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Health Delivery and Technology in Today's

DIABETES CARE

Applying Evidence Based Treatments to Personalized Care

ABIM CME MOC ACCREDITED

Saturday, April 28, 2018

The Inn at St. John's · Plymouth, MI

Grand Hotel
MACKINAC ISLAND MICHIGAN

The 2018 Diabetes Care conference is sponsored by Grand Hotel

medicine.umich.edu/dept/intmed

HOW TO DOWNLOAD AN ELECTRONIC VERSION OF THIS SYLLABUS

1. Go to: www.intmedcmeregister.org/download/0108ef
2. View and/or save the file.

The syllabus will be available to download until Friday, May 11, 2018.

COURSE SURVEY & CME CERTIFICATE

You will receive an e-mail by Monday, April 30, 2018 (to the e-mail address you provided when you registered) with the subject line "U-M Diabetes Care Course Survey and CME Certificate". If you don't see this e-mail in your Inbox folder, please make sure to check your Junk/Spam folder. This e-mail will contain a link which will take you to the course survey:

1. Click the "Take the Survey" link.

2. After completing the survey, click the arrow button at the bottom of the page to submit.

3. Click the "U-M Diabetes Care CME Cert" link. You will need Adobe Reader to view the file.

4. Save and/or print your certificate. *Note: Once you close this page, you will not be able to access the certificate again online.* If this happens, please call (734) 232-3469 or send an e-mail to intmedcme@umich.edu to obtain a copy.

NOTE: If you are using your smart phone to take the survey:
Once the CME certificate file opens, you can forward the certificate to your preferred e-mail address to access on your computer, where you can either save and/or print it.

The survey will be available online until Monday, May 14, 2018.

If you have any questions, please call (734) 232-3469 or send an e-mail to intmedcme@umich.edu

ATTENTION: ABIM Physicians

Please refer to the following page for information on how to obtain your certificate listing CME credit, and also MOC credit, if needed.

ATTENTION: ABIM Physicians

ABIM MOC CREDIT

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Disclosure of Participant Information:
At the beginning of the posttest evaluation, participants will be required to submit their ABIM ID, First Name, Last Name, and Date of Birth (month and day). This information, along with data verifying completion of the activity, will be sent to the ACCME, who will forward it to ABIM to record the individual's MOC credit. Your completion of the posttest evaluation implies your approval of the above mentioned information to be submitted to ABIM on your behalf.

How to Earn MOC Credit:
ABIM Physicians attending this activity will receive an email by Monday, April 30, 2018 with the subject line "U-M Diabetes Care Course Survey and CME Certificate". If you don't see this email in your Inbox folder, please make sure to check your Junk/Spam folder. This email will contain a link to the course survey and the posttest evaluation. The participant must take the posttest and pass with a score of 70% or higher. You may take the posttest as many times as needed to achieve a passing score. Participation in the posttest is not required. It is only for ABIM Board Certified physicians who want to earn MOC points.

1. Click the "Take the Survey" link. This will take you to the course survey.
2. After completing the course survey, click the forward arrow button at the bottom of the page

   If you require CME credit only:
   - Click the "Advancing Outpatient Diabetes Care CME Certificate" link. You will need Adobe Reader to view the file.
   - Save and/or print your certificate. **Note: Once you close this page, you will not be able to access the certificate again online**. If this happens, please call (734) 232-3469 or send an email to intmedcme@umich.edu to obtain a copy.

   If you require MOC credit in addition to CME credit:
   - Click the "Take the Posttest for MOC Credit" link. This will take you to the posttest evaluation.
   - After completing the posttest evaluation, click the forward arrow button to submit.
   - If your score is 70% or higher, you will receive a link to your certificate, which will list both CME and MOC credits earned.
   - If your score is less than 70%, you will receive a link to take the posttest again.
   - Save and/or print your certificate. **Note: Once you close this page, you will not be able to access the certificate again online**. If this happens, please call (734) 232-3469 or send an email to intmedcme@umich.edu to obtain a copy.

NOTE
If you are using your smartphone to take the course survey and posttest evaluation: Once the CME certificate file opens, you can forward the certificate to your preferred email address to access on your computer, where you can either save and/or print it.

Both the course survey and posttest evaluation will be available online until Monday, May 14, 2018.

If you have any questions, please call (734) 232-3469 or send an email to intmedcme@umich.edu

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DEPARTMENT OF INTERNAL MEDICINE CME COURSE CALENDAR

Thank you for attending the **Health Delivery and Technology in Today's Diabetes Care** course. We hope you enjoy it.

The U-M Department of Internal Medicine offers continuing medical education (CME) activities to provide lifelong learning experiences for physicians and other healthcare professionals that highlight innovative procedures and technologies, examine current methods of treatment, and update you on cutting-edge advances in the understanding and treatment of disease. The scope of our educational efforts provides the highest quality learning activities that lead to excellence in patient care.

We offer a variety of courses each year. The content of our activities includes primary care, specialty and subspecialty topics in the broad field of medicine. We target and welcome all physicians and other healthcare professionals, locally, nationally, and globally.

Updates in Nephrology for the Primary Care Provider
Saturday, May 5, 2018
The Inn at St. John's, Plymouth, MI

6th Annual Internal Medicine Spring Review
Friday - Sunday, May 18-19, 2018
The Inn at St. John's, Plymouth, MI

Update on Arrhythmias and Syncope
Saturday, June 2, 2018
The Inn at St. John's, Plymouth, MI

36th Annual Internal Medicine Update
Friday - Sunday, July 27-29, 2018
Grand Hotel, Mackinac Island, MI

31st Annual Cardiology Update
Friday - Sunday, August 17-19, 2018
Grand Hotel, Mackinac Island, MI

Clinical Issues in the Care of Older Adults
Thursday, September 27, 2018
The Kensington Hotel, Ann Arbor, MI

Gastroenterology Update: A Case-Based Approach to Common GI Problems
Friday - Saturday, September 28-29, 2018
The Inn at St. John's, Plymouth, MI

31st Annual Update in Pulmonary and Critical Care Medicine
Friday - Saturday, October 26-27, 2018
The Inn at St. John's, Plymouth, MI

State of the Art: Kidney and Pancreas Transplantation
Thursday, October 18, 2018
Embassy Suites, Livonia, MI

5th Annual Practical Guide to Cardiovascular Imaging: What Referring Providers Need to Know
Saturday, November 3, 2018
The Inn at St. John's, Plymouth, Michigan

21st Annual Liver Disease Wrap-Up
Saturday, December 8, 2018
The Inn at St. John's, Plymouth, MI

FOR MORE INFORMATION AND TO REGISTER:
www.medicine.umich.edu/dept/intmed • (734) 232-3469 • intmedcme@umich.edu

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PROGRAM SCHEDULE

Saturday, April 28, 2018

7:30 am Registration and Continental Breakfast

8:00 Welcome and Announcements
Rodica Pop-Busui, MD, PhD

All lectures will follow an interactive, case-based approach

8:05 **Diabetes Medications and Cardiovascular Disease: Winning on 2 Fronts**
Rodica Pop-Busui, MD, PhD

8:50 **Pumps & CGM: What The Primary Care Provider Needs to Know**
Jennifer Iyengar, MD

9:35 **New Insulins: How Do They Work, When Would You Prescribe Them?**
Roma Gianchandani, MD

10:20 **How to Counsel and Manage Your Patients Before and During Pregnancy for Optimal Outcomes**
Jennifer Wyckoff, MD

11:05 Break

11:20 **When and How to Treat Hyperglycemia in Post-Transplant Patients**
Palak Choksi, MD

12:05 pm **Your Patient Has Chronic Liver Disease and Diabetes: What Do You Use Next to Treat Hyperglycemia?**
Nazanene Esfandiari, MD

12:50 **Case-Based Interactive Lessons: Treat the Infected Diabetes Foot**
Brian Schmidt, DPM

1:35 Course Adjourns

COURSE DIRECTOR

Rodica Pop-Busui, MD, PhD
Course Director
Professor,
Division of Metabolism, Endocrinology & Diabetes
Department of Internal Medicine
Co-Director, Michigan Peripheral Neuropathy Center

U-M PROGRAM FACULTY

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Division of Metabolism,
Endocrinology & Diabetes
Department of Internal Medicine

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Associate Professor,
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Brian Schmidt, DPM
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Jennifer Wyckoff, MD
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Katie Ursitti
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Erin Van Wasshnova
Program Coordinator,
Department of Internal Medicine
Continuing Medical Education

DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIPS WITH COMMERCIAL INTERESTS

The Accreditation Council for Continuing Medical Education (ACCME) requires that the planners and presenters of continuing medical education activities disclose relevant financial relationships with commercial interests, any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

Program Name: Health Delivery and Technology in Today's Diabetes Care
Program Date: Saturday, April 28, 2018

The following planners/speakers <u>have no relevant financial relationships</u>:

Peter Arvan, MD, PhD
Palak Choksi, MD
Nazanene Esfandiari, MD
Roma Gianchandani, MD
Jennifer Iyengar, MD
Brian Schmidt, DPM
Jennifer Wyckoff, MD

The following planners/speakers **<u>have relevant financial relationships</u>** with an ACCME-defined commercial interest.

<u>Planner/Faculty Member</u>	<u>Nature of Relationship</u>	<u>Company</u>
Rodica Pop-Busui, MD, PhD	Grant/Research Support	Astra Zeneca

M-LINE

M-LINE is a toll-free number for referring physicians and their staff seeking access to clinical services and faculty at the Health System. M-LINE physician representatives work closely with personnel across the Health System to provide efficient, personalized service and will stay on the line with your call until your request is met to your satisfaction.

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Health Delivery and Technology in Today's DIABETES CARE

Applying Evidence Based Treatments to Personalized Care

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Diabetes Medications and Cardiovascular Disease: Winning on 2 Fronts

Rodica Pop-Busui MD, PhD
Professor of Internal Medicine,
Metabolism, Endocrinology and Diabetes,
Associate Chair Clinical Research
University of Michigan, Ann Arbor, MI

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Disclosures

- Astra Zeneca Research Grant to University of Michigan

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Objectives

- Brief historical overview on diabetes medications and cardiovascular disease risk
- Cardiovascular disease and diabetes current trends
- Discuss evidence-based findings regarding glucose control targets in patients with diabetes.
- Review effects of diabetes medications and their optimal use in the presence of cardiovascular disease and other complications.

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Brief historical overview

- In December 2008, the FDA issued guidance to pharmaceutical industry setting new expectations for the development of antidiabetes drugs for type 2 diabetes by mandating long-term cardiovascular outcomes trials (CVOTs) for safety.
- Since 2008, 9 CVOTs have been reported, 13 are under way, and 4 have been terminated.

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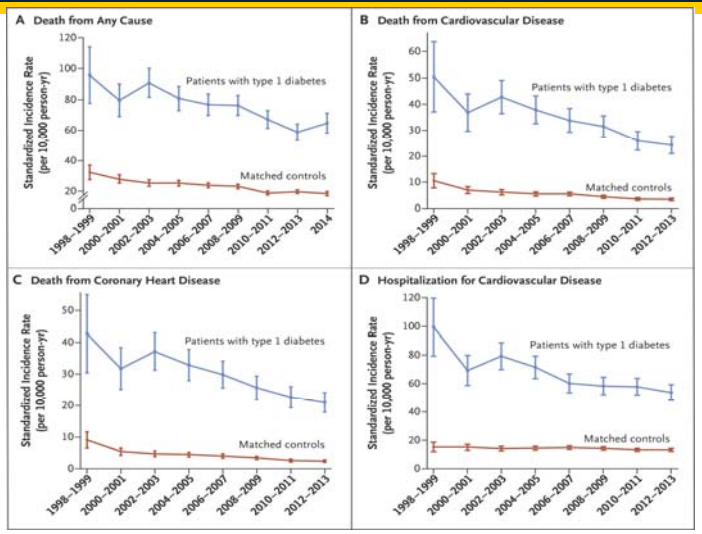
Major Cardiovascular Outcomes in Patients with Type 1 Diabetes and Matched Controls – Swedish Registry



Rawshani A et al. N Engl J Med 2017;376:1407-1418

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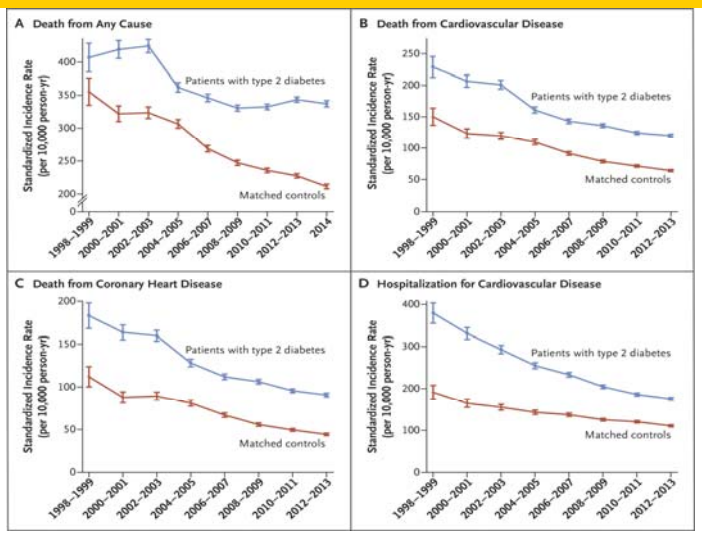
Major Cardiovascular Outcomes in Patients with Type 2 Diabetes and Matched Controls- Swedish Registry



Rawshani A et al. N Engl J Med 2017;376:1407-1418

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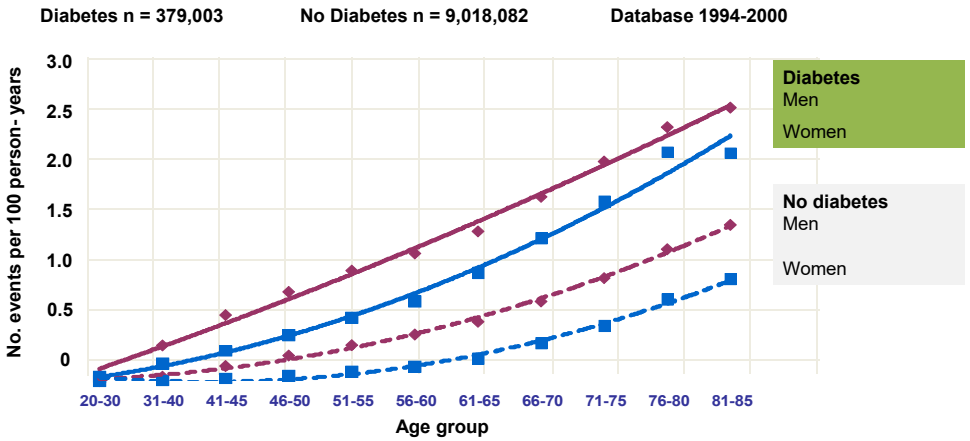
Myocardial infarction at a Younger Age Among Those with Diabetes



Booth GL, et al. *Lancet* 2006;368:29-36.

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Who Should have Stress Testing and/or Functional Imaging to Screen for ASCVD?

Typical or atypical cardiac symptoms

Associated diseases:
- PAD
- Carotid bruits
- TIA
- Stroke

Resting ECG abnormalities
(*e.g.* Q waves)

Exercise ECG stress testing

If cannot exercise or resting ECG abnormality present:
- Pharmacologic stress echo
- Pharmacologic stress nuclear imaging
- Coronary calcium (>40 years age)
- Other imaging techniques depending of local expertise

***PAD*, peripheral arterial disease; *TIA*, transient ischemic attack**

ADA Standards of Medical Care -2018

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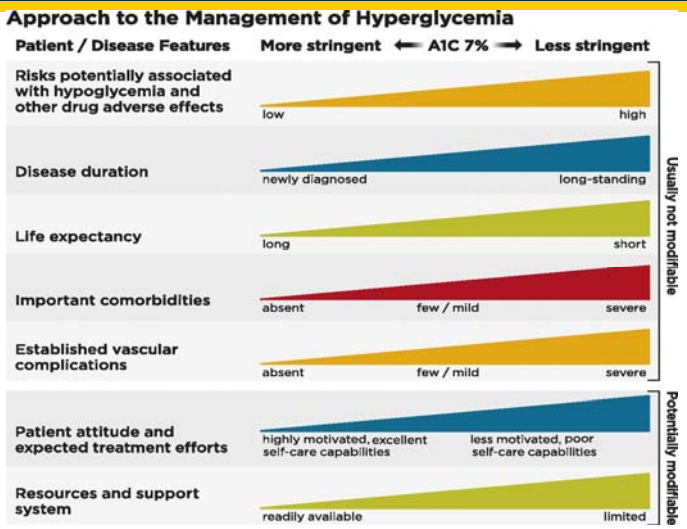
A1c Targets

American Diabetes Association



American Diabetes Association Diabetes Care 2018;41:S55-S64

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A1C Targets

≤6.5	Adults with type 2 diabetes to reduce the risk of CKD and retinopathy if at low risk of hypoglycemia
≤7.0	**MOST ADULTS WITH TYPE 1 OR TYPE 2 DIABETES**
7.1 ↓ 8.5	**7.1-8.0%**: Functionally dependent* **7.1-8.5%:** • Recurrent severe hypoglycemia and/or hypoglycemia unawareness • Limited life expectancy • Frail elderly and/or with dementia**
Avoid higher A1C to minimize risk of symptomatic hyperglycemia and acute and chronic complications	
End of life	A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia

*** Based on class of antihyperglycemic medication(s) utilized and person's characteristics**

2018 Diabetes Canada CPG – Chapter 8. Targets for Glycemic Control

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Guidance Statement Update: the American College of Physicians

ACP American College of Physicians® Leading Internal Medicine, Improving Lives

CLINICAL GUIDELINE

Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Timothy J. Wilt, MD, MPH; Devan Kansagara, MD, MCR; Carrie Horwitch, MD, MPH; Michael J. Barry, MD; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians*

Ann Intern Med. 2018;168:569-576

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Statement the American College of Physicians

Guidance Statement 1: ***Clinicians should personalize goals for glycemic control in patients with diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.***

Guidance Statement 2: ***Clinicians should aim to achieve an HbA1c level between 7% and 8% in most patients with type 2 diabetes.***

Guidance Statement 3: ***Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA1c levels less than 6.5%***

Ann Intern Med. 2018;168:569-576

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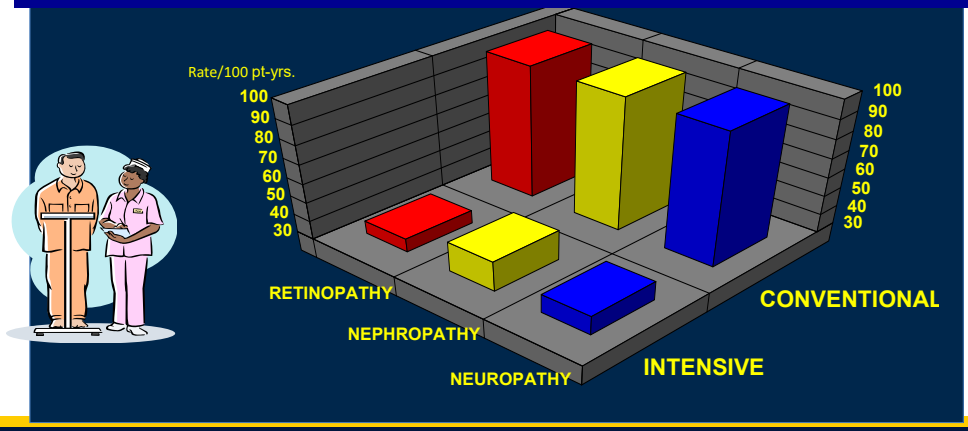
The Diabetes Control and Complications Trial

Intensive Glucose Control: 60-70% RR in Complications



N Engl J Med, 1993
Diabetologia, 1998

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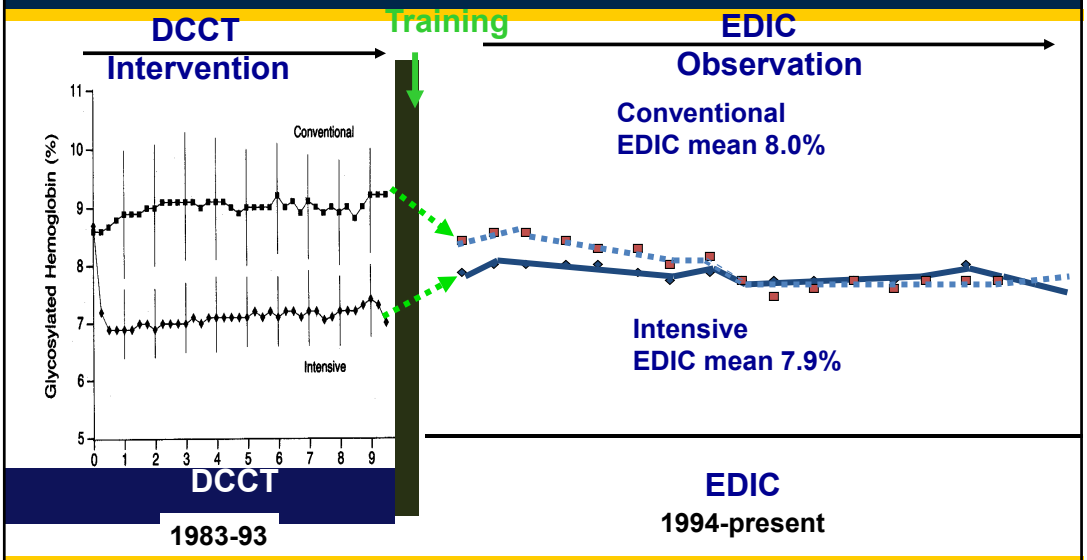
EDIC Study: Glucose Control is Difficult to Maintain



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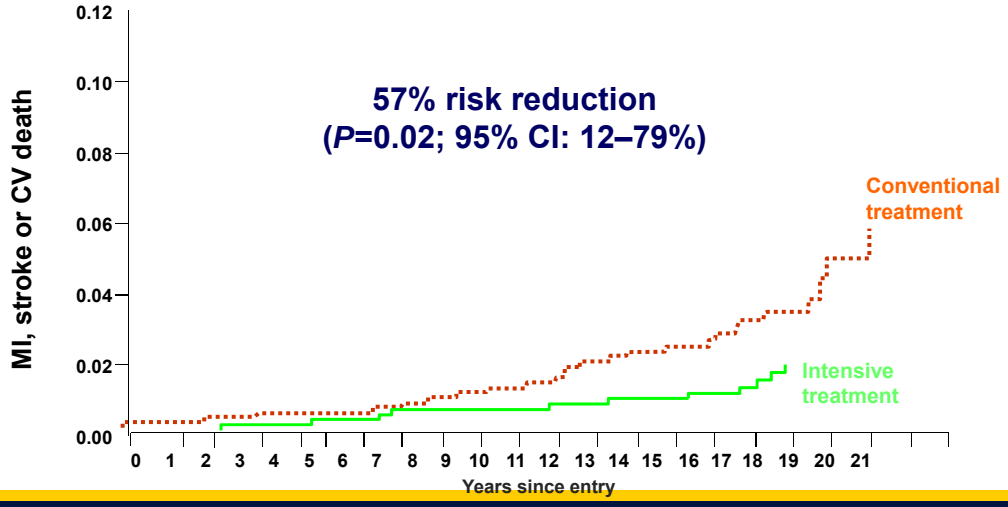
DCCT/EDIC: Early intensive glucose control leads to long-term reduction nonfatal MI, stroke or CVD death



DCCT/EDIC Study Research Group. *N Engl J Med* 2005;353:2643–2653.

