engl J Med* 2013;369:1327–35; 3. Green *et al. N Engl J Med* 2015;373:232–42

Different drugs, different trials, different results

Drug	Lixisenatide QD	Liraglutide QD	Semaglutide QW	Exenatide XR QW	Albiglutide QW
Structure (sequence homology)	Exendin-4 (50%)	GLP-1 (97%)	GLP-1 (94%)	Exendin-4 (53%)	GLP-1 (97%) Albumin-fusion
In vivo EC_{50}, nmol/kg*	0.02	0.5	NA	0.01	1.4
$t_{½}$	2–4 h	11.6–13 h	7 days	2 weeks	~5 days
Dose	20 µg	0.6–1.8 mg	0.5, 1 mg	2 mg	30, 50 mg

*Dose producing 50% maximal glucose AUD following OGTT in db/db mice (data on file). Exenatide EC_{50} values from exenatide, not exenatide XR.
QD, once daily; QW, once weekly; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; HbA_{1c}, glycosylated haemoglobin; MACE, major adverse cardiovascular event;
1. Pfeffer MA et al. *N Engl J Med* 2015;373:2247–2257; 2. Marso SP et al. *N Engl J Med* 2016;375:311–322; 3. Marso SP et al. *N Engl J Med* 2016;:1834–1844;
4. Holman RR et al. *N Engl J Med* 2017;377:1228–1239; 5. Hernandez AF et al. *Lancet* 2018; http://dx.doi.org/10.1016/S0140-6736(18)32261-X [Epub ahead of print];

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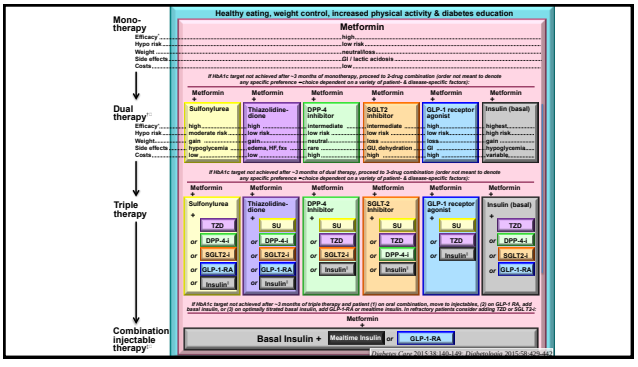
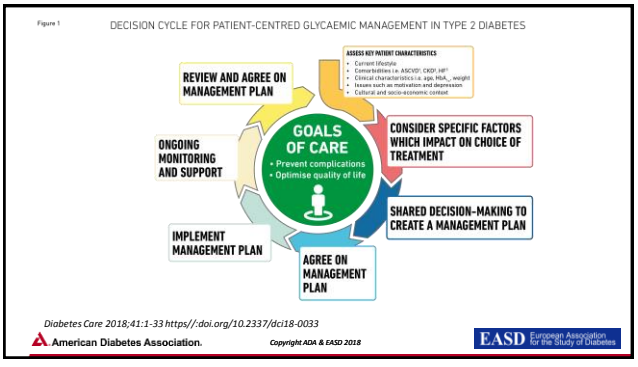
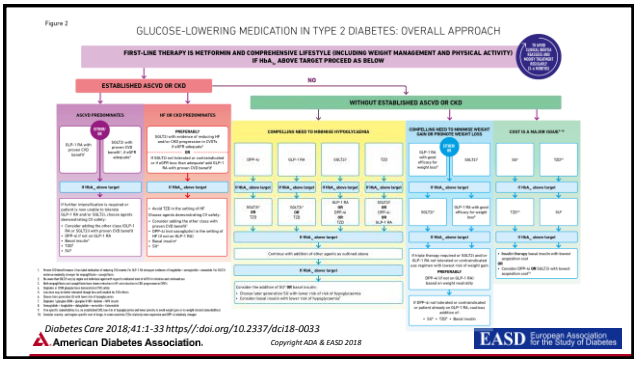


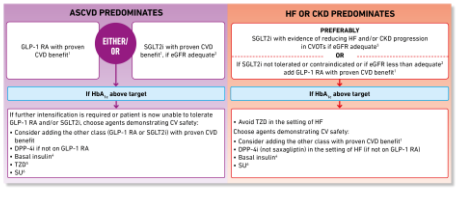
A Changing Paradigm in Diabetes Care?