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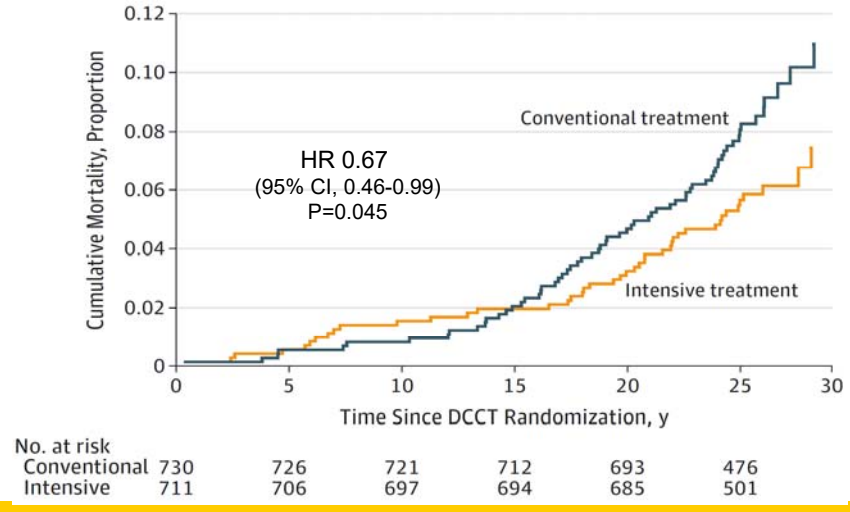
DCCT/EDIC: Early intensive glucose control leads to long-term reduction in mortality



DCCT/EDIC Research Group. JAMA 2015;313:45-53.

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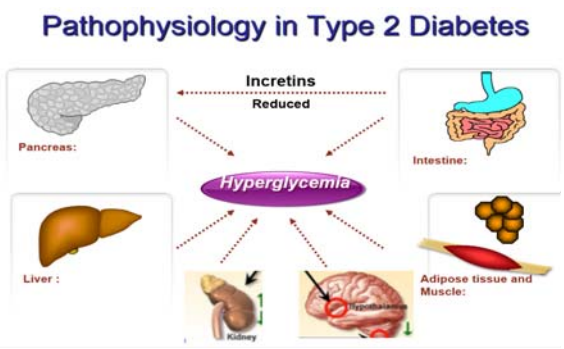
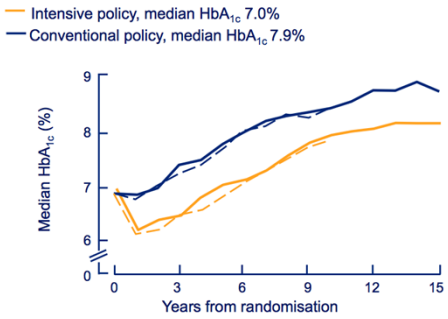
Type 2 Diabetes: Complex Pathology Progressive Disease





Br J Diabetes Vasc Dis. 2003; 3 (Supplement 1): S24-S40.
Lancet 1998;352:837–53

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UKPDS: Legacy Effect of Early Intensive Glucose Control

2007: After total of 20 years follow-up

Aggregate Endpoint		**1997**	**2007**
Any diabetes related endpoint	*RRR:*	12%	**9%**
	P:	0.029	**0.040**
Microvascular disease	*RRR:*	25%	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	16%	**15%**
	P:	0.052	**0.014**
All-cause mortality	*RRR:*	6%	**13%**
	P:	0.44	**0.007**

Holman R, et al. *N Engl J Med* 2008;359.

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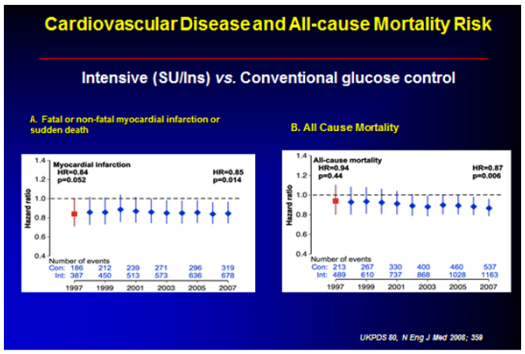
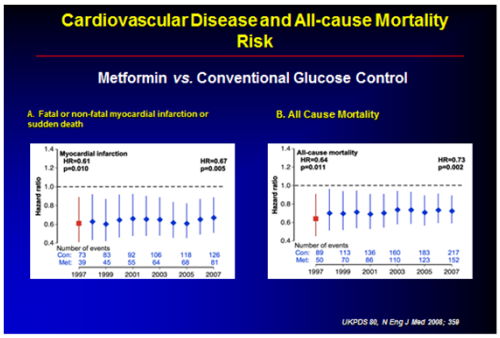
UKPDS-10-Year Follow-up of Intensive Glucose Control in T2D





N Engl J Med 2008;359:1577-1589

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ACCORD Trial
10,251 High Risk Type 2 DM (> 55, prior CVD)

	BP		Lipid		
	Intensive (SBP<120)	Standard (SBP<140)	Statin + Placebo	Statin + Fenofibrate	
Intensive Glycemia (A1C<6%)	1178	1193	1383	1374	5128*
Standard Glycemia (A1C 7-7.9%)	1184	1178	1370	1391	5123*
	2362*	2371*	2753*	2765*	10,251

Primary endpoint: First occurrence after randomization of a major CVD event: nonfatal MI, nonfatal stroke or CVD; anticipated mean follow-up 5.6 years

The ACCORD Study Group. *N Engl J Med* 2008;358(24):2545-2559

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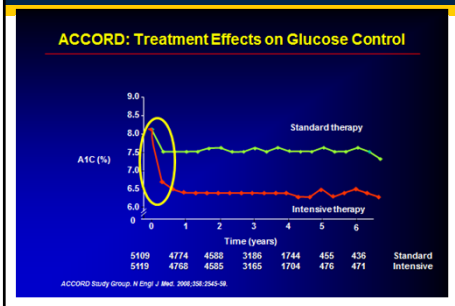
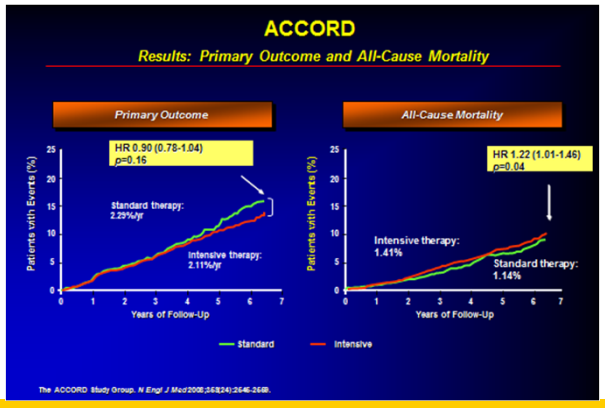
ACCORD Trial





The ACCORD Study Group. *N Engl J Med* 2008;358(24):2545-2559.

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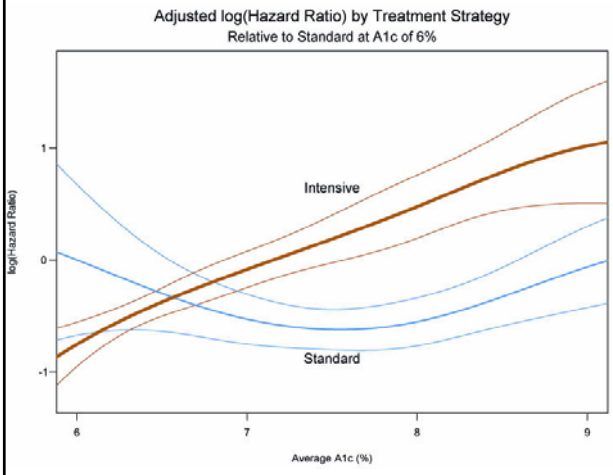
Mortality Risk and Glycemia in the ACCORD Trial



Higher levels of A1c : higher risk of mortality in the ACCORD population of T2D persons

Intensive glucose-lowering strategy, using treatment methods available at the time caused in the first 3 years a 22% increase of deaths.

This adverse outcome was associated with high A1c levels at baseline, and it occurred among individuals who attempted the intensive strategy but failed to reduce A1c from their baseline levels and continued to have A1c levels > 7%

A contribution from severe hypoglycemia in the intensively treated group has not been confirmed.

Circulation. 2010 Aug 24; 122(8): 844–846

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ACCORD Retinopathy
*Progression of Diabetic Retinopathy and Moderate Vision Loss**

Treatment	*Progression of Diabetic Retinopathy no./total no. (%)*	*Adjusted Odds Ratio (95% CI)*	*p-Value*	*Moderate Vision Loss no./total no. (%)*	*Adjusted Hazard Ratio (95% CI)*	*p-Value*
Glycemia therapy		0.67 (0.51-0.87)	0.003		0.95 (0.80-1.13)	0.56
Intensive	104/1429 (7.3)			266/1629 (16.3)		
Standard	149/1427 (10.4)			273/1634 (16.7)		
Dyslipidemia therapy†		0.60 (0.42-0.87)	0.006		1.04 (0.83-1.32)	0.73
With fenofibrate	52/806 (6.5)			145/908 (16.0)		
With placebo	80/787 (10.2)			136/893 (15.2)		
Antihypertensive therapy		1.23 (0.84-1.79)	0.29		1.27 (0.99-1.62)	0.06
Intensive	67/647 (10.4)			145/749 (19.4)		
Standard	54/616 (8.8)			113/713 (15.8)		

*Moderate vision loss was defined as loss of visual acuity by three or more lines in either eye.
†Dyslipidemia therapy consisted of simvastatin plus either fenofibrate or placebo.

Chew Y et al. *N Engl J Med*. 2010.

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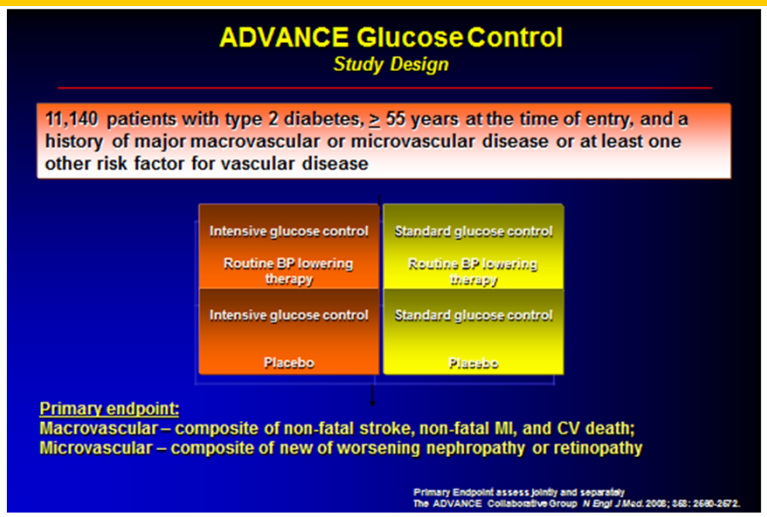
ADVANCE Trial



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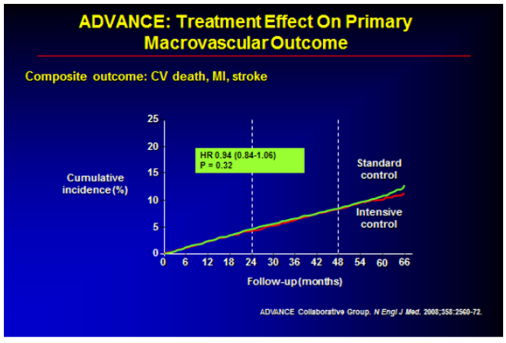
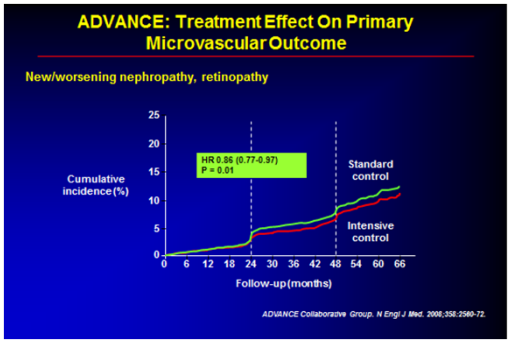
ADVANCE Trial





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Objectives

- Brief historical overview on diabetes medications and cardiovascular disease risk
- Cardiovascular disease and diabetes
- Discuss evidence-based findings regarding glucose control targets in patients with diabetes.
- **Review effects of diabetes medications and their optimal use in the presence of cardiovascular disease and other complications.**

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Available Drugs

Oral Agent Class	Products	Mechanism	↓ A1C	$
Biguanides	Metformin	↓hepatic glucose production	1 – 1.5%	Low
SUs	Glyburide, glipizide, glimepiride	↑ insulin secretion	1 – 1.5%	Low
TZDs	Pioglitazone, Rosiglitazone	↑ insulin sensitivity	1 – 1.5%	Low
DPP-4 inhibitors	Sitagliptin, saxagliptin, linagliptin, alogliptin, vildagliptin	↑ incretin levels (increases insulin and decreases glucagon)	0.7 – 0.8%	High
SGLT-2 inhibitors	Canagliflozin, dapagliflozin, empagliflozin	↑ glucosuria	0.5 – 1%	High
Injectable Class	**Products**	**Mechanism**	**↓ A1C**	**$**
GLP-1R agonists	Exenatide, liraglutide, albiglutide, dulaglutide	↑ insulin, ↓ glucagon, ↓ gastric emptying, ↑ satiety	1 – 1.5%	High
Insulins	NPH, glargine, detemir, degludec, regular, lispro, aspart, glulisine, fiasp	Replaces inadequate insulin supply	Unlimited	Varies
Alpha Glucosidase Inhibitors	Acarbose, miglitol	↓ Carb absorption	0.5 – 0.8%	Low
Colesevelam		Reduces absoption	0.5	Low
Bromocriptine			0.2 – 0.4	Low

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Case

- 61-year old African American man with type 2 diabetes presents to the office for follow-up and medication titration.
- He was diagnosed with diabetes 9 years ago, and was recommended lifestyle initially.
- Other comorbidities are obesity, hypertension, and class 2 heart failure. He is a former smoker and has a sedentary lifestyle.
- In the office BP was 145/89 mmHg , a random blood glucose obtained at 11.30 am is 69 mg/dl, and his HbA1c is 8.5%.

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Case

- Other pertinent laboratory tests are creatinine of 1.8 mg/dl, eGFR 45 ml/min, LDLc 90 mg/dl , Triglycerides 320 mg/dl, HDLc 29 mg/dl

- Current medications are:
  - metformin 1,000 mg twice a day,
  - glyburide 5 mg twice a day,
  - ASA 81 mg/day,
  - HCTZ 25 mg/day,
  - simvastatin 40 mg/day.

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• Question 1

What is the most appropriate next step in the management of this patient ?

a) Discontinue metformin
b) Refer to dietician for portion control and low carbohydrate diet
c) Discontinue glyburide
d) Increase HCTZ to 50 mg/day
e) Reduce metformin to 1,000 mg a day

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8. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2018*

Diabetes Care 2018;41(Suppl. 1):S73–S85 | https://doi.org/10.2337/dc18-S008

- **Metformin may be safely used in patients with estimated glomerular filtration rate (eGFR) as low as 30 mL/min/ 1.73 m^2**
- **The FDA recently revised the label for metformin to reflect its safety in patients with eGFR > 30 mL/ min/**
- **1.73 m^2**

https://www.fda.gov/Safety/MedWatch
SafetyInformationSafetyAlertsforHumanMedicalProducts

How would you manage glycemia next?

- **A. Add glipizide 10 mg twice a day**
- **B. Add sitagliptin 100 mg/day**
- **C. Add exenatide weekly**
- **D. Add liraglutide once/day in the am**
- **E. Add glargine at night**
- **F. Add empagliflozin**
- **G. Add canagliflozin**
- **H. Add degludec at night**

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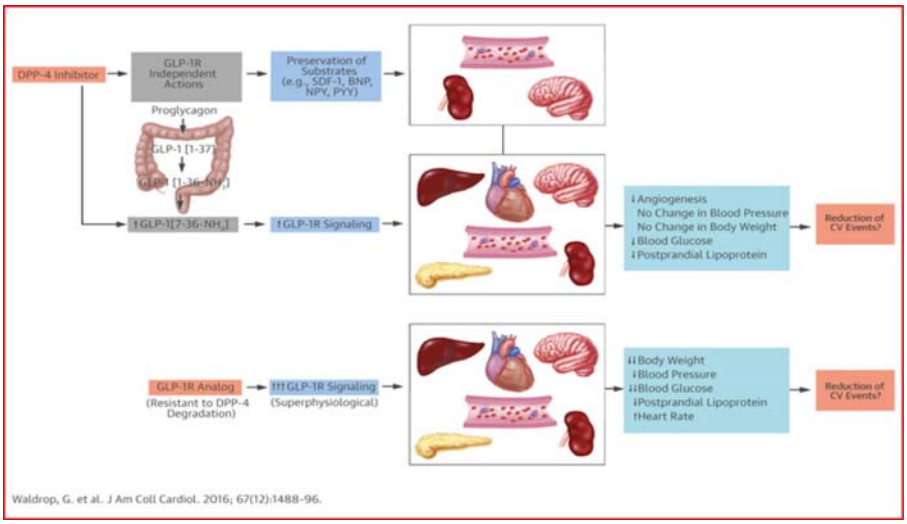
Incretin-dependent Cardiovascular Effects of Dipeptidyl Peptidase–4 Inhibitors (DPP-4i) and Glucagon-Like Peptide–1 Receptor Agonists (GLP-1Ra



Greer Waldrop et al. JACC 2016;67:1488-1496

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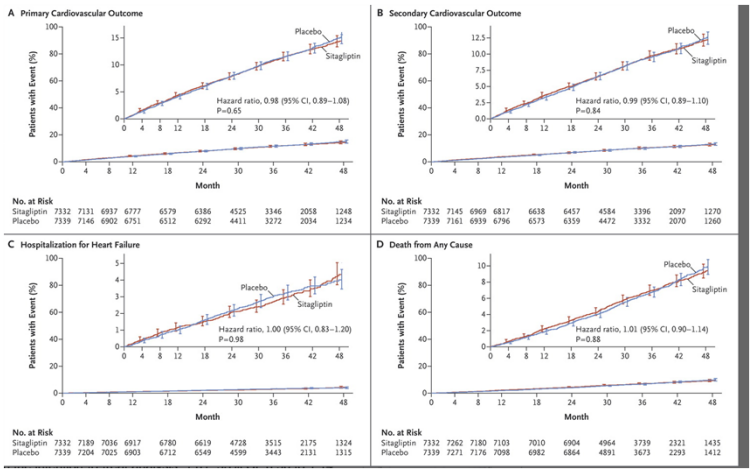
Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes



- **Weak glucose lowering effect**
- **No effect on other complications**
- **Low Incidence of hypoglycemia**

N Engl J Med 2015; 373:232-242

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Cardiovascular Outcomes Trials With DPP-4 Inhibitors

TABLE 1 Effects of Dipeptidyl Peptidase-4 Inhibitors on the Risk of Hospitalization for Heart Failure in Large-Scale Cardiovascular Outcomes Trials in Patients With Type 2 Diabetes

Drug (Ref. #) (Trial)	Study Features	Proportion of Patients With Heart Failure at Study Entry	Use of Nonstudy Antidiabetic Medications	Total Number of Heart Failure Hospitalizations Following Randomization	HR (95% CI) for Effect of DPP-4 Inhibitor
Sitagliptin (31,46) (TECOS)	14,735 patients with T2D with CVD followed for 3.0 yrs	18.0%	Metformin 81.6% Insulin 23.2% TZD 2.7% (30% reduced risk of starting insulin)	457	1.00 (0.83-1.19) (no data for subgroup with no baseline HF)
Saxagliptin (32,44) (SAVOR-TIMI 53)	16,492 patients with T2D with CVD or with multiple CV risk factors followed for 2.1 yrs	12.8%	Metformin 69.5% Insulin 41.1% TZD 6.0% (modest insulin sparing; NS during first year)	517	1.27 (1.07-1.51) (in patients with no baseline HF: 1.30 [2.03-2.65], p = 0.03)
Alogliptin (33,45) (EXAMINE)	5,380 patients with T2D with ACS followed for 1.5 yrs	27.9%	Metformin 66.2% Insulin 29.9% TZD 2.4% (no data on post-randomization insulin)	195	1.19 (0.90-1.58) (in patients with no baseline HF: 1.76 [1.07-2.90], p = 0.03)
Omarigliptin (34) (Protocol 018)	4,202 patients with T2D with CVD followed for 1.8 yrs	15.2%	Metformin 77.4% Insulin 34.9% TZD 1.1% (no data on post-randomization insulin)	53	0.60 (0.35-1.05) (no data for subgroup with no baseline HF); potential concern about competing risk

Definition of heart failure at baseline was not standardized across the trials. Number of heart failure hospitalizations following randomization includes both treatment groups. In the omarigliptin trial, the hazard ratio for heart failure hospitalization should be interpreted in light of a potential competing risk of death (higher in the omarigliptin group; HR: 1.28).