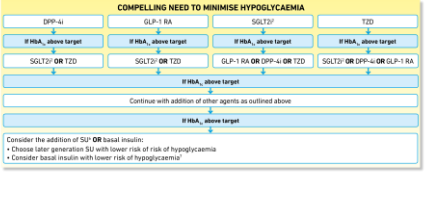
Medication	NNT to Prevent Death
Statins (for 5 years)	100
Anti-hypertensives (for 5 years)	125
Aspirin	333
Empagliflozin (for 3 years)	39
Liraglutide (for 3 years)	98

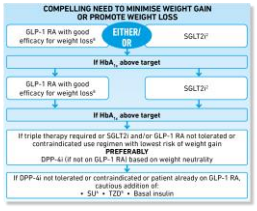
NNT = number needed to treat to prevent one event over an interval of time.
The NNT Group, 2010-2017, http://www.thennt.com.
Krumholz, Lipska KJ, Is Hemoglobin A1c the Right Outcome for Studies of Diabetes? JAMA, 2017.



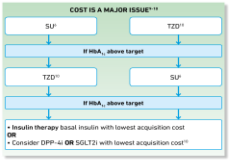








American Diabetes Association. Copyright ADA & EASD 2018 EASD European Association for the Study of Diabetes



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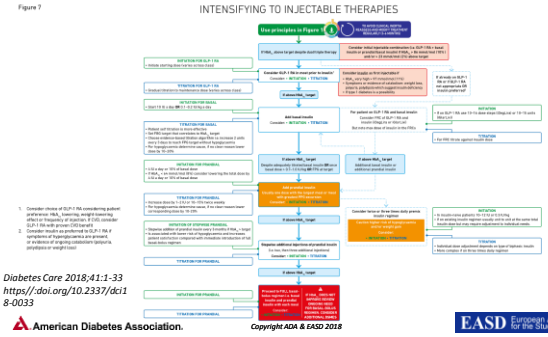

Diabetes Care 2018;41:1-33 https://doi.org/10.2337/dci18-0033

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Key Knowledge Gaps

Evolving areas:

- Implementation science
- Basic science
- Personalized/precision medicine
- Informatics
- Overweight/obesity management
- Targeting and individualization of lifestyle and DSMES
- Preserving and enhancing beta-cell function
- Translational research
- Drug development
- Complications

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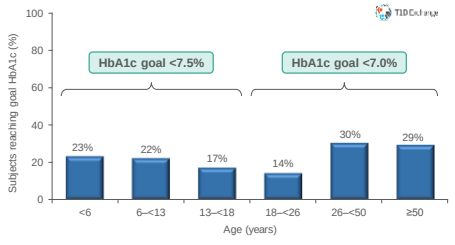
Only a small percentage of type 1 diabetes patients achieve target HbA1c levels



Miller KM et al. *Diabetes Care* 2015;38:971.

TYPE 1 DIABETES

30

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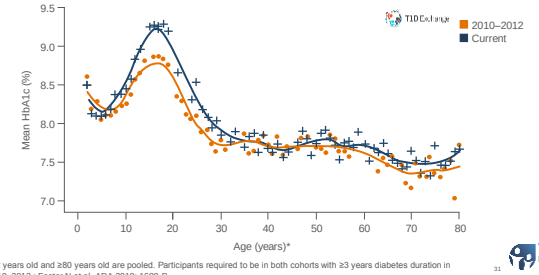
Therapy advances have NOT prevented HbA1c rise

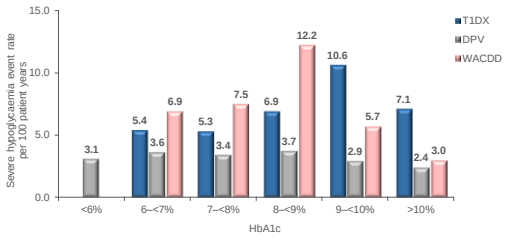


*≤2 years old and ≥80 years old are pooled. Participants required to be in both cohorts with ≥3 years diabetes duration in 2010–2012.; Foster N et al. ADA 2018; 1689-P

TYPE 1 DIABETES

31

Risk of severe hypoglycaemia is not associated with HbA1c

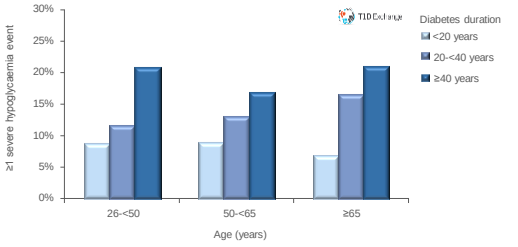


DPV, Diabetes Patienten Verlaufsdokumentation (Prospective Diabetes Registry); T1DX, Type 1 Diabetes Exchange; WACDD, Western Australian Children Diabetes Database; Haynes A et al. *Pediatric Diabetes* 2017;18:643.

TYPE 1 DIABETES

32

12-month frequency of severe hypoglycaemia according to age and diabetes duration

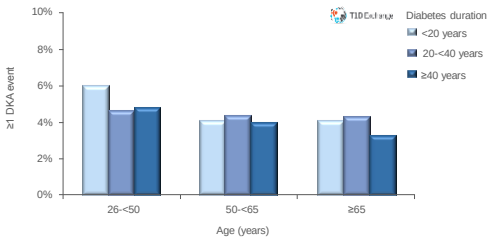


Weinstock RS, et al. *J Clin Endocrinol Metab* 2013;98:3411.

TYPE 1 DIABETES

33

12-month frequency of DKA according to age and diabetes duration



DKA, diabetic ketoacidosis.
Weinstock RS, et al. *J Clin Endocrinol Metab* 2013;98:3411.

TYPE 1 DIABETES

34

What's new for type 1 diabetes

- Continuous glucose monitoring
- Flash CGM
- Implanted CGM
- Low glucose suspend
- Sensor augmented pump therapy
- SGLT2 inhibitors (not FDA approved)

1. Dexcom press release. Available at: https://www.dexcom.com/news/fda-authorizes-dexcom-g6 (Accessed September 2018)
2. Abbott press release. Available at: http://abbott.mediaroom.com/2018-07-27-Abbotts-FreeStyle-R-Libre-14-Day-Flash-Glucose-Monitoring-System-Now-Approved-in-U-S (Accessed September 2018)
3. Senseonics press release. Available at: http://www.senseonics.com/investor-relations/news-releases/2018/06-21-2018-201353063 (Accessed September 2018);
4. Medtronic press release. Available at: http://newsroom.medtronic.com/phoenix.zhtml%3Fc%3D251324%26p%3Dirol-newsArticle%26ID%3D2009123 (Accessed September 2018);

DEPICT, inTandem, EASE, and canagliflozin trials

Study	DEPICT	inTandem	EASE	Canagliflozin
Interventions (randomization)	DAPA 5 mg / DAPA 10 mg / Placebo:Insulin (1:1:1)	SOTA 200 mg / SOTA 400 mg / Placebo:Insulin (1:1:1)	EMPA 2.5 mg / EMPA 10 mg / EMPA 25 mg / Placebo:Insulin (1:1:1:1)	CANA 100 mg / CANA 300 mg / Placebo:Insulin (1:1:1)
Primary endpoint	24-week change in HbA_{1c} with DAPA 5 mg or 10 mg vs placebo	Proportion with HbA_{1c} <7.0% and no severe hypoglycemia and no DKA	Change from baseline in HbA_{1c} at 26 weeks	Proportion with HbA_{1c} reduction ≥0.4% and no increase in body weight at 18 weeks
Important secondary endpoints	• Proportion with hypoglycemia events and frequency and severity of the hypoglycemia events • Safety and tolerability by assessment of AEs, vital signs, DKA, physical examination findings, laboratory values	• Change from baseline in proportion with HbA_{1c} <7.0% • Change from baseline in body weight • Mean change from baseline in mean daily bolus insulin dose • Change from baseline in FPG	• Change from baseline in body weight • Change from baseline in total daily insulin dose • Incidence rate of symptomatic hypoglycemic AEs with confirmed plasma glucose <54 mg/dL and/or severe hypoglycemic AEs per patient year	• Change from baseline in HbA_{1c} and FPG • Proportion with HbA_{1c} <7.0% change