ACS = acute coronary syndrome; CV = cardiovascular; CVD = cardiovascular disease; EXAMINE = Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome; HF = heart failure; NS = not significant; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis In Myocardial Infarction 53; T2D = type 2 diabetes; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; TZD = thiazolidinedione.

JACC Heart Fail.2018 Mar 1. pii: S2213-1779(18)30041-6. doi

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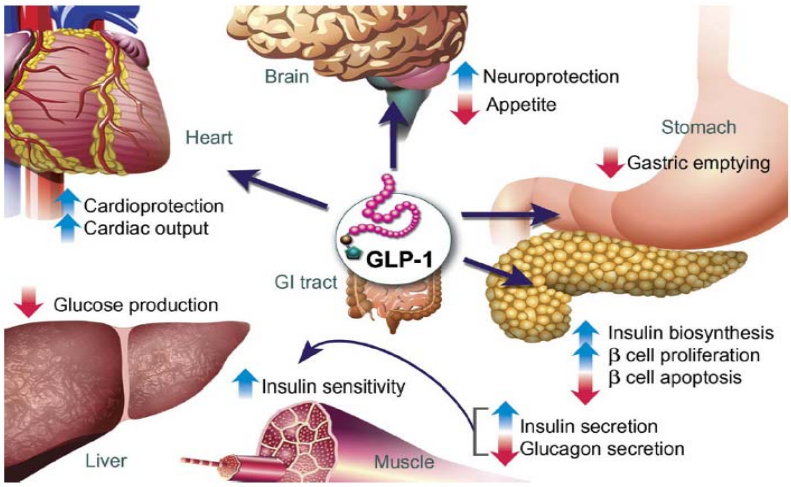
GLP-1 Actions in Peripheral Tissues



Drucker, Cell Metab, 3, 2006

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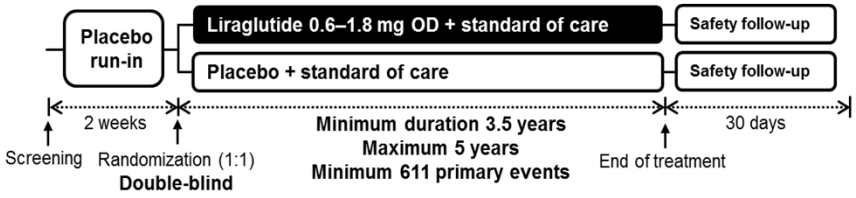
LEADER: Study Design



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure
  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

CV: Cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; HbA1c: glycated hemoglobin; MEN-2: multiple neoplasia type 2; MTC: medullary thyroid cancer; OAD: oral antidiabetic drug; OD: once daily; T2DM: type 2 diabetes mellitus

Mason June 13 2016, New Orleans, LA, USA.

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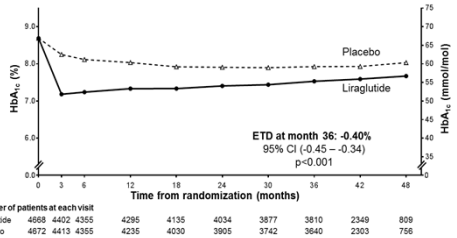
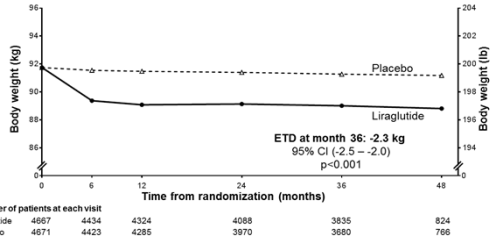
LEADER: Metabolic Outcomes

HbA1c



Body Weight



Data are estimated mean values from randomization to month 48.
CI: confidence interval; ETD: estimated treatment difference; HBA1c: glycated hemoglobin

Marso et al, N Engl J Med 375;4,311

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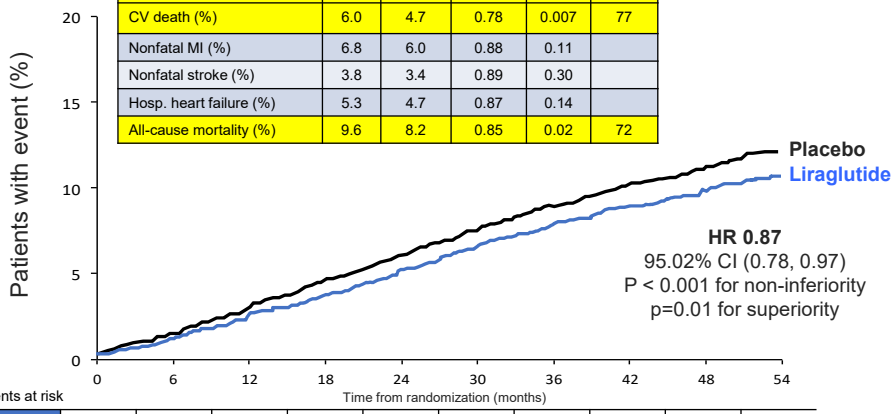
Liraglutide reduced CV events

CV death, non-fatal MI, or non-fatal stroke

	PBO	LIRA	HR	P	NNT4
CV death, MI, stroke (%)	14.9	13.0	0.87	0.01	53
CV death (%)	6.0	4.7	0.78	0.007	77
Nonfatal MI (%)	6.8	6.0	0.88	0.11	
Nonfatal stroke (%)	3.8	3.4	0.89	0.30	
Hosp. heart failure (%)	5.3	4.7	0.87	0.14	
All-cause mortality (%)	9.6	8.2	0.85	0.02	72



Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

Marso SP et al. N Engl J Med 2016;375(4):311-22.

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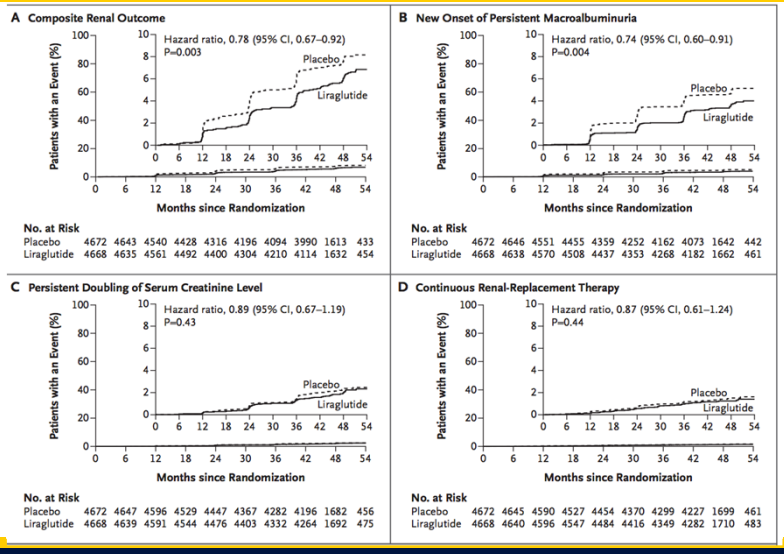
Liraglutide and Renal Outcomes in Type 2 Diabetes



N Engl J Med 2017;377:839-48.

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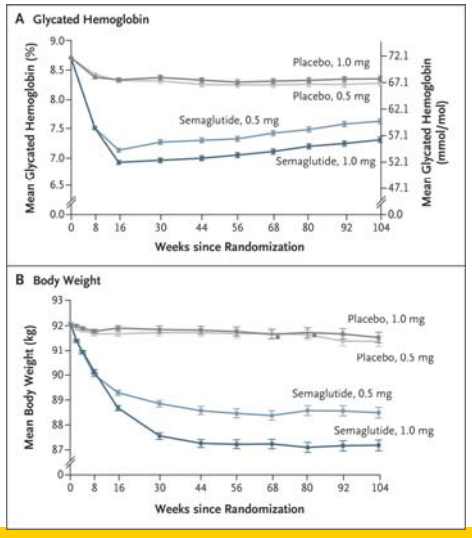
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes- SUSTAIN-6

3297 patients with T2D on standard-care regimen to receive:

- **once-weekly semaglutide (0.5 mg or 1.0 mg) s.c.**
- **placebo**

Duration : 104 weeks



Marso SP et al. N Engl J Med 2016;375:1834-1844.

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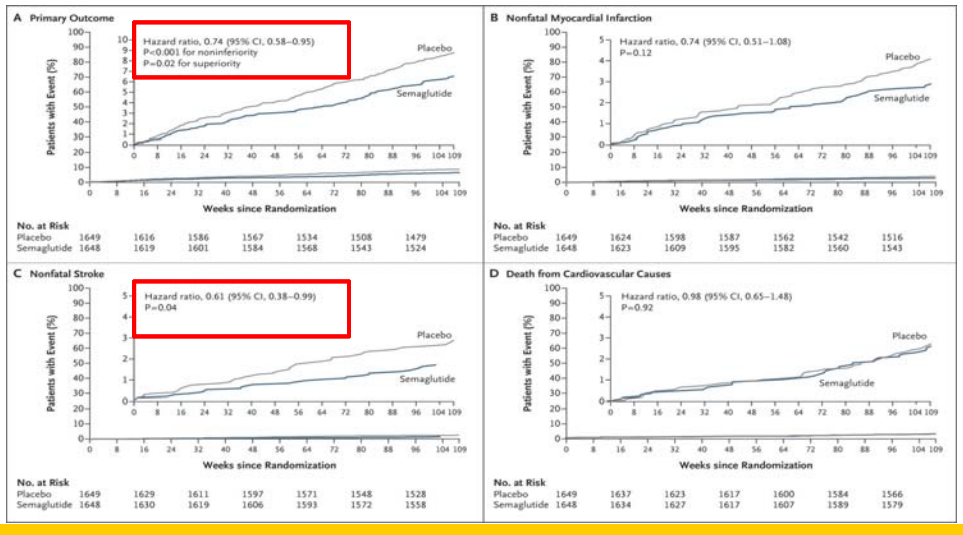
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes- SUSTAIN-6



Marso SP et al. N Engl J Med 2016;375:1834-1844.

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Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes- SUSTAIN-6

Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	no./100 person-yr	no. (%)	no./100 person-yr		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with the study treatments as fixed factors and stratified according to all combinations of stratification factors used in the randomization.
† The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
‡ The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization (coronary or peripheral), and hospitalization for unstable angina or heart failure.
§ Retinopathy complications include vitreous hemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation.
¶ New or worsening nephropathy includes persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 ml per minute per 1.73 m^2 of body-surface area (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy.

Marso SP et al. N Engl J Med 2016;375:1834-1844.

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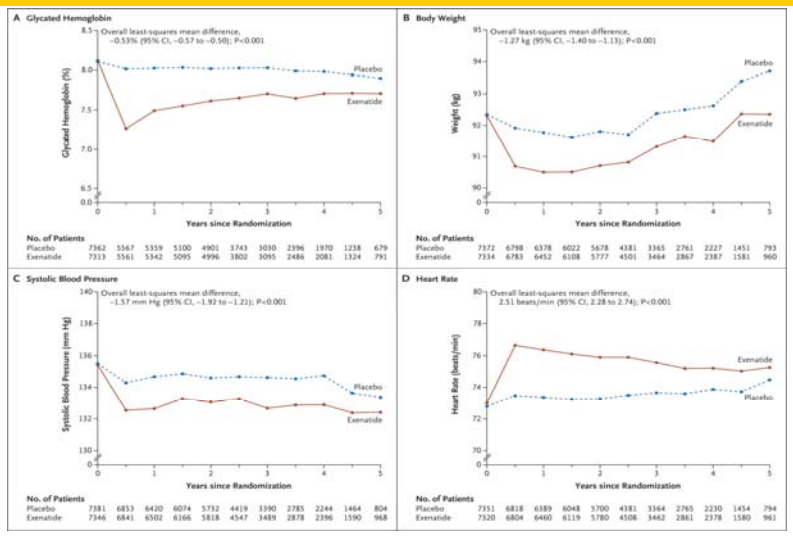
Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes – Pragmatic Design , Usual Care setting

~ Patients with T2D with/without previous CVD

Randomized to
- **2 mg exenatide ER sc**
- **matching placebo**
- **once weekly.**



Holman RR et al. N Engl J Med ;377:1228-1239

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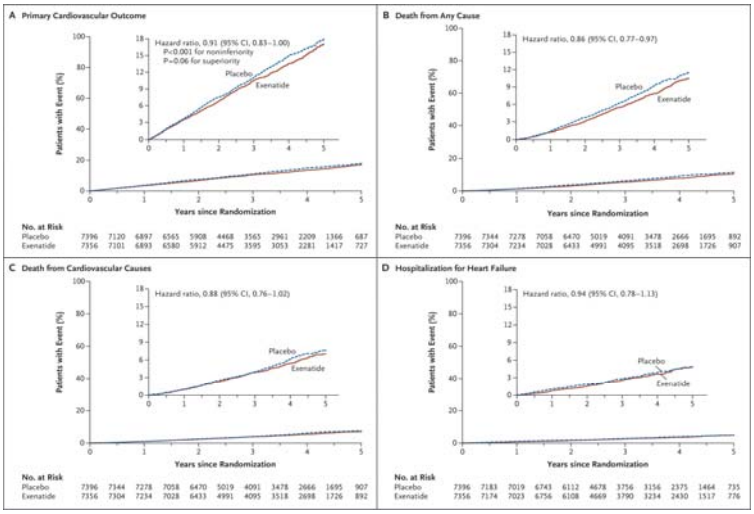
Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes

Median 3.2 years of follow-up



Holman RR et al. N Engl J Med ;377:1228-1239

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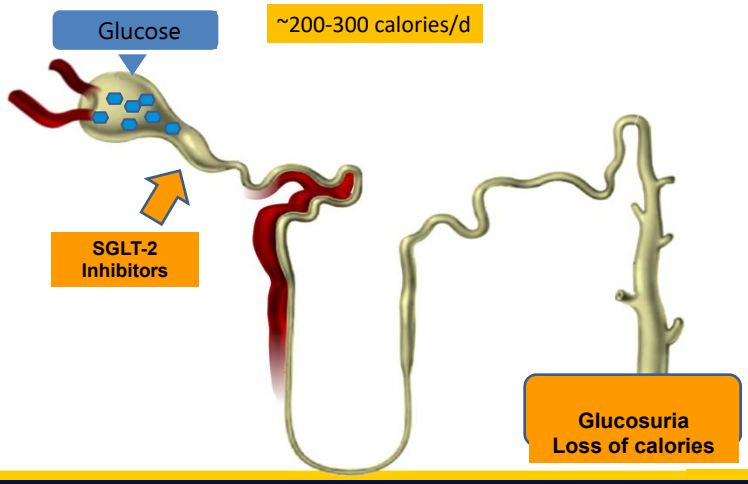
SGLT-2 Inhibitor – Mechanism of Action



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EMPA-REG

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

N Engl J Med 2015; 373:2117-2128 | November 26, 2015 | DOI: 10.1056/NEJMoa1504720

Randomized, double blind, placebo-controlled trial

Placebo: 2333 versus Empagliflozin 4687: 10 mg/d, or 25 mg/d

590 sites, 42 countries

A1c: 7-9%

Mean age: 65

71% were men

Follow up for 3.1 years

NEJM 2015; 373: 2117-2128

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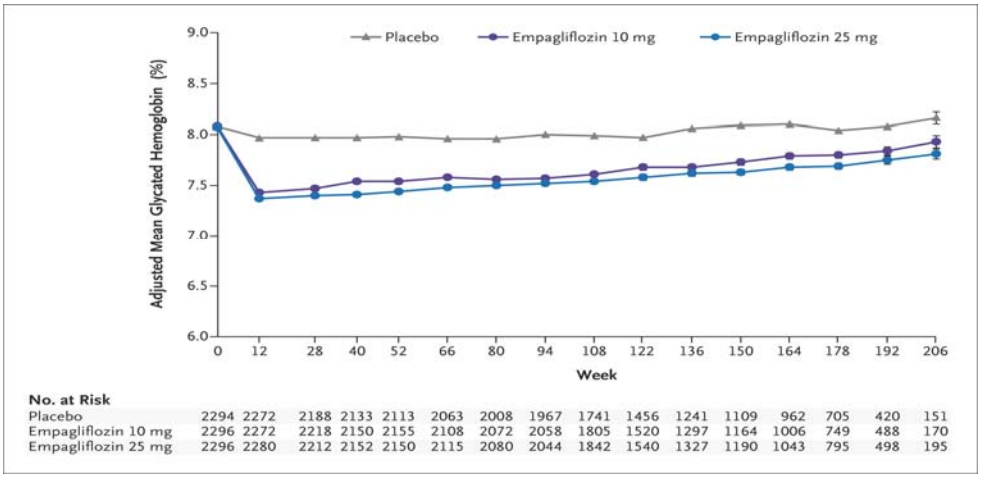
EMPA-REG Hemoglobin A1C Levels



Zinman et al. NEJM 2015; 373: 2117-2128

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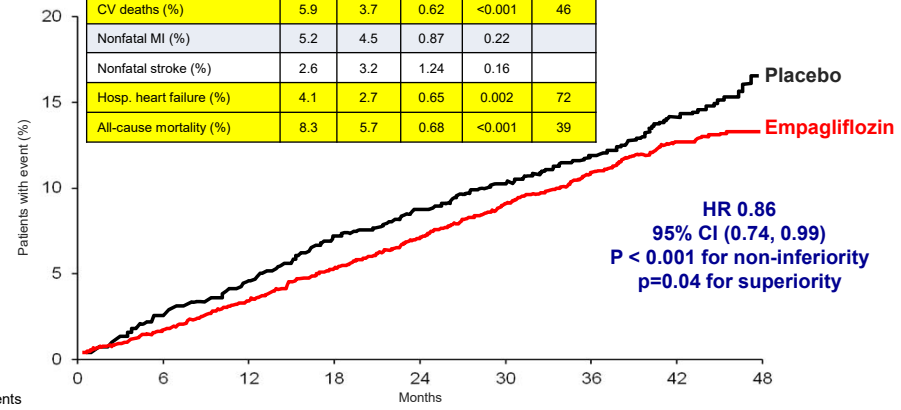
Empagliflozin reduced CV events

CV death, non-fatal MI, or non-fatal stroke

	PBO	EMPA	HR	P	NNT3
CV death, MI, stroke (%)	12.1	10.5	0.86	0.04	63
CV deaths (%)	5.9	3.7	0.62	<0.001	46
Nonfatal MI (%)	5.2	4.5	0.87	0.22	
Nonfatal stroke (%)	2.6	3.2	1.24	0.16	
Hosp. heart failure (%)	4.1	2.7	0.65	0.002	72
All-cause mortality (%)	8.3	5.7	0.68	<0.001	39



No. of patients									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Zinman B et al. N Engl J Med 2015; DOI: 10.1056/NEJMoa1504720

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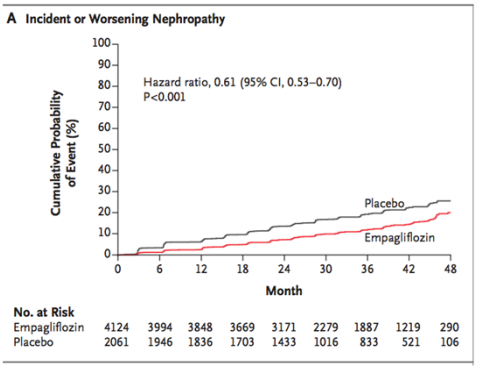
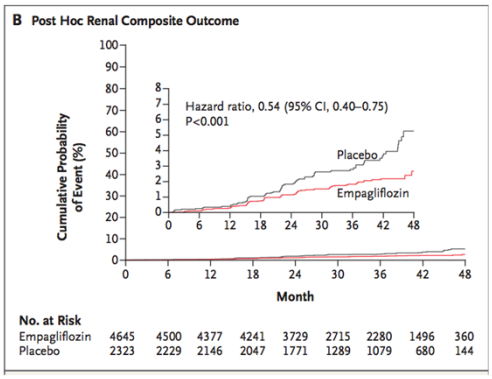
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

First occurrence of a prespecified renal composite outcome of incident or worsening nephropathy



Renal composite outcome (a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease)



N Engl J Med 2016;375:323-34.