AE, adverse event; CANA, canagliflozin; DAPA, dapagliflozin; DKA, diabetic ketoacidosis; EMPA, empagliflozin; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; SOTA, sotagliflozin

TYPE 1 DIABETES

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EASE Phase 3 results published last week

Diabetes Care 1

Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials

https://doi.org/10.2337/dc18-1749

Julio Rosenstock,[1] Jan Marquard,[2] Lori M. Laffel,[3] Dietmar Neubacher,[4] Stefan Kaspers,[2] David Z. Cherney,[5] Bernard Zinman,[6] Jay S. Skyler,[7] Jyothis George,[2] Nima Soleymanlou,[8] and Bruce A. Perkins[6]

Rosenstock J, et al. *Diabetes Care* 2018; https://doi.org/10.2337/dc18-1749

37 TYPE 1 DIABETES

Available evidence of efficacy

- ~0.5% HbA1c reduction with empagliflozin 10 and 25 mg versus intensified insulin alone in adults with T1D
- ~0.3% HbA1c reduction with empagliflozin 2.5 mg versus intensified insulin alone in adults with T1D; 0.35% HbA1c reduction with 2.5 mg when baseline HbA1c ≥8.0%
- ~3 kg weight loss, increase of 3 hrs/day glucose time in range (TiR >70–180 mg/dl), ~10% reduction in insulin needs, and ~3 mmHg decrease in SBP with empagliflozin 10 and 25 mg
- Empagliflozin 2.5 mg demonstrated improved HbA1c with reduced insulin dosing (-6.4%), and beneficial trends for weight (-1.8 kg), SBP (-2.1 mmHg) and CGM outcomes (+1 hour/day for TiR >70-180 mg/dl)

Rosenstock J, et al. *Diabetes Care* 2018; https://doi.org/10.2337/dc18-1749

38 TYPE 1 DIABETES

Available evidence of safety

- Increased risk of DKA with empagliflozin 10 and 25 mg, similar to other SGLTis in persons with T1D
- Risk factors include illness/infection, inadequate insulin administration, carbohydrate depletion, severe dehydration, female sex, and insulin pump use
- DKA rate with empagliflozin 2.5 mg was low and similar to placebo
- Empagliflozin did not increase rate of investigator-reported hypoglycaemia events, including severe hypoglycaemia, and empagliflozin reduced rate of patient-reported events (including nocturnal events)

Rosenstock J, et al. *Diabetes Care* 2018; https://doi.org/10.2337/dc18-1749

39 TYPE 1 DIABETES

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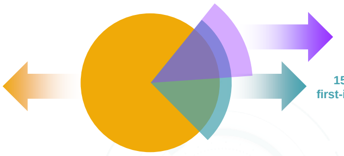
Overview of drug development

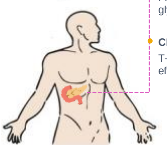


Current diabetes landscape[2,a]

	New molecular entities	Preclinical projects	Phase 1	Phase 2	Phase 3	Approved but not yet marketed
Total	432	482	97	125	42	3
First-in-class		414	77	92	16	-
Orphan	10	-	1	8	2	-

[a]As of 2017
1. GBI Research report; Frontier Pharma: Type 2 Diabetes Mellitus - Therapies Targeting GPCRs and Protein Kinases Dominate Pipeline, with Strong Repositioning Opportunities into Associated Areas, Including Obesity and Cardiovascular Disease. Available at: https://www.researchandmarkets.com/research/2tn6hd/type_2_diabetes?w=5; 2. Analysis Group report; The Biopharmaceutical Pipeline: Innovating Therapies in Clinical Development. Available at: http://phrma-docs.phrma.org/files/dmfile/Biopharmaceutical-Pipeline-Full-Report.pdf