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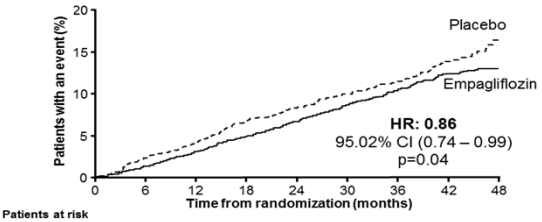
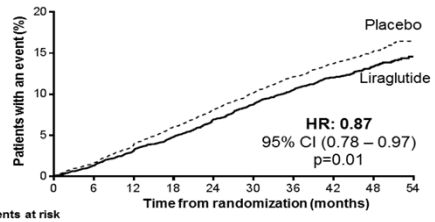
Perspective: Empagliflozin and Liraglutide

EMPA-REG OUTCOME
CV death, non-fatal MI, or non-fatal stroke



Patients at risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

LEADER
CV death, non-fatal MI, or non-fatal stroke



Patients at risk									
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

Zinman B et al. *N Engl J Med* 2015; 373: 2117-2128
Marso et al, N Engl J Med 375;4,311

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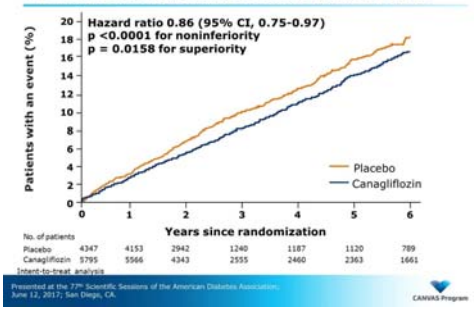
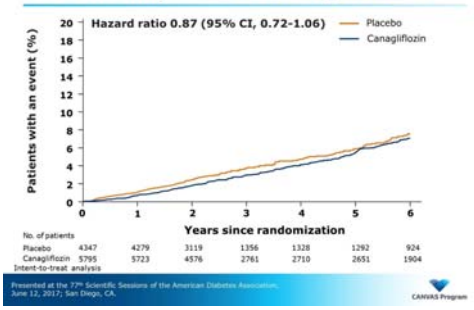
Canagliflozin and CVD Outcomes (CANVAS)

Primary MACE Outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



CV Death Component of Primary Outcome



Canagliflozin not FDA approved for CVD prevention

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

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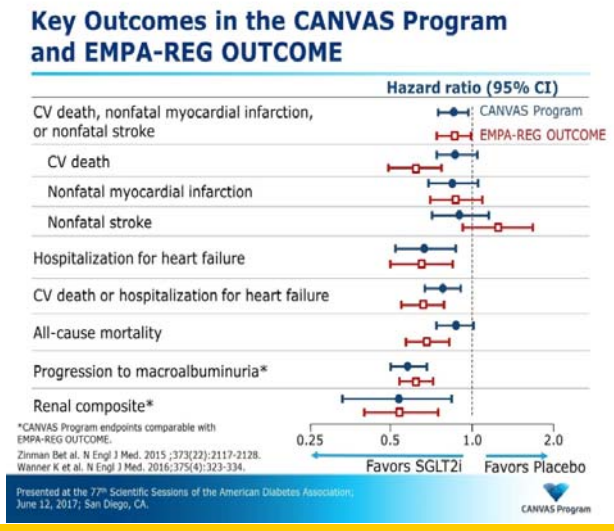
• Perspective: Empagliflozin and Canagliflozin



Higher amputation risk

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

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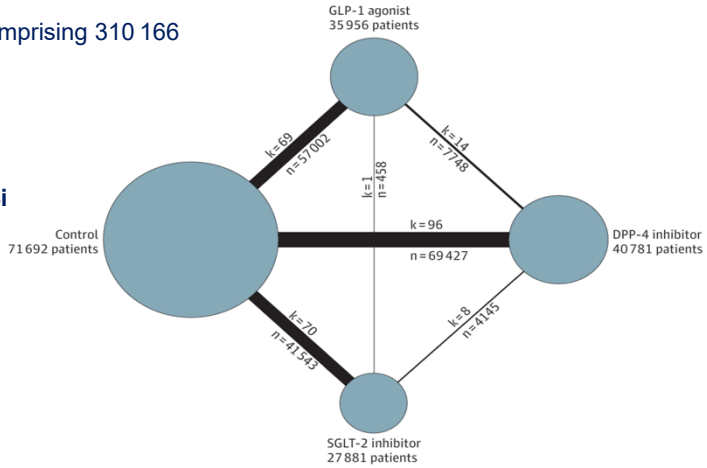
Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors and All-Cause Mortality in Patients With Type 2 Diabetes

176 310 participants enrolled, comprising 310 166 participant-years

Direct comparisons:
14 trials : GLP-1RA vs a DPP-4i

8 trials: SGLT-2i vs. a DPP-4i

1 trial : SGLT-2i vs. a GLP-1RA



DPP-4 " dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; k, the number of comparisons; n, the number of patients per comparison; SGLT-2, sodium-glucose cotransporter 2.

JAMA. 2018;319(15):1580-1591. doi:10.1001/jama.2018.3024

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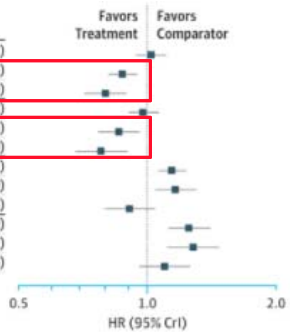
Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes

Primary Outcome: All-Cause Mortality

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor		0.1 (-0.3 to 0.6)	1.02 (0.94 to 1.11)
GLP-1 agonist	vs Control	-0.6 (-1.0 to -0.3)	0.88 (0.81 to 0.94)
SGLT-2 inhibitor		-1.0 (-1.5 to -0.6)	0.80 (0.71 to 0.89)
Control		-0.1 (-0.4 to 0.2)	0.98 (0.90 to 1.06)
GLP-1 agonist	vs DPP-4 inhibitor	-0.5 (-0.9 to -0.2)	0.86 (0.77 to 0.96)
SGLT-2 inhibitor		-0.9 (-1.2 to -0.4)	0.78 (0.68 to 0.90)
Control		0.6 (0.3 to 1.0)	1.14 (1.06 to 1.23)
DPP-4 inhibitor	vs GLP-1 agonist	0.7 (0.2 to 1.3)	1.17 (1.04 to 1.30)
SGLT-2 inhibitor		-0.4 (-0.9 to 0.2)	0.91 (0.79 to 1.04)
Control		0.9 (0.4 to 1.5)	1.25 (1.12 to 1.40)
DPP-4 inhibitor	vs SGLT-2 inhibitor	1.0 (0.4 to 1.7)	1.28 (1.11 to 1.47)
GLP-1 agonist		0.4 (-0.1 to 0.9)	1.10 (0.96 to 1.26)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	88	2955 (5.2)	57022
DPP-4 inhibitor	49	1171 (3.9)	30178
GLP-1 agonist	32	1195 (4.4)	27373
SGLT-2 inhibitor	29	714 (3.6)	19587



JAMA. 2018;319(15):1580-1591. doi:10.1001/jama.2018.3024

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Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes

Cardiovascular Mortality

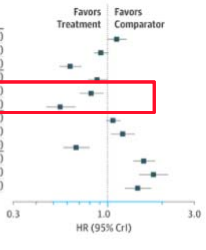
Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor		0.0 (-0.3 to 0.4)	1.00 (0.91 to 1.11)
GLP-1 agonist	vs Control	-0.5 (-0.8 to -0.1)	0.85 (0.77 to 0.94)
SGLT-2 inhibitor		-0.8 (-1.1 to -0.3)	0.79 (0.69 to 0.91)
Control		0.0 (-0.3 to 0.3)	1.00 (0.90 to 1.10)
GLP-1 agonist	vs DPP-4 inhibitor	-0.5 (-0.8 to -0.1)	0.85 (0.74 to 0.98)
SGLT-2 inhibitor		-0.7 (-1.1 to -0.2)	0.79 (0.66 to 0.94)
Control		0.5 (0.2 to 0.9)	1.17 (1.06 to 1.30)
DPP-4 inhibitor	vs GLP-1 agonist	0.5 (0.1 to 1.1)	1.18 (1.02 to 1.36)
SGLT-2 inhibitor		-0.2 (-0.7 to 0.3)	0.93 (0.78 to 1.10)
Control		0.8 (0.3 to 1.3)	1.27 (1.10 to 1.46)
DPP-4 inhibitor	vs SGLT-2 inhibitor	0.8 (0.2 to 1.5)	1.27 (1.07 to 1.51)
GLP-1 agonist		0.2 (-0.3 to 0.8)	1.08 (0.91 to 1.29)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	50	1833 (3.6)	50869
DPP-4 inhibitor	27	763 (3.1)	24519
GLP-1 agonist	19	704 (3.0)	23554
SGLT-2 inhibitor	19	468 (2.5)	18407

Heart failure

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor		0.4 (0.0 to 0.8)	1.13 (1.00 to 1.28)
GLP-1 agonist	vs Control	-0.2 (-0.5 to 0.1)	0.93 (0.84 to 1.02)
SGLT-2 inhibitor		-1.1 (-1.3 to -0.8)	0.62 (0.54 to 0.72)
Control		-0.3 (-0.5 to 0.0)	0.88 (0.78 to 1.00)
GLP-1 agonist	vs DPP-4 inhibitor	-0.4 (-0.7 to -0.1)	0.82 (0.70 to 0.95)
SGLT-2 inhibitor		-1.1 (-1.3 to -0.8)	0.55 (0.46 to 0.67)
Control		0.2 (-0.1 to 0.5)	1.08 (0.98 to 1.18)
DPP-4 inhibitor	vs GLP-1 agonist	0.6 (0.1 to 1.1)	1.22 (1.05 to 1.42)
SGLT-2 inhibitor		-0.9 (-1.2 to -0.5)	0.67 (0.57 to 0.80)
Control		1.0 (0.6 to 1.4)	1.60 (1.39 to 1.84)
DPP-4 inhibitor	vs SGLT-2 inhibitor	1.3 (0.8 to 2.0)	1.81 (1.50 to 2.18)
GLP-1 agonist		0.8 (0.4 to 1.3)	1.48 (1.25 to 1.76)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	55	1370 (2.8)	48362
DPP-4 inhibitor	24	544 (2.4)	22327
GLP-1 agonist	21	638 (2.7)	23363
SGLT-2 inhibitor	19	266 (1.7)	15989



JAMA. 2018;319(15):1580-1591. doi:10.1001/jama.2018.3024

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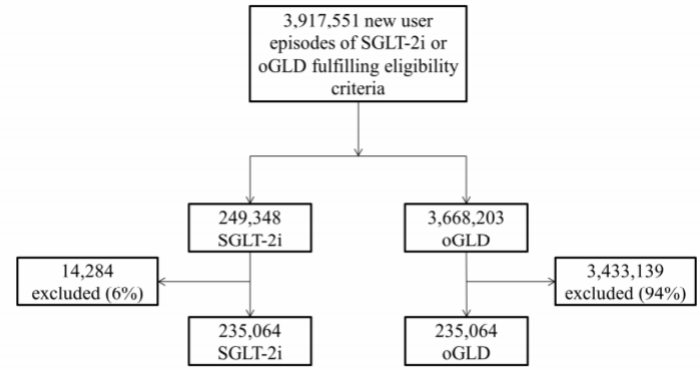
Lower Cardiovascular Risk Associated with SGLT-2i in >400,000 Patients: The CVD-REAL 2 Study

New users of SGLT-2i and other glucose lowering drugs identified via claims, medical records and national registries across six countries in Asia Pacific, Middle East and North America

Propensity matching
Established CVD: 27%
HBP: 62%
Women: 45%
Metformin: 74%
SU: 50%
DPP-4I: 55%
Insulin: 20%



Kosiborod et al DOI: 10.1016/j.jacc.2018.03.009

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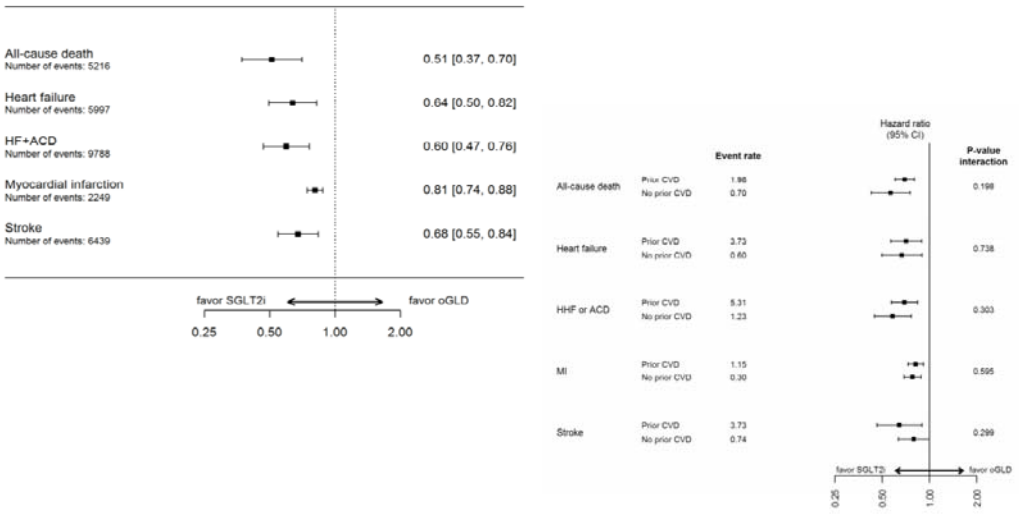
Lower Cardiovascular Risk Associated with SGLT-2i in >400,000 Patients: The CVD-REAL 2 Study



Kosiborod et al DOI: 10.1016/j.jacc.2018.03.009

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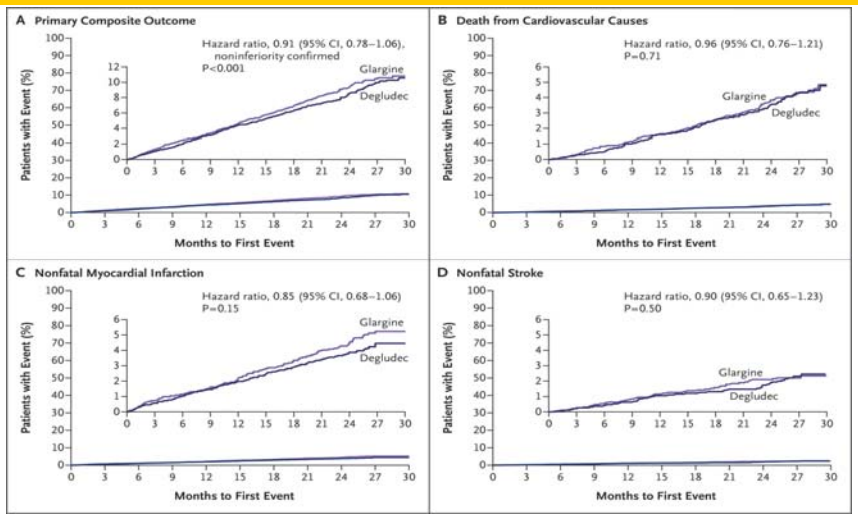
DEVOTE: Insulin Degludec and Cardiovascular Outcomes



Marso SP et al. N Engl J Med 2017;377:723-732.

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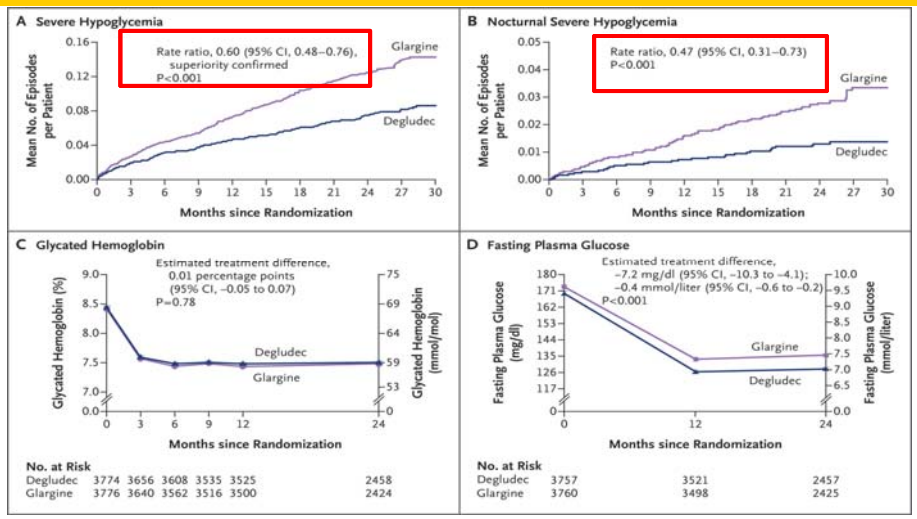
DEVOTE: Severe Hypoglycemia and Glucose Control.



Marso SP et al. N Engl J Med 2017;377:723-732.

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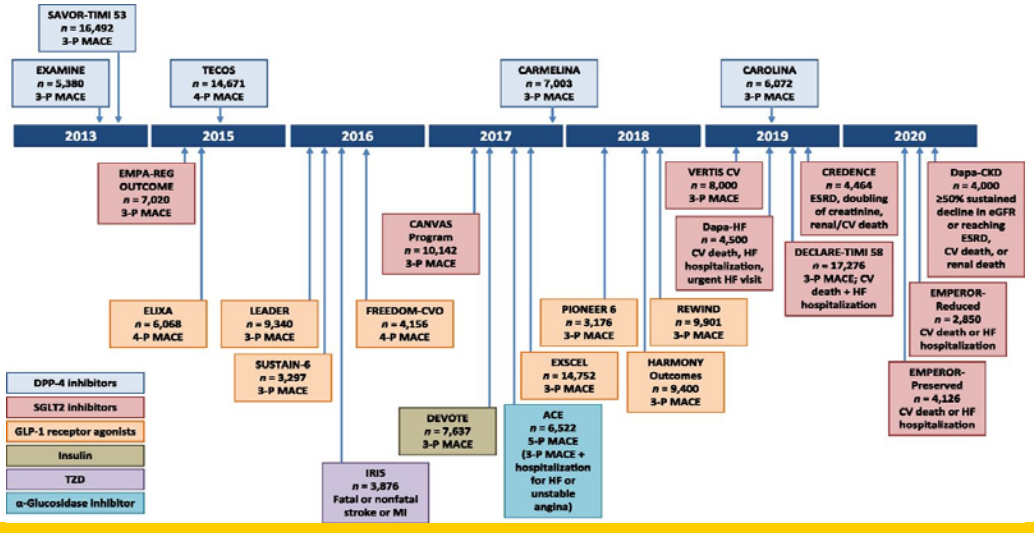
Take Home Message: Strong Evidence Completed and On-going CVOTs



William T. Cefalu et al. Dia Care 2018;41:14-31

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Take Home Message

- Each of the completed trials demonstrated noninferiority of their respective drugs to placebo for their primary cardiovascular (CV) composite end point.
- Notably, four additionally provided evidence of CV benefit in the form of significant decreases in the primary CV composite end point, two suggested reductions in CV death, and three suggested reductions in all-cause mortality

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Profiles of Antidiabetic Medications

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	SU: Moderate/Severe; GLN: Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30; Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m²; Genital Mycotic Infections; Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin); Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF / CARDIAC / ASCVD	Neutral	See #1	See #2	See #3	Neutral	Moderate; May Reduce Stroke Risk	Neutral; Possible ASCVD Risk	Neutral; Benefit	Neutral; Safe	CHF Risk; Neutral	Neutral
BONE	Neutral	Neutral	Mild Fracture Risk	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits; Likelihood of adverse effects; Use with caution

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

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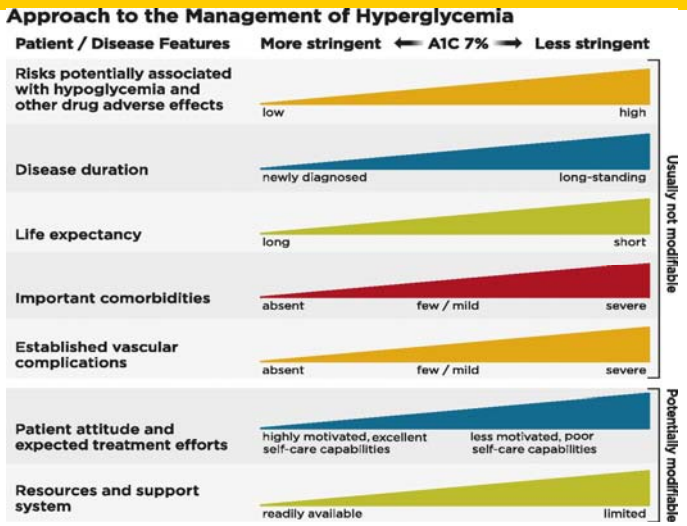
Take Home Message A1c Targets



American Diabetes Association Diabetes Care 2018;41:S55-S64

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Take Home Messages

In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with eGFR >30 mL/min/1.73m^2, an antihyperglycemic agent with demonstrated CV outcome benefit should be added to reduce the risk of:

a) **major CV events [Grade A, Level 1A for empagliflozin; Grade A, Level 1A for liraglutide; Grade C, Level 2 for canagliflozin]**

b) **heart failure hospitalization [Grade B, Level 2 for empagliflozin; Grade C, Level 2 for canagliflozin],**

c) **progression of nephropathy : empagliflozin; liraglutide canagliflozin**

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Take Home Messages

- **In people <u>without</u> clinical CVD in whom A1C target is not achieved with current therapy, if affordability and access are not barriers, people with type 2 diabetes and their providers who are concerned about hypoglycemia and weight gain may prefer an incretin agent (DPP-4 inhibitor or GLP-1 receptor agonist) and/or an SGLT2 inhibitor to other agents as they improve glycemic control with a low risk of hypoglycemia and weight gain.**

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Pumps & CGM: What the Primary Care Provider Needs to Know

"Have you thought about an insulin pump upgrade?"

By: Jenni Iyengar
Clinical Assistant Professor
Metabolism, Endocrinology & Diabetes
University of Michigan

Disclosures

- None

Agenda

- What do pumps & CGMs do (and what do they NOT do)
- What patients might benefit from diabetes technologies
- What does pump & CGM combos mean for the future of diabetes management

Let's Talk Pumps

Medtronic

Tslim

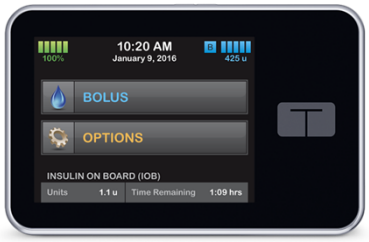
OmniPod

Animas

What does what?

Insulin Pump:

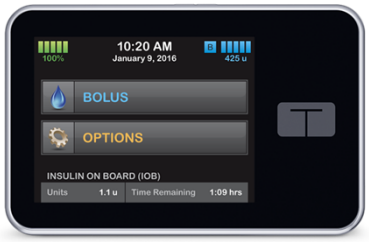
Gives you insulin



What does what?

Insulin Pump:

Gives you insulin



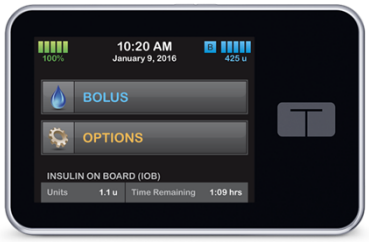
Continuous Glucose Monitor:

Measures your blood sugar

What does an insulin pump do?

Insulin Pump:

Gives you insulin

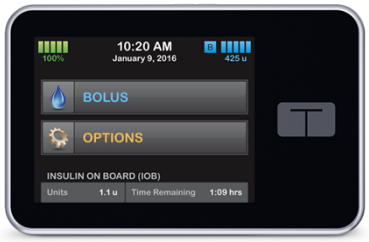


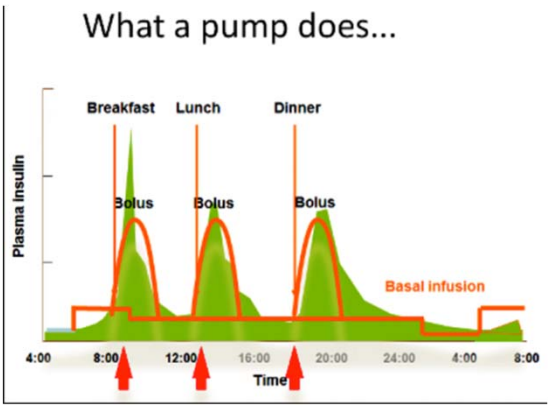
- Attached to body, small catheter under skin
- Administers insulin
- Gives a small continuous amount of insulin
- Gives a "bolus" of insulin when the patient indicates that they have eaten or that their sugar is high

What does an insulin pump do?

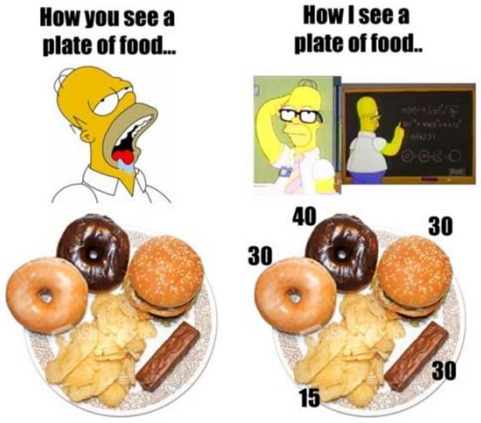
Insulin Pump:

Gives you insulin





What does an insulin pump do?

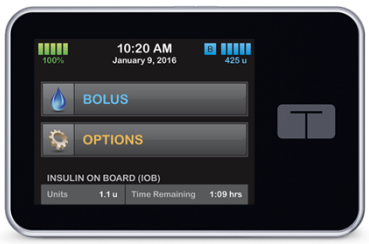


- Basal Rate: Small amount of continuous insulin (equivalent to long-acting insulin)
- Carb Ratio: how many grams of carbohydrate are "covered" by each unit of insulin
- Sensitivity Factor: the number of points 1 unit of rapid acting insulin lowers your blood glucose.

What does an insulin pump do?

Insulin Pump:

Gives you insulin



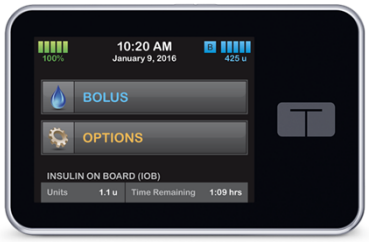
Patient Expectations:

- Check their sugar (4x a day!)
- Be comfortable carb counting
- Bolus for meals & correction
- Pump maintenance & troubleshooting

What does an insulin pump do?

Insulin Pump:

Gives you insulin



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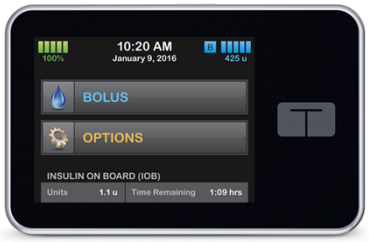
What does an insulin pump do?

Insulin Pump:

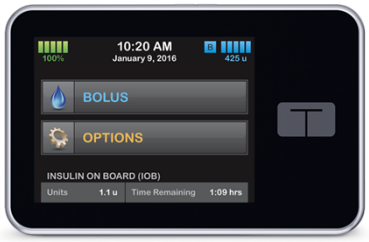
Gives you insulin



What does an insulin pump do?

Insulin Pump:

Gives you insulin



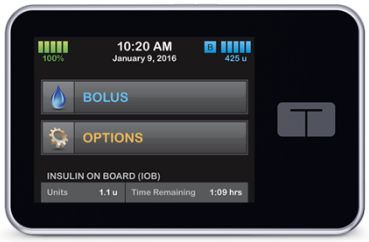
Advantages:

- Vary basal rates by time of day
- Does the math for you
- Remembers amounts given
- Avoid “stacking”
- Ease of bolusing

What does an insulin pump do?

Insulin Pump:

Gives you insulin



Features:

- Temporary basal rates
- Square/dual wave boluses
- Possibly CGM integration

So who is a good pumping candidate?

Table 6
Proposed Clinical Characteristics of Suitable Insulin Pump Candidates

Patient clinical characteristics	
T1DM	**T2DM**
Patients with T1DM who do not reach glycemic goals despite adherence to maximum MDI, especially if they have: • Very labile diabetes (erratic and wide glycemic excursions, including recurrent DKA) • Frequent severe hypoglycemia and/or hypoglycemia unawareness • Significant "dawn phenomenon," extreme insulin sensitivity Special populations (e.g., preconception, pregnancy, children, adolescents, competitive athletes) Patients with T1DM who, after investigation and careful consideration, feel that CSII would be helpful in achieving and maintaining treatment targets and improve their ability to cope with the challenges of managing their diabetes	Selected patients with insulin-requiring T2DM who satisfy any or all of the following: • C-peptide positive, but with suboptimal control on a maximal program of basal/bolus injections (Note: CMS will not reimburse for pumps or pump supplies in T2DM patients who are not C-peptide deficient) • Substantial "dawn phenomenon" • Erratic lifestyle (e.g., frequent long-distance travel, shift work, unpredictable schedules leading to difficulty maintaining meal timing) • Severe insulin resistance, candidate for U500 insulin by CSII Selected patients with other DM types (e.g., postpancreatectomy)

Abbreviations: CMS = Centers for Medicare & Medicaid Services CSII = continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; DM = diabetes mellitus; MDI = multiple daily injections; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

Medicare Criteria

Box 2
U.S. Centers for Medicare & Medicaid Services (CMS) Insulin Pump Patient Eligibility Criteria (88)

To be eligible for CMS insulin pump coverage, patients must meet 1 of the following criteria:

(A) Patient has completed a comprehensive diabetes education program and has been receiving MDI insulin with frequent self-adjustments for at least 6 months before pump initiation. Patient has documented SMBG frequency an average of ≥4 times per day during the previous 2 months. Patient must also meet ≥1 of the following criteria:

- HbA_{1c} >7.0%
- History of recurrent hypoglycemia
- Wide fluctuations in blood glucose before mealtime
- "Dawn phenomenon" with FPG frequently >200 mg/dL or a history of severe glycemic excursions

(B) Patient on pump therapy before enrollment with a documented SMBG an average of ≥4 times per day during the month before enrollment.

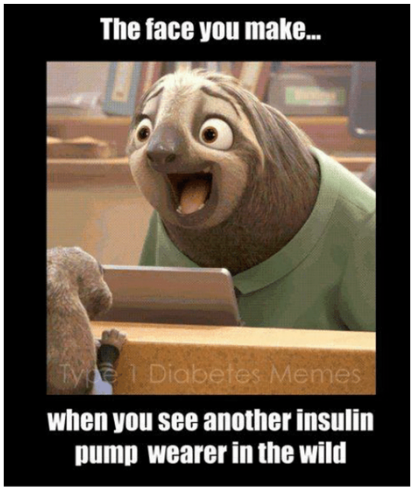
(C) Fasting C-peptide ≤110% lower limit of normal or ≤200% lower limit of normal if CrCl ≤50 mL/min with concurrent FPG ≤225 mg/dL; or beta-cell autoantibody positive (+ICA or +GAD antibodies)

Abbreviations: CrCl = creatinine clearance; FPG = fasting plasma glucose; GAD = glutamate decarboxylase, HbA_{1c} = hemoglobin A_{1c}; ICA = islet cell antibodies; MDI = multiple daily injections; SMBG = self-monitored blood glucose

AACE Guidelines

So who is a good pumping candidate?

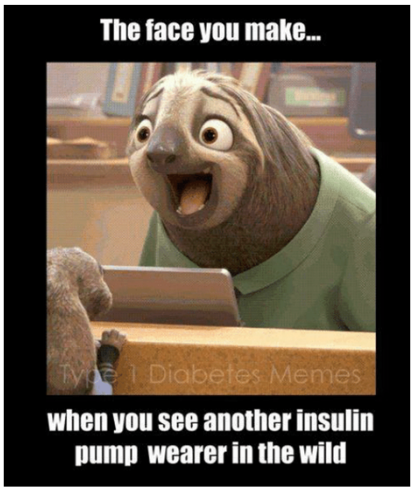
- Modestly above goal despite multiple daily injections
- At goal with multiple daily injections but looking to ease burden of management
- Frequent lows due to exercise
- Grazers, stackers
- Very low requirements
- Looking to address patterns



Does this happen to you?

So who is a NOT good pumping candidate?

- The patient who doesn't want to check their blood sugars
- The patient who is on basal only insulin therapy
- The patient with an A1c of 14%
- Anyone who doesn't want to invest significant time in their diabetes management



Does this happen to you?

But what about the “artificial pancreas”

…sit tight, we need to explain a CGM first

Let’s Talk CGM

DexCom

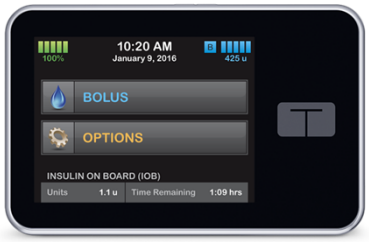
Freestyle Libre

Medtronic

What does a CGM do?

Insulin Pump:

Gives you insulin



Continuous Glocose Monitor:

Measures your blood sugar

What does a CGM do?

- Sensor sits under skin
- Monitors blood sugar
- Bluetooth transmitter attached
- Readings every 5 min
  - Receiver
  - Phone/Watch
  - Pump
- SOME require fingersticks for calibration

Continuous Glocose Monitor:

Measures your blood sugar

What does a CGM do?

Advantages:

- Low blood sugars -> treat them before they happen!
- Safety before and during activities such as driving
- Spot post-meal highs
- Adjust based on trend arrows

Continuous Glucose Monitor:

Measures your blood sugar

Dosing off trends

New Approach to Adjusting Insulin Doses Using Trend Arrows in Adults: Pre-meal and Corrections ≥4 Hours Post-meal

Trend Arrows		Correction Factor* (CF)	Insulin Dose Adjustment (U)
Receiver	App		
⇈	↑	<25	+4.5
		25–<50	+3.5
		50–<75	+2.5
		≥75	+1.5
↑	↗	<25	+3.5
		25–<50	+2.5
		50–<75	+1.5
		≥75	+1.0
↗	→	<25	+2.5
		25–<50	+1.5
		50–<75	+1.0
		≥75	+0.5
→	→	<25	No adjustment
		25–<50	No adjustment
		50–<75	No adjustment
		≥75	No adjustment
↘	→	<25	-2.5
		25–<50	-1.5
		50–<75	-1.0
		≥75	-0.5
↓	↘	<25	-3.5
		25–<50	-2.5
		50–<75	-1.5
		≥75	-1.0
⇊	↓	<25	-4.5
		25–<50	-3.5
		50–<75	-2.5
		≥75	-1.5

What does a CGM do?

Approved for **NON-ADJUNCTIVE** use by FDA

You can dose your insulin off the number you see on your device WITHOUT a fingerstick.

Continuous Glucose Monitor:

Measures your blood sugar

CGM MARD

- Medtronic Enlite = 3-4 calibrations per day 13.6% error
- Medtronic Guardian 2 calibrations = 10.6%
- Medtronic Guardian 4 calibrations = 9.6%

- Dexcom G4 2 calibrations per day = 9-13%
- Dexcom G5 2 calibrations per day = 9%
- Dexcom G6 0 calibrations per day = 9.3%

- Abott's Freestyle Libre 0 calibrations = 9.7%

Medicare Criteria

Therapeutic CGM may be covered by Medicare when all of the following criteria are met:

- The beneficiary has diabetes mellitus; and,
- The beneficiary has been using a home blood glucose monitor (BGM) and performing frequent (four or more times a day) BGM testing; and,
- The beneficiary is insulin-treated with multiple daily injections (MDI) of insulin or a continuous subcutaneous insulin infusion (CSII) pump; and,
- The patient's insulin treatment regimen requires frequent adjustment by the beneficiary on the basis of therapeutic CGM testing results.

DexCom

Special Considerations

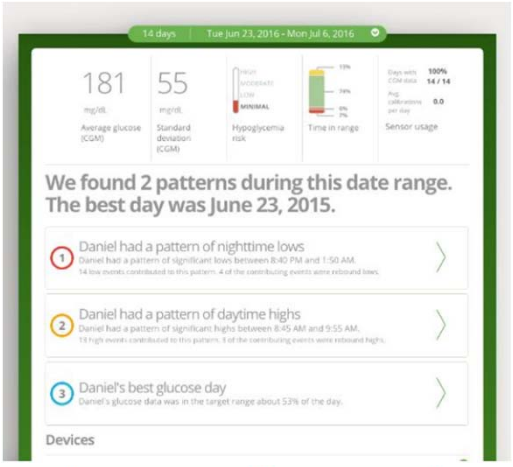
- Approved for dosing
- Private insurance customers can send data to phone (Android, iphone)
- Medicare customers need to send to receiver
- Order through a DME
- Typically can upgrade once a year

Freestyle Libre

Special Considerations

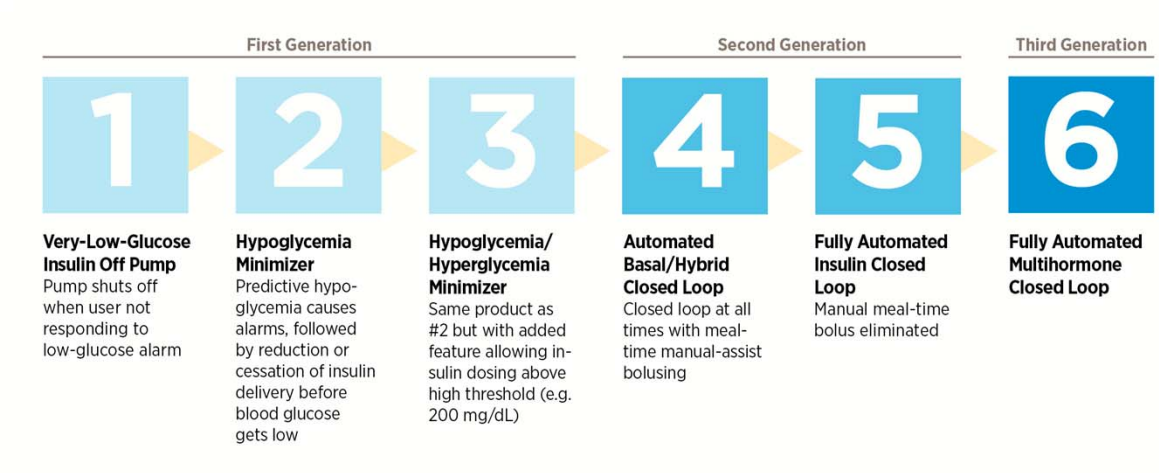
- Approved for dosing
- NO alarms or alerts
- Most cost effective
  - Reader = $75
  - Sensor = $25-45/sensor
    or $75-135/month
- Covered by Medicare not Medicaid
- Stocked in pharmacies but may need to order through DME to get insurance coverage

Reviewing Data

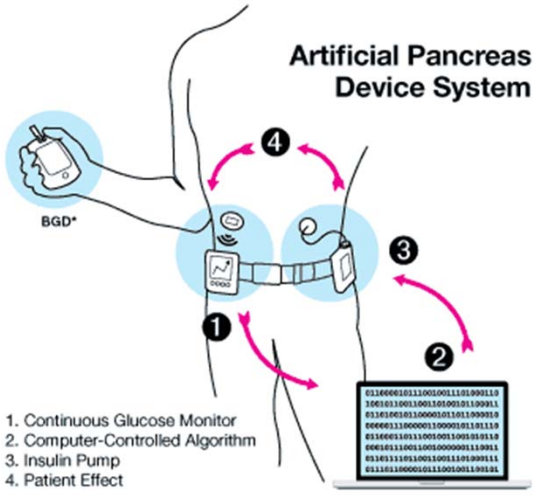


95251: Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; interpretation and report. (Do not report more than once per month)	1.23	$44.00	Paid under physican fee schedule	$85

JDRF Artificial Pancreas Pathway



What makes something an artificial pancreas?



http://www.fda.gov/

You do you – Permission Granted!

Wear a pump and NOT a CGM
Wear a CGM but NOT a pump
Wear different brands of pump and CGM
Wear a CGM that displays readings on a pump
Wear a CGM that can suspend your pump
Wear a hybrid closed loop system

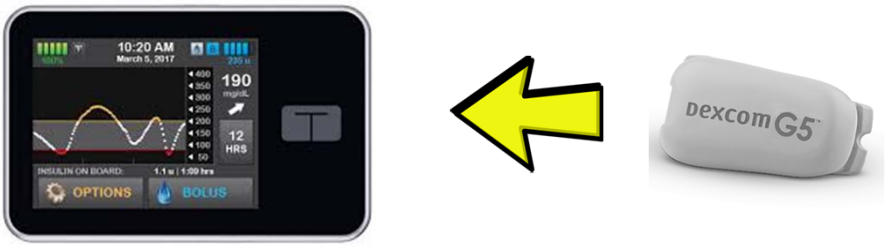
Choose Your Own Adventure

Choosing a system that is right for you

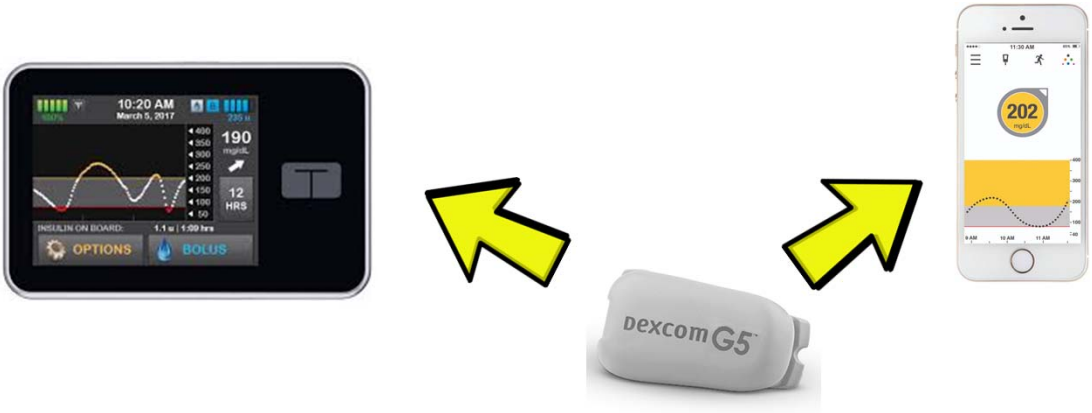
Tslim

Choosing a system that is right for you

Choosing a system that is right for you



Choosing a system that is right for you

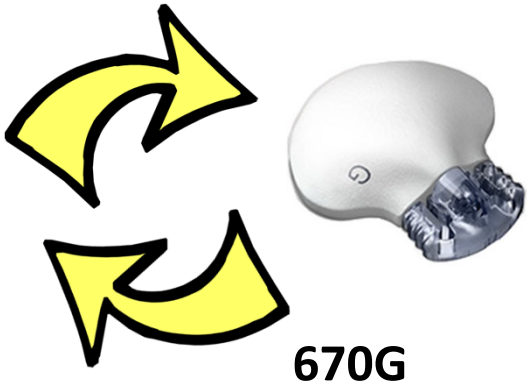


Choosing a system that is right for you

Omnipod

Choosing a system that is right for you

Choosing a system that is right for you



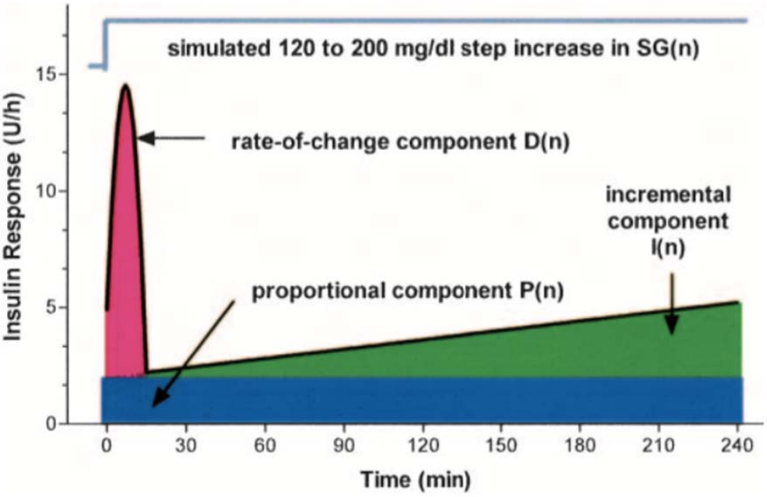
670G
Hybrid Closed Loop

Choosing a system that is right for you

No basal rates?!?