Cell-based therapies: Restoring endogenous insulin production in patients with T1D



- **PEC-Encap; encapsulated islet cells derived from stem cells[1]**
  Two-year data from the STEP ONE trial (NCT02239354) demonstrated formation of viable mature insulin-expressing cells, with some cells persisting for two years
- **DRI BioHub; bioengineered mini-organ[2]**
  First patient treated in a phase 1/2 clinical trial (NCT02213003) has demonstrated stable glycemic control without exogenous insulin and without episodes of hypoglycemia
- **CLBS03 therapy; utilizing immunoprotective T_{regs}[3]**
  T-Rex, a landmark phase 2 trial (NCT02691247), is underway to evaluate the safety and efficacy of CLBS03 as a treatment for T1D

hESC, human embryonic stem cell; T_{reg}, regulatory T cell; T1D, Type 1 diabetes
1. ViaCyte press release. Available at: https://viacyte.com/archives/press-releases/two-year-data-from-viacytes-step-one-clinical-trial-presented-at-ada-2018 (Accessed September 2018); 2. Baidal DA, et al. *N Engl J Med* 2017; 376:1887–1889; 3. Caladrius press release. Available at: https://www.caladrius.com/press-release/caladrius-biosciences-announces-completion-of-enrollment-of-phase-2-t-rex-clinical-trial-of-clbs03-for-type-1-diabetes (Accessed September 2018)

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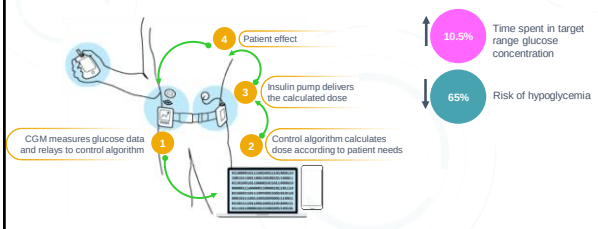
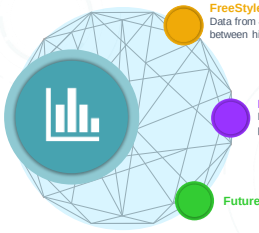
The artificial pancreas system: Combining new technologies to provide fully automated T1D treatment

- A randomized, open-label, crossover study (N=29) demonstrated that closed-loop therapy under free-living conditions improved glycemic control and reduced risk of hypoglycemia vs conventional insulin pumps



CGM, continuous glucose monitoring; HCL, hybrid closed-loop; T1D, Type 1 diabetes
Bally L, et al. Lancet Diabetes Endocrinol 2017;5:261–270

A digital ecosystem: Exploiting real-world patient data to deliver improved diabetes management



FreeStyle Libre[1]
Data from 400 million glucose measurements has demonstrated an association between higher frequency of monitoring and improved glycemic control in T1D

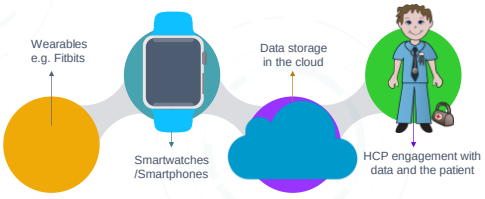
Medtronic in collaboration with IBM Watson Health[2]
Medtronic has collected 125 million patient days of data from insulin pumps, which is being used to develop next-generation control algorithms

Future technology

T1D, Type 1 diabetes
1. Abbott press release. Available at: http://abbott.mediaroom.com/2017-02-15-Real-World-Data-from-Abbotts-FreeStyle-Libre-Show-Association-Between-Higher-Frequency-of-Glucose-Monitoring-and-Improved-Glucose-Control-for-People-with-Diabetes (Accessed September 2018). 2. Medtronic press release. Available at: http://www.medtronic.com/us-en/about/news/ibm-diabetes.html (Accessed September 2018)

Consumer-driven technology has the potential to aggregate patient data to aid in monitoring and treatment of diabetes

- Use of technology to collect real-time data remotely would reduce the number of clinic visits required, improving patient convenience (may even improve adherence to treatment)



HCP, healthcare professional