Proportional-Integral-Derivative with insulin feedback algorithm (PID-IFB)

Proportional-Integral-Derivative Model



Steil, Garry M., et al. "Feasibility of automating insulin delivery for the treatment of type 1 diabetes." *Diabetes* 55.12 (2006): 3344-3350.

Choosing a system that is right for you

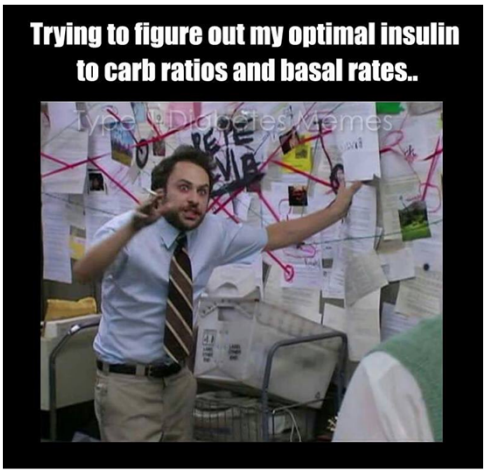
- You DO still need to bolus for carbs
- You DO still need to enter fingersticks
- You WILL be ”exited” if your sugar is too high
- Your WILL be ”exited” if your sugar is too low
- You cannot set your own target

Choosing a system that is right for you

Two modes: hybrid closed loop (auto) and open loop (manual) mode

In open loop mode you have BOTH threshold suspend and predictive low glucose suspend.

Choosing a system that is right for you



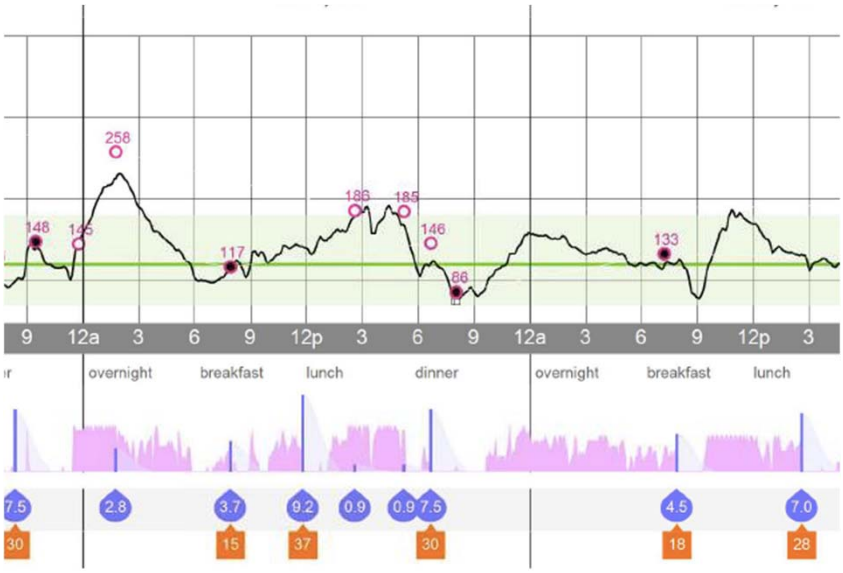
"Control knobs" – Traditional Pump

- Basal rate
- Carb ratio
- Correction
- Insulin on board
- Target
- Temp basal
- Pattern

Choosing a system that is right for you

"Control knobs" – Closed loop mode

- Carb ratio
- Insulin on board
- Temp target



Choosing a system that is right for you

So who is a good 670G candidate?

- Okay with fingersticks
- Need to bolus for meals consistently
- Sugars generally in a range that will keep you auto mode
- Willing to interact with your pump to keep it in auto mode
- Trust the pump – give it time to do its thing

**If zero fingersticks is the most important thing to your patient then a Dexcom or Freestyle Libre may be a better choice even if they are on a pump

Summary

- Insulin pump gives you insulin
  - Allows for fine tuning of patients on multiple daily injections
  - NOT an automatic device, needs significant patient input
- Continuous Glucose Monitor gives you blood sugar readings every 5 minutes
  - Trends and real time data are useful
  - Patient needs to respond to the data or it doesn't help management
- Hybrid Close Loop Systems
  - Allows pump to make adjustments in response CGM data
  - Still needs lots of patient input (fingersticks, carbs, exits). Patient needs to be ready to put in the time.

Thank you!


?
Some people wear their hearts on their sleeves; I put my pancreas on my hip.
haidee

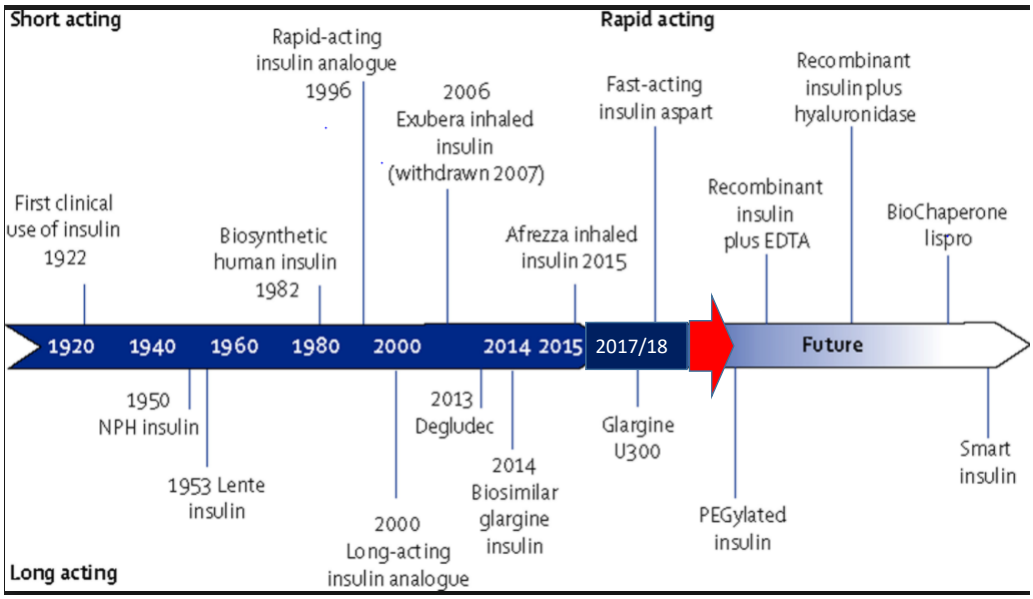
Health Delivery and Technology in Today's Diabetes Care

New Insulins: How Do They Work, When Would You Prescribe Them?

Roma Gianchandani, M.D.
Internal Medicine/Metabolism Endocrinology and Diabetes

4/28/2018

Insulin discovery Timeline



https://beyondtype1.org/the-10-most-expensive-liquids-in-the-world/

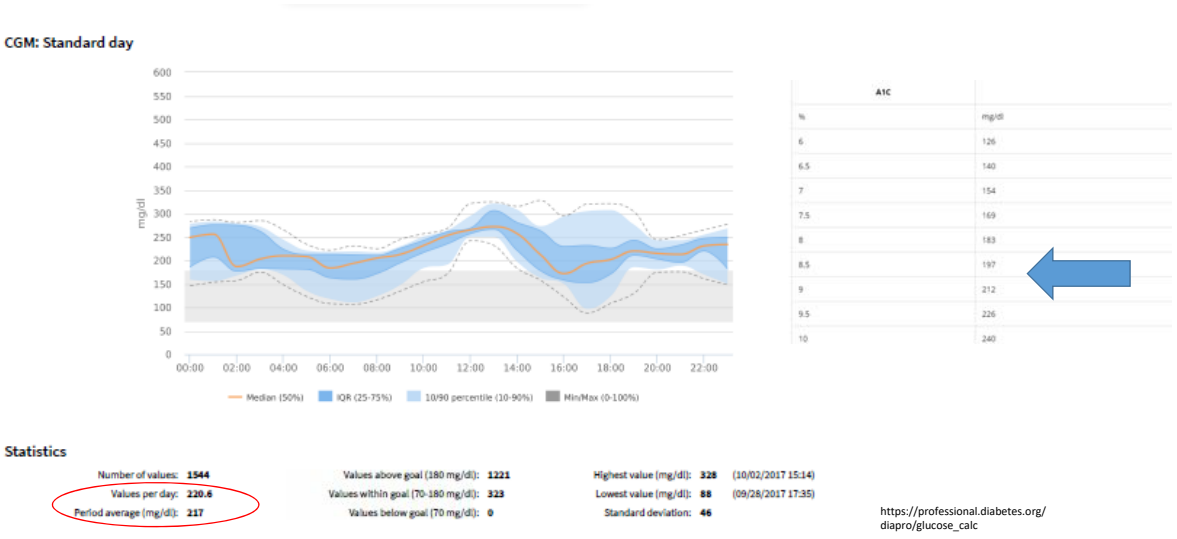
When To Start Insulin for T2DM

- Hyperglycemic emergencies
- When combination oral/NII agents -inadequate
- Symptomatic hyperglycemia and/or markedly high HbA1c
- Significant side effects of oral/NII agents
- Special circumstances
  - steroids, infection, pregnancy
- Hepatic or renal disease
- Patient preference/ flexibility

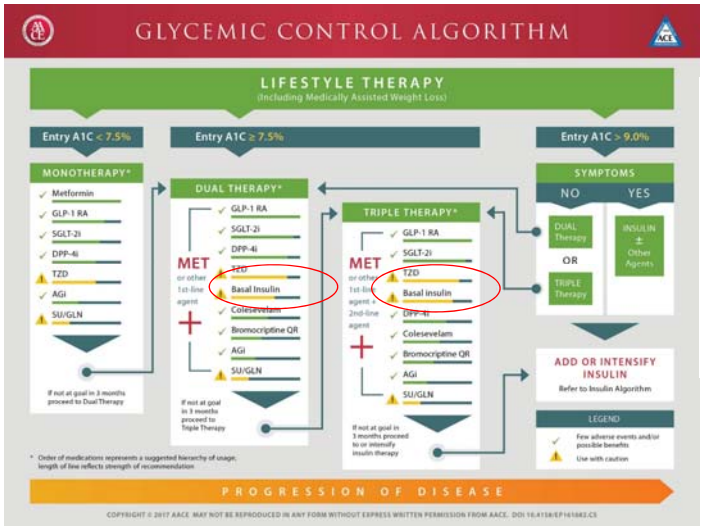
Holman et al. *NEJM.* 2009; 361:1736-1747; Lebovitz HE. *Diabetes Rev.* 1999;7(3):139-153

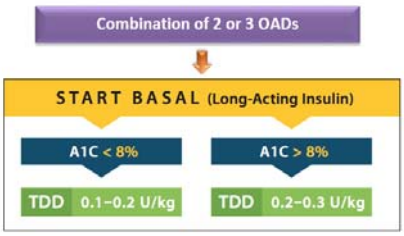
Case – starting basal insulin

- History
  - 56 year Asian M- T2DM for 16 years
  - A1c <7% on orals until 2 yrs ago
  - Last 2 yrs- A1c 8 - 8.5% despite 3 med and intense lifestyle changes.
- Meds for DM
  - metformin- 1000mg am / 500mg pm
  - linagliptin 5 mg qd
  - trulicity weekly
  - glimepiride & acrabose –Dced several months ago
- Physical Exam
  - BP-138/72, BMI-29
  - Rest – normal
- Labs
  - A1c- 8.7%, Creat-1.3, eGFR-62
  - C-peptide- 2.2 with BG-230mg/dl
  - Patient with CGM trial



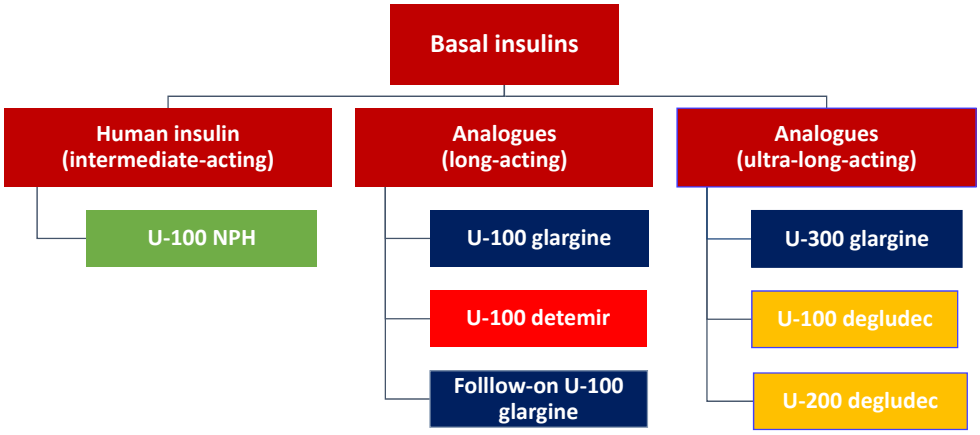
Basal Insulin as Add-On to NIA in T2D





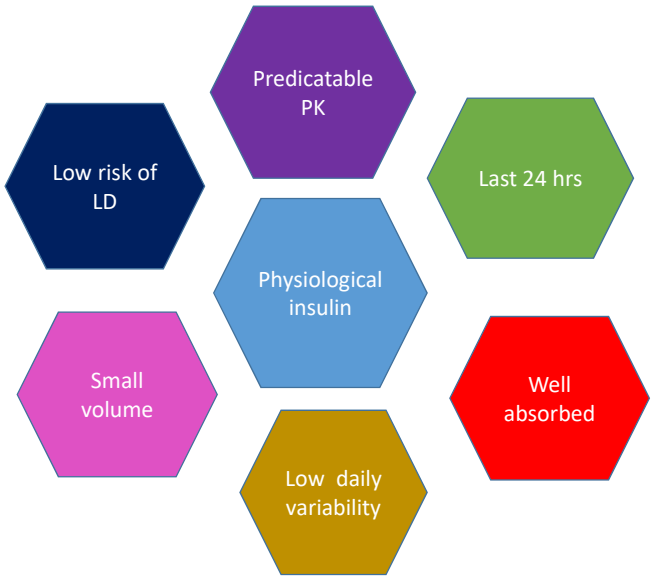
AACE Guidelines
Endocrine Practice 2017

Current Basal Insulins



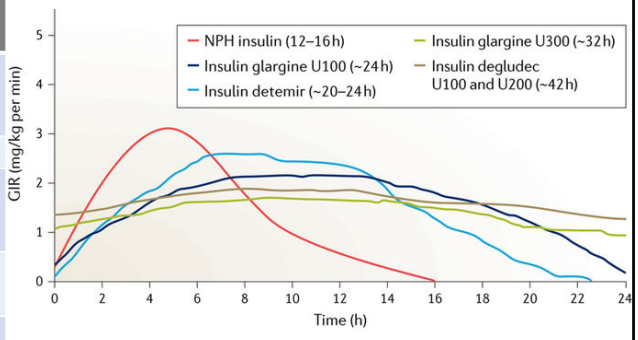
FDA = U.S. Food and Drug Administration;
NPH = neutral protamine hagedorn.

? Need for new basal insulins



Pharmacokinetics of Basal Insulins

	NPH Insulin	Insulin Glargine	Insulin Detemir	Follow-on Insulin Glargine	Glargine U-300	Degludec
Insulin type	Human; intermediate -acting	Analogue; long-acting	Analogue; long-acting	Analogue; long-acting	Analogue; long-acting	Analogue; long-acting
Onset	2-4 hours	1.3 hours	1.3 hours	1.3 hours	6 hours	1 hour
Peak	4-10 hours	No pronounced peak	Relatively flat	No pronounced peak	Flat	Flat
Effective duration	10-16 hours	Up to 24 hours	22-24 hours	Up to 24 hours	≤36 hours	Up to 42 hours
Half-life	Unknown*	14 hours	5-7 hours		~23 hours	~25 hours
Steady state	Unknown	2 days	2 days		4 days	2-3 days



Nature Reviews | Endocrinology
volume13, pages385–399(2017)

Porcellati. Diabetes Care 30(10)2447-2452, 2007
Lucidi P, et al. *Diabetes Care*. 2011;34:1312-1314.
Niswender K. *Clinical Diabetes*. 2009;27:60-68.
US Food & Drug Administration. Drugs@FDA: FDA Approved Drug Products. http://www.accessdata.fda.gov.
*NPH insulin (isophane insulin suspension) package insert

Comparison of newer insulin

Parameter	U-500 (pen)	Follow-on U-100 Glargine	U-300 Glargine	U-100 Degludec	U-200 Degludec
Insulin units/pen	1500 U	300 U	450 U	300 U	600 U
Half life		23	23	25	25
Duration of action -hours	Up to 24	24	36	>42	>42
Pens/carton	2	3	3 or 5	1 or 5	1 or 3
Injection time	Twice or thrice daily	Same time daily	Same time daily	Daily, any time (≥ 8 h since last inj)	Daily, any time (≥ 8 h since last inj)
Starting dose (in patients switching from another basal insulin)					
-U-100glargine	Use TDD	Same dose	Same dose[a]	Same dose	Same dose
-U-100 detemir	Use TDD	Same dose	Same dose	Same dose	Same dose
-U-100 NPH	Use TDD	80% of NPH	80% of NPH	Same dose	Same dose

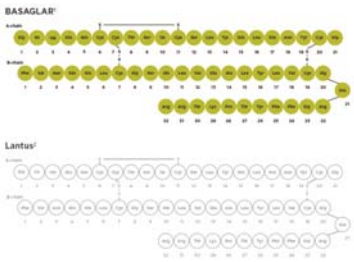
[a] Expect to use a higher daily dose of U-300 glargine to maintain the same level of glycemic control.

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatF

Follow-on Insulin Glargine U-100

Biosimilar/bioequivalent/follow-on

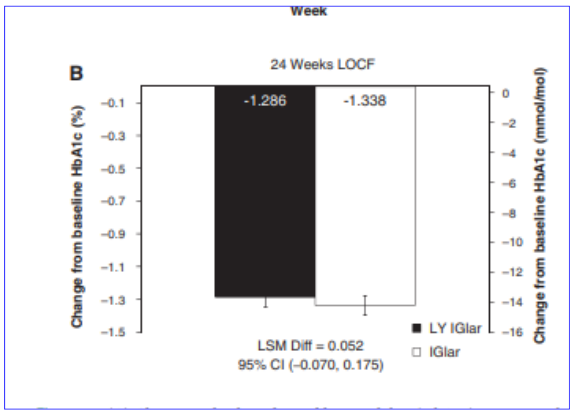
Identical sequence



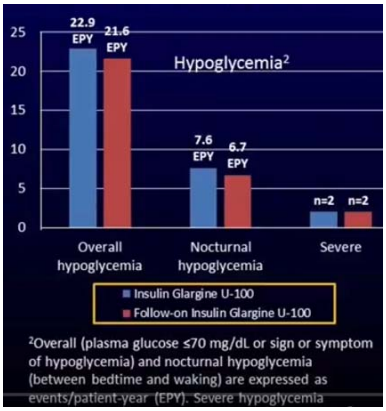
https://www.basaglar.com/hcp

Efficacy and safety of Follow-on Insulin glargine U-100

Glycemic efficacy



Hypoglycemia



Rosenstock, Diabetes, Obesity and Metabolism 17: 734–741, 2015

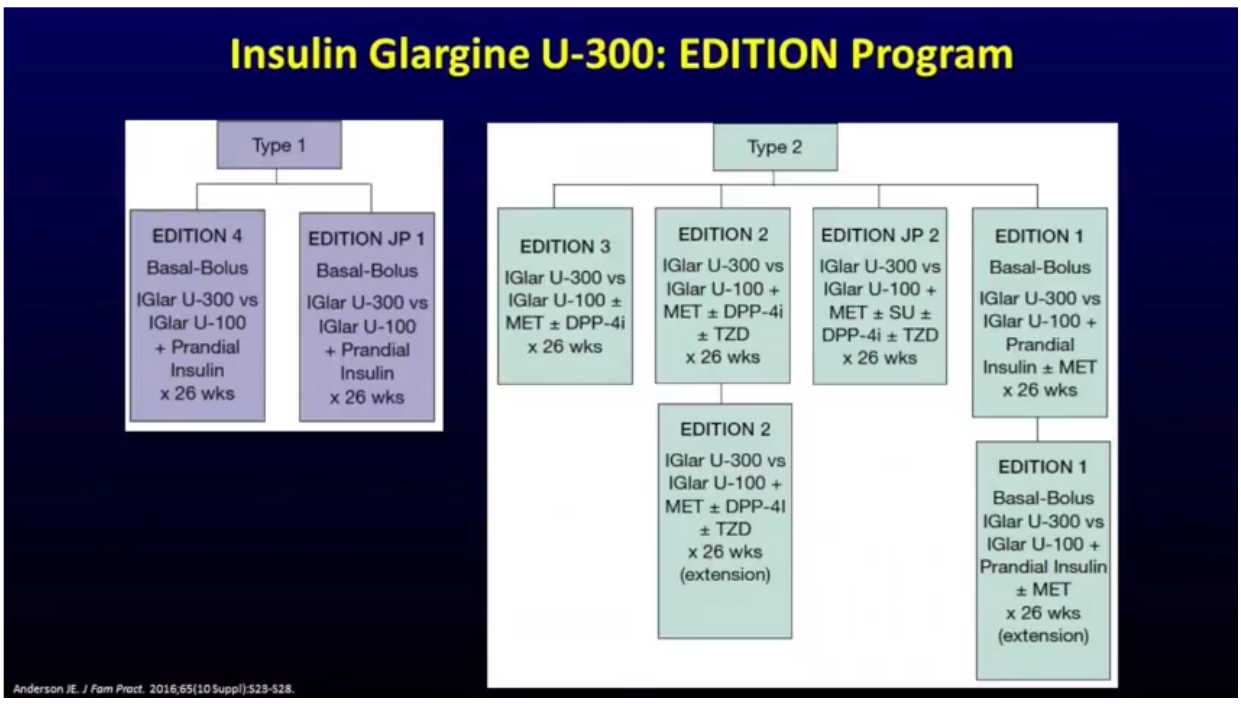
Follow-on glargine U-100 insulin

- Pen only
- Maximum 80 units
- 300 units/pen

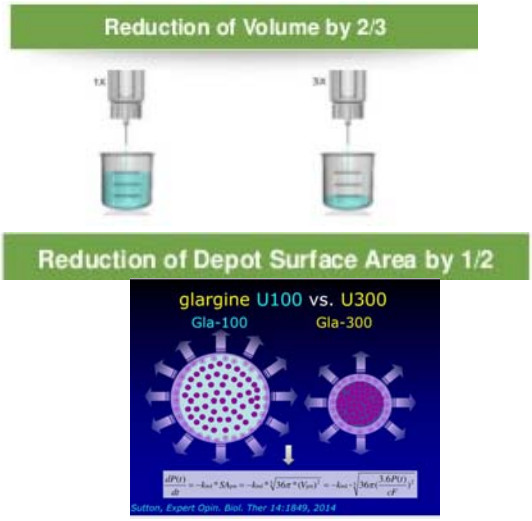
Not actual size

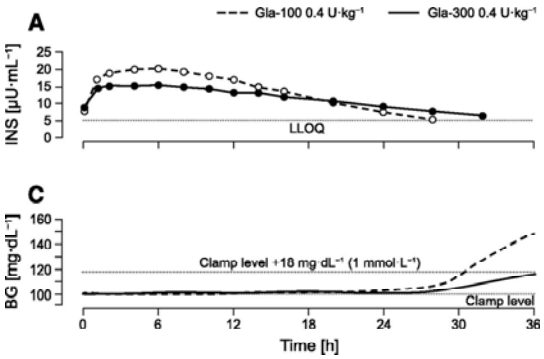
https://www.basaglar.com/hcp

Glargine U-300



Pharmacokinetics of Glargine U-300





Reinhard H.A. Becker et al. Dia Care 2015;38:637-643

American Diabetes Association.

Glargine U-300 vs U-100
No Difference in GLYCEMIC EFFICACY

2496 participants of 3 EDITION trials

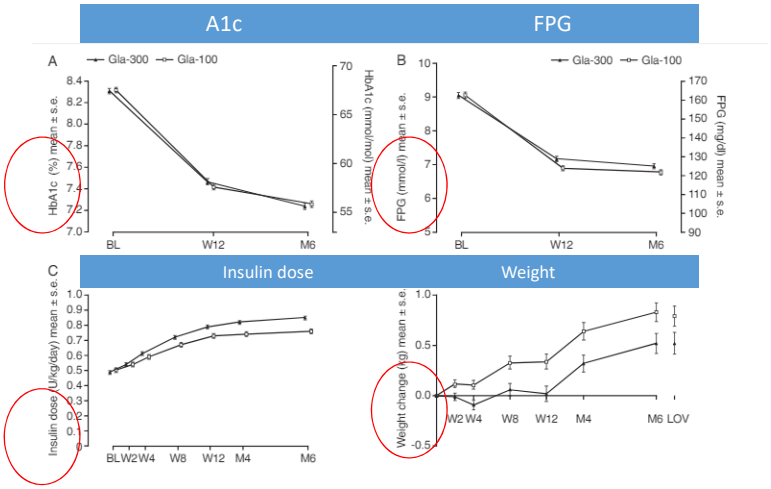


Figure 1. (A) Glycated haemoglobin (HbA1c), (B) Laboratory-measured fasting plasma glucose (FPG), (C) Insulin dose [modified intention-to-treat (mITT) population and (D) body weight (safety population) by visit during the 6-month treatment period for pooled analysis of all three studies. Gla-100, insulin glargine 100 U/ml; Gla-300, insulin glargine 300 U/ml; LS, least squares; BL, baseline; M, month; s.e, standard error; W, week. LOV, last on-treatment value defined as the last measurement made prior to or on the day of the last investigational product intake during the main 6-month on-treatment period.

Ritzel, Diabetes, Obesity and Metabolism 17: 859–867, 2015.

Glargine U-100 vs U-300
Significant difference in HYPOGLYCEMIA

- Anytime of the day

BG< 70 or < 54mg/dl

- **Nocturnal hypoglycemia**

NTT =16 patients to prevent 1 confirmed BG < 70 mg/dl

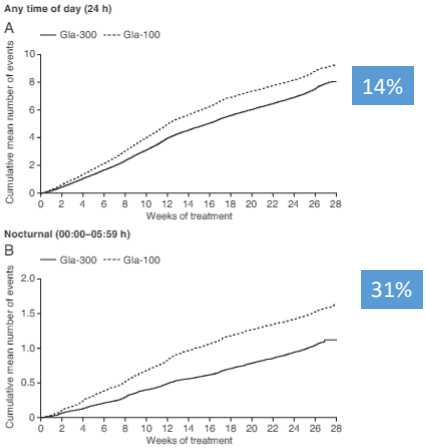


Figure 2. Cumulative mean number of confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemic events (A) at any time of day (24 h) and (B) during the night (00:00–05:59 hours) for pooled analysis of all three studies (safety population). Gla-100, insulin glargine 100 U/ml; Gla-300, insulin glargine 300 U/ml.

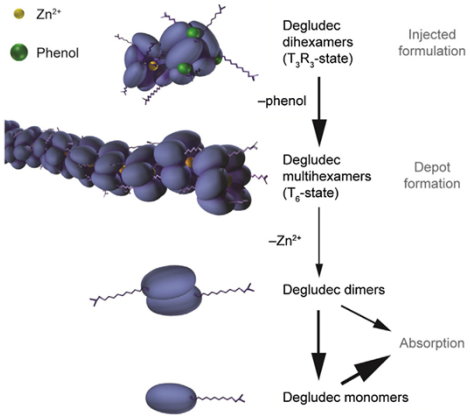
Ritzel, Diabetes, Obesity and Metabolism 17: 859–867, 2015.

U-300 Insulin Glargine

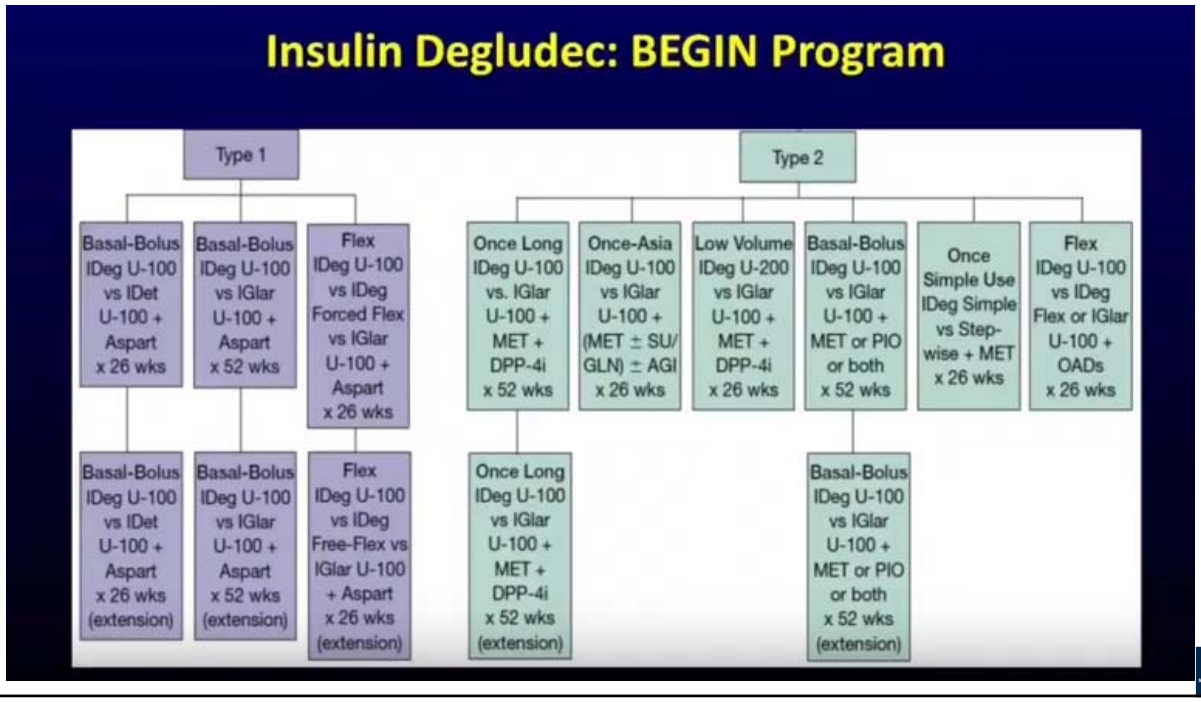
- Only available in a pen (green vs purple/grey – U-100)
- 1.5 ml of insulin- 450 units/pen
- 1 unit increments -max 80 units/dose (240 units/dose in development)
- 1:1 dosing conversion from U-100 glargine/detemir
- Last 6 weeks at room temperature
- 3 pens per box

1. http://www.pdr.net/full-prescribing-information/toujeo?druglabelid=3688. Accessed March 26, 2015.
2. http://www.pdr.net/drug-summary/lantus?druglabelid=520. Accessed March 26, 2015.

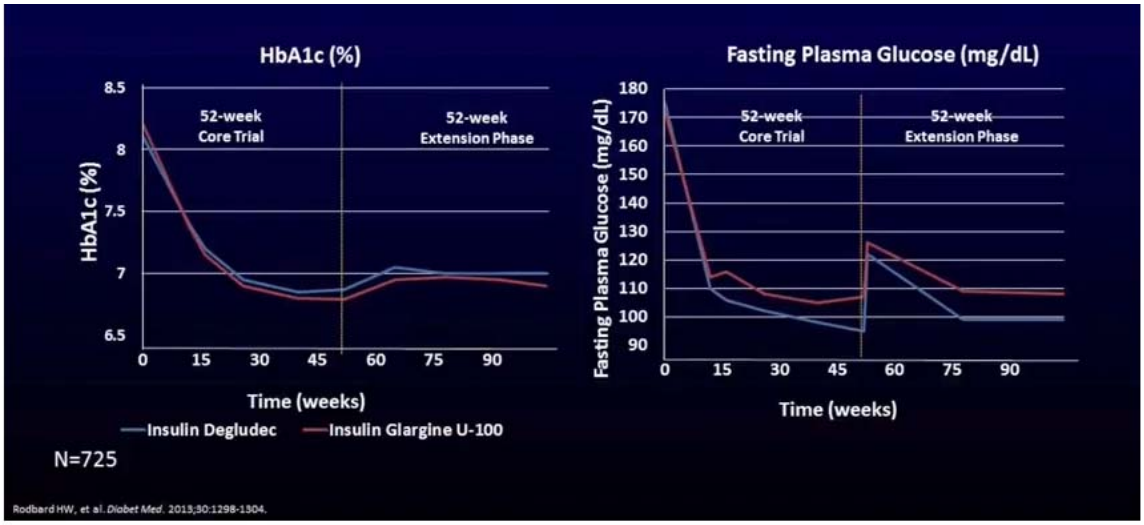
Degludec U-100 and U-200



Insulin Degludec: BEGIN Program

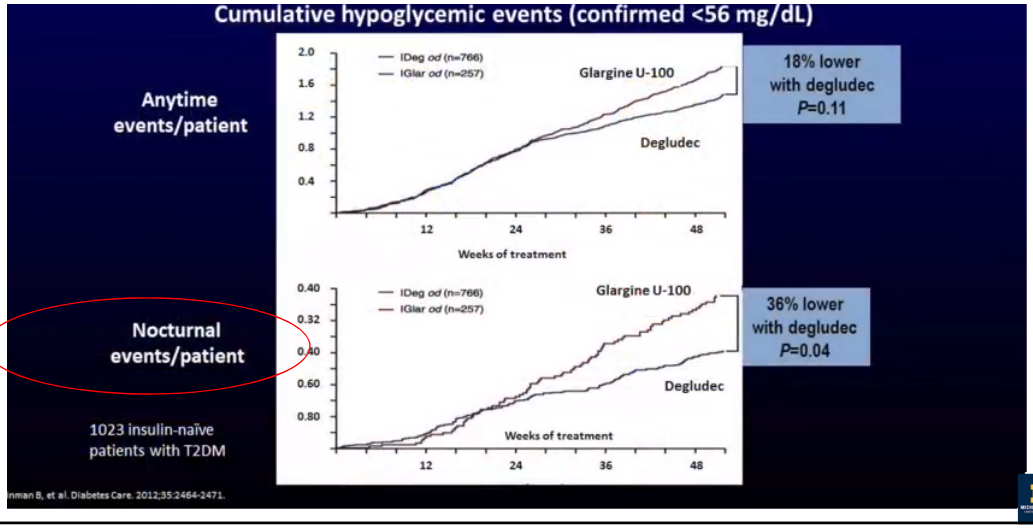


Degludec vs U-100 Glargine
No Difference in GLYCEMIC EFFICACY



Rodbard HW, et al. *Diabet Med*. 2013;30:1298-1304.

Degludec vs U-100 Glargine
Significant difference in HYPOGLYCEMIA



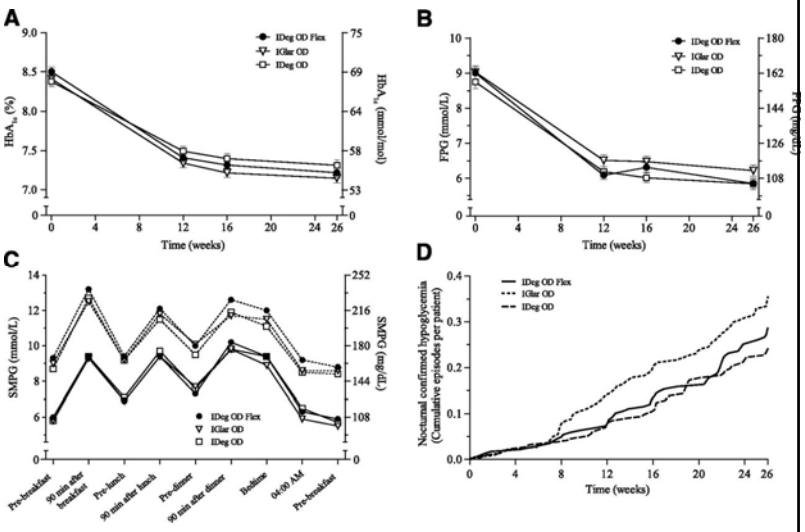
Rodbard HW, et al. Diabetes Care. 2012;35:2464-2471.

Flexible dosing 8-40 hours after last injection

- 26-wk randomized, open-label, treat-to-target trial (N=687)
- Glargine once daily at same time each day
- Degludec once daily
  - Fixed: same time each day
  - Flexible: schedule to create 8-40 hour dosing intervals

*HbA1c 8.4-8.5% at baseline

Change from baseline* to 26 weeks	Degludec		Glargine
	Flexible	Fixed	
HbA1c (%)	-1.28	-1.07	-1.26
FPG (mg/dL)	-58	-54	-50
Confirmed or severe hypoglycemia (events/patient-year)	3.6	3.6	3.5
Confirmed or severe nocturnal hypoglycemia (events/patient-year)	0.6	0.6	0.8



Luigi Meneghini et al. Dia Care 2013;36:858-864

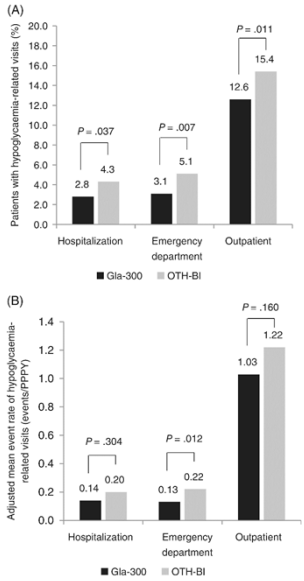
American Diabetes Association.

Insulin Degludec

U-100 degludec FlexTouch pen
- 100 U/mL (3.0 mL)
- I unit dosing increments
- Can deliver injection of 80 units
- Pen contains 300 units
- 5 pens in a box-1500 units

U-200 degludec FlexTouch pen
- 200 U/mL (3.0 mL)
- 2 units dosing increments
- Can deliver injection of 160 units
- Pen contains 600 units
- 3 pens in a box-1800 units

Real-world evidence concerning clinical and economic outcomes of switching to insulin glargine 300 units/mL vs other basal insulins in patients with type 2 diabetes using basal insulin



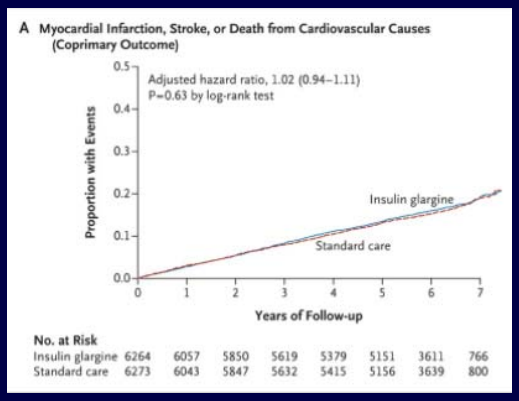
Real-world evidence concerning clinical and economic outcomes of switching to insulin glargine 300 units/mL vs other basal insulins in patients with type 2 diabetes using basal insulin, Volume: 20, Issue: 5, Pages: 1293-1297, First published: 22 December 2017, DOI: (10.1111/dom.13199)

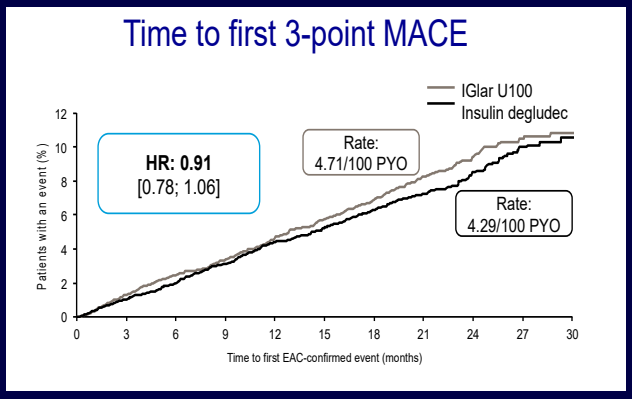
New Insulin Formulations: Advantages /Disadvantages

Compared to Glargine U-100 formulation

	A1C reduction	Hypoglycemia Risk	Additional Benefits/Risks	Disadvantage
Glargine U-300	⟷	↓ nocturnal	↑ Dosing Flexibility	Over dose-Prolonged hypo
Degludec	⟷	↓ nocturnal	↑ Dosing Flexibility	Need to reduce dose several days before NPO

DEVOTE and ORIGIN : CV Outcomes Trials





N Engl J Med 2012; 367:319-328

Devote Trial. New Engl J Med, June 2017

Starting Dose: Basal Insulin as Add-On to Oral Antidiabetic Drug in Patients with T2D

Combination of 2 or 3 OADs

START BASAL (Long-Acting Insulin)

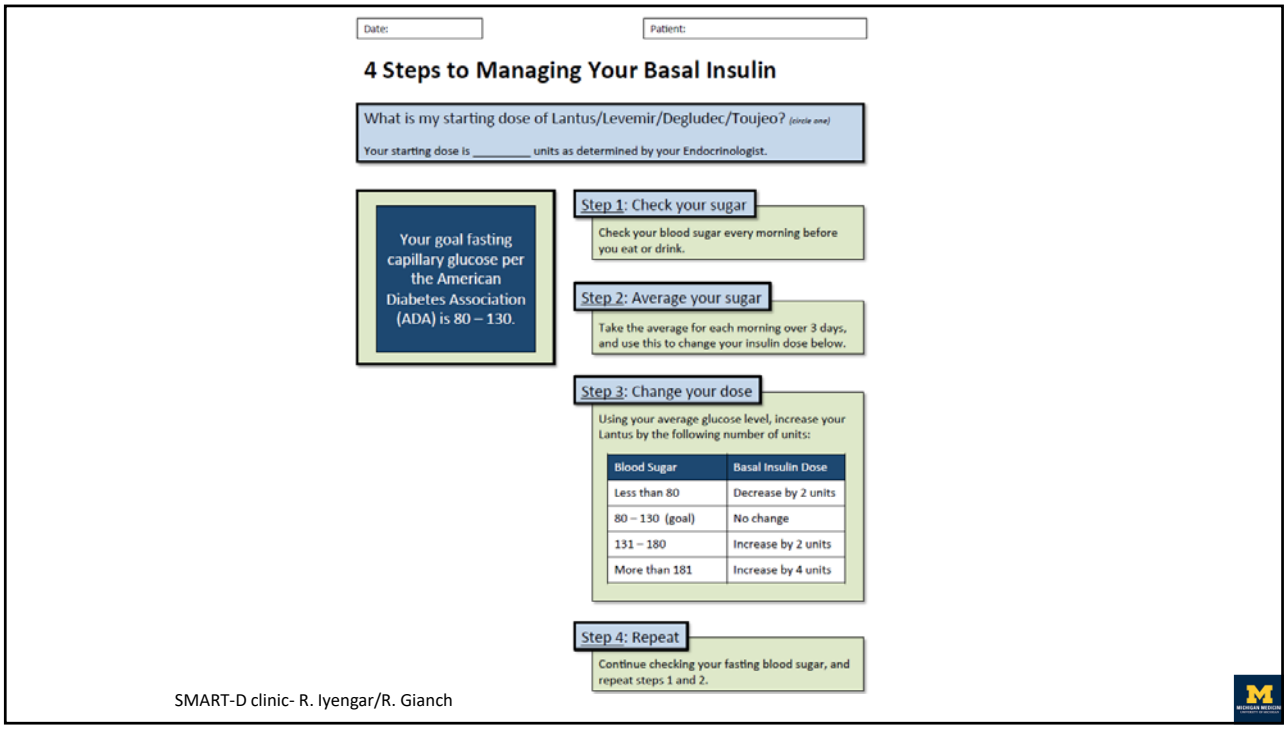
Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent

Start: 10 U/day or 0.1–0.2 U/kg/day
Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target
For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10–20%

A1C < 8%	A1C > 8%
TDD 0.1–0.2 U/kg	TDD 0.2–0.3 U/kg

ADA
Diabetes Care 2018

AACE Guidelines
Endocrine Practice 2017



Date: Patient:

4 Steps to Managing Your Basal Insulin

What is my starting dose of Lantus/Levemir/Degludec/Toujeo? *(circle one)*

Your starting dose is _____ units as determined by your Endocrinologist.

Your goal fasting capillary glucose per the American Diabetes Association (ADA) is 80 – 130.

Step 1: Check your sugar

Check your blood sugar every morning before you eat or drink.

Step 2: Average your sugar

Take the average for each morning over 3 days, and use this to change your insulin dose below.

Step 3: Change your dose

Using your average glucose level, increase your Lantus by the following number of units:

Blood Sugar	Basal Insulin Dose
Less than 80	Decrease by 2 units
80 – 130 (goal)	No change
131 – 180	Increase by 2 units
More than 181	Increase by 4 units

Step 4: Repeat

Continue checking your fasting blood sugar, and repeat steps 1 and 2.

SMART-D clinic- R. Iyengar/R. Gianch

Case – starting basal insulin

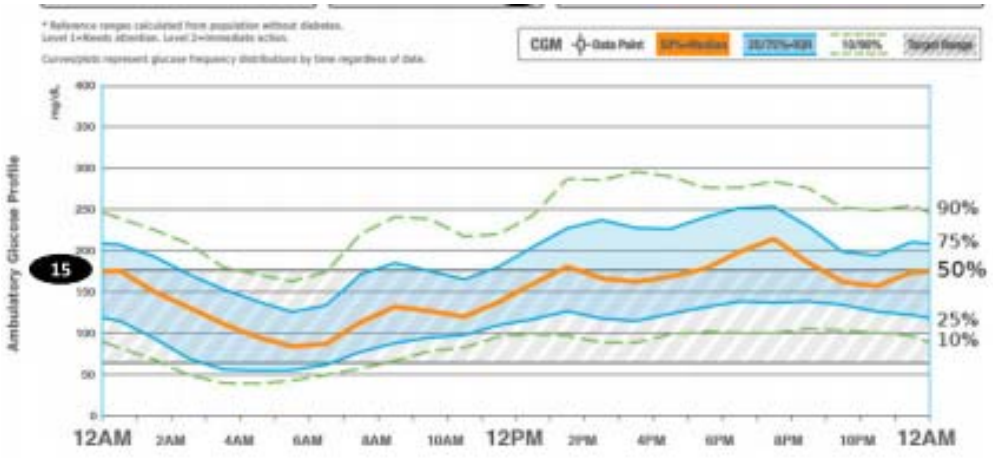
- History
  - 56 year Caucasian- T2DM for 14 years
  - A1c 7%
  - Am BG 100-140 but few episodes of BG 70 mg/dl at 4 am –unpredictable, 2 times a week. No activity or food difference
- Meds
  - metformin- 1000mg am / 500 mg pm
  - Glargine U-100 , 24 units hs, reduction in dose by over 10 units in last month. Tried am and hs dose but still has early am hypoglycemia
- Physical Exam
  - BP-138/72, BMI-32
  - Rest – normal
- Labs
  - A1c- 8%, Creat-1.3, eGFR-62

May consider changing to Glargine U -300 or Degludec

Newer Prandial Insulins

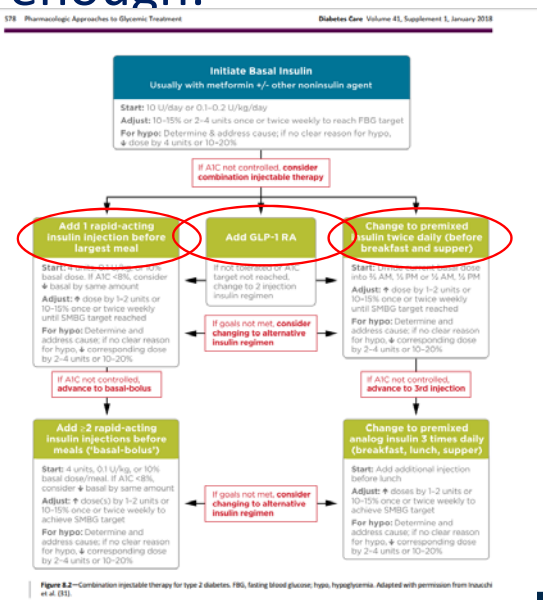
Case – starting basal insulin

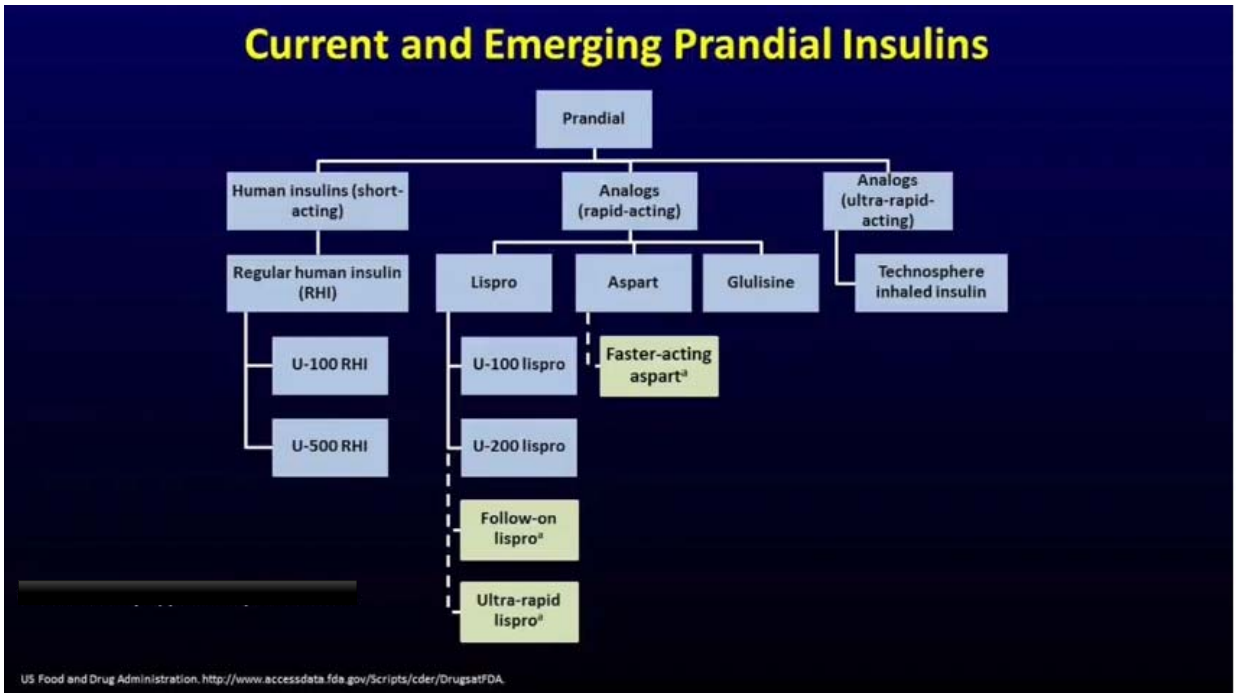
- History
  - 56 year AA - T2DM for 16 years
  - A1c <7% until 2 yrs ago
  - Last 2 yrs- A1c 8.4% despite basal insulin, GLP1-RA, lifestyle changes.
- Meds
  - metformin- 1000mg am / 500 mg pm
  - Glargine U-300 24 units hs
  - Dulaglutide weekly
- Physical Exam
  - BP-138/72, BMI-31
  - Mild neuropathy
- Labs
  - A1c- 8.3%, Creat-1.3, eGFR-62
  - C-peptide-1.9 with FPG-150 mg/dl
  - Patient with CGM trial



When basal insulin is not enough: What next?

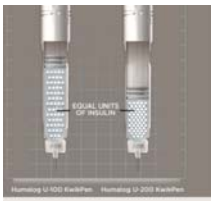
- Combine with other hormones
- Basal plus (stepwise basal-bolus)
- Basal-bolus
- Premix insulins

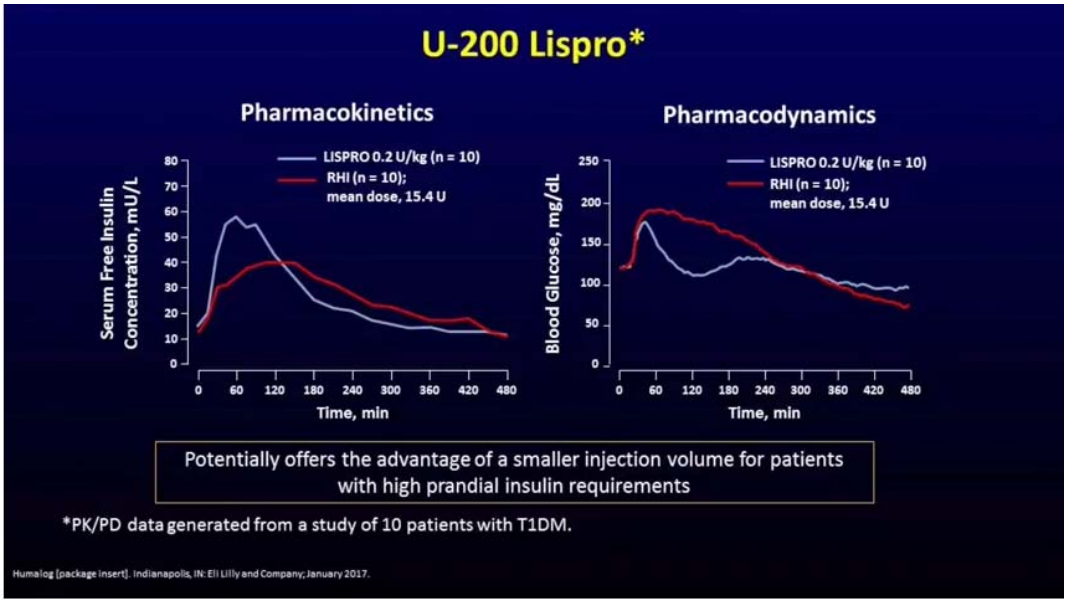




U-200 Lispro

- Bioequivalent with similar time to peak concentration as U-100 lispro
- Same dose in half the liquid volume.
- Each pen has 600 units
- 2 pens/box – 1200 units/box





Faster insulin aspart

- Addition of
  - Niacinamide(Vit. B3) - increases absorption
  - L- Arginine -stabilizing amino acid
- Enters blood stream within minutes
- Can be taken
  - start of meal
  - 20 mins after

Russell Jones, DC, 3/2017

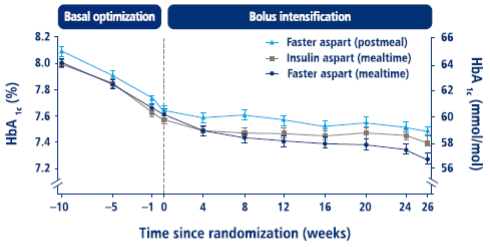
Faster insulin aspart

- Pens or vials
- Not approved for peds or pumps yet
- In one CSII study

  CSII delivery of faster aspart had a greater glucose-lowering effect than IAsp after a meal test.

Faster insulin aspart

Glycemic control-overall



7.5% with PMFA
7.4% with IAsp
7.3% with MFA

Figure 1—Mean HbA_{1c} over time. During run-in, observed mean HbA_{1c} was reduced from 8.1% (64.9 mmol/mol) to 7.6% (59.9 mmol/mol) for subjects subsequently randomized to receive postmeal faster aspart (n = 382), from 8.0% (64.0 mmol/mol) to 7.6% (59.7 mmol/mol) for subjects subsequently randomized to receive mealtime insulin aspart (n = 380), and from 8.0% (64.0 mmol/mol) to 7.6% (59.3 mmol/mol) for subjects subsequently randomized to receive mealtime faster aspart (n = 381). During the 26-week treatment period, the observed mean HbA_{1c} decreased to 7.5% (58.6 mmol/mol) with postmeal faster aspart, 7.4% (57.6 mmol/mol) with mealtime insulin aspart, and 7.3% (56.4 mmol/mol) with mealtime faster aspart. Error bars: ±SEM.

Glycemic control - postprandial

Meal Aspart was best for PP BG reduction

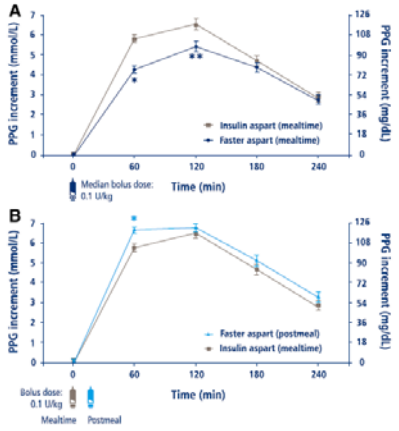
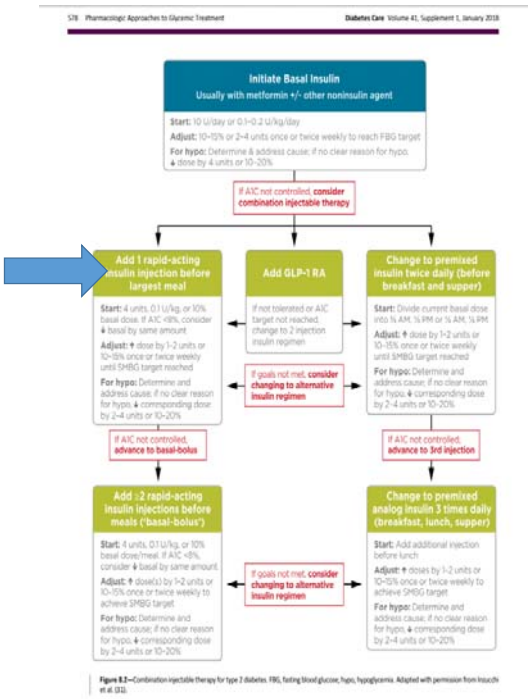
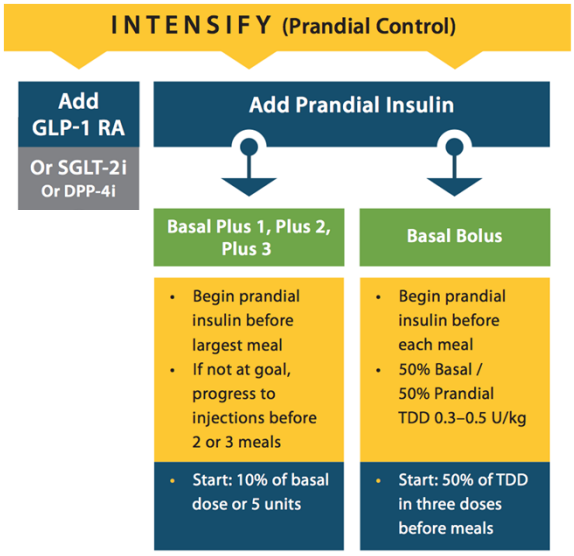


Figure 2—*A*: PPG increment at week 26 for mealtime faster aspart versus insulin aspart. Observed data. One-hour and 2-h PPG increments statistically significantly in favor of mealtime faster aspart: $^*P < 0.0001$ and $^{**}P = 0.0375$, respectively. *B*: PPG increment at week 26 for postmeal faster aspart versus insulin aspart. Observed data. Mealtime insulin aspart dosed 0 to 2 min before meal; postmeal faster aspart dosed 20 min after meal. Change in 1-h PPG increment significantly in favor of insulin aspart: $^*P = 0.0001$. Error bars: ±SEM. The conversion factor between millimoles per liter and milligrams per deciliter is 18.

Russell Jones, DC, 3/2017





AACE Guidelines
Endocrine Practice 2017

Insulin plus GLP1-RA combinations

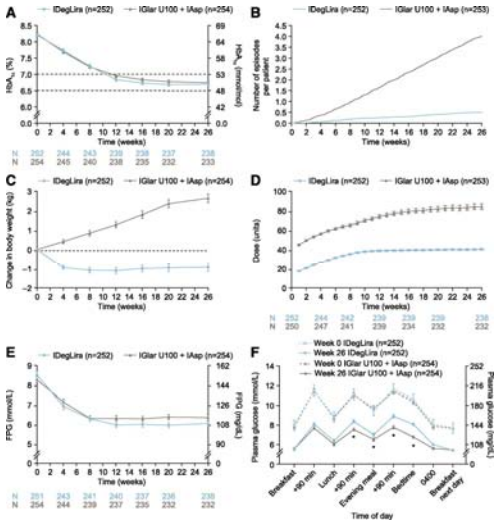
Basal plus meal covered by GLP-1RA

IDegLira vs Glargine U-100- DUAL V trial

	IDegLira	Glargine U-100
A1c reduction -%	-1.7	-1.2
Patients achieving A1c < 7% (%)	68	46
Average insulin dose - units	41	66
Weight change -Lbs	-3	+4

DUAL V11- IDegLira vs basal bolus at week 26.

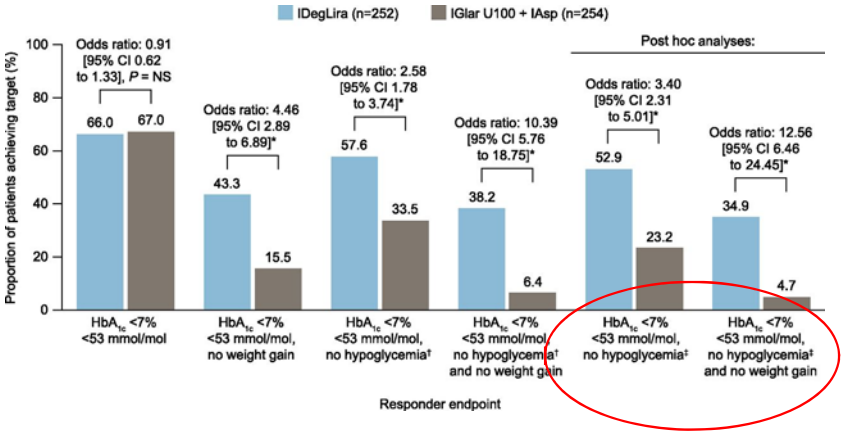
Results for HbA1c (A), severe or BG-confirmed symptomatic hypoglycemia (B), change in body weight (C), daily total insulin dose (D), FPG (E), and nine-point SMPG profiles (F).



Liana K. Billings et al. Dia Care 2018;41:1009-1016

American Diabetes Association.

DUAL V11- IDegLira vs basal bolus at week 26.



IDegLira group

- Smaller doses of insulin
- Smaller doses of liraglutide
- No significant weight gain
- Lower rates of hypoglycemia
- No increased adverse events
- Improved FPG

Liana K. Billings et al. Dia Care 2018;41:1009-1016

American Diabetes Association.

IDegLira

- 3 ml Pen= 100 units degludec and 3.6mg liraglutide/ml
- 5 pens/box
- Dose increment – 1 unit degludec and 0.036mg of liraglutide- fixed
- Start with 16 units of IDegLira
- Max dose -50 units- 50 units of degludec and 1.8 mg liraglutide

Below goal - 2 units	Goal No change	Above goal + 2 units

IGlarLixi

- 3 ml pen- 1ml - 100 units glargine and 33 mcg lixisenatide
- 5 pens/box
- Dose increments -1 unit
- Start dose
  - 15 units - for pts treated with lixi or < 30 units of basal insulin/day
  - 30 units – pts on 30-60 units of basal insulin/day
- Max dose 60 units of glargine

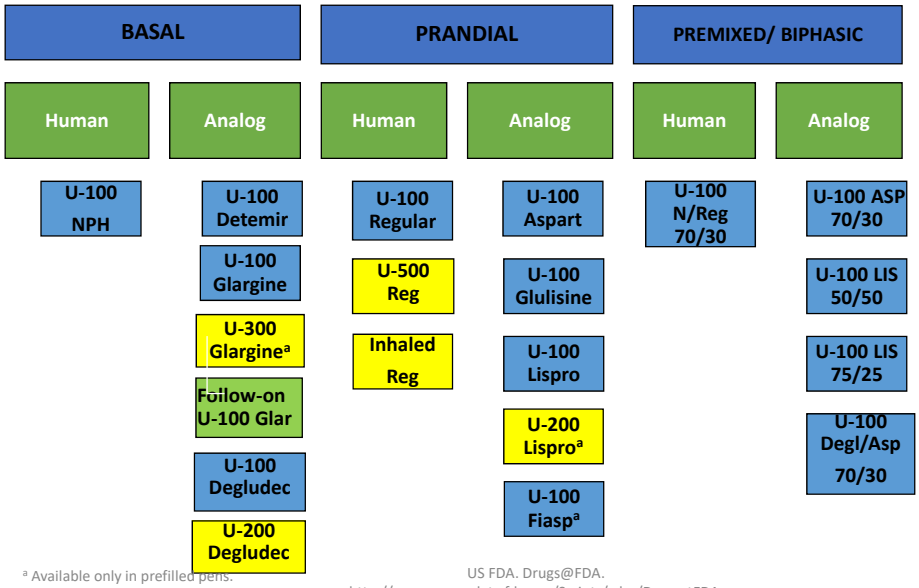
Below Goal - 2 units	Goal No change	Above Goal + 2 units

IGlarLixi Hypoglycemia and GI SE

	IGlarLixi	Glargine	Lixi
GASTROINTESTINAL %			
Nausea	9.6	3.6	24
Vomiting	3.2	1.5	6.4
Diarrhea	9	4.3	9
HYPO (PTS WITH EVENTS)			
BG < 70 mg/dl	25.6	23.6	6.4
Severe Hypoglycemia	0	0.2	0

Rosenstock,Diabetes Care 2016;39:2026–2035 |

Available Insulins



[a] Available only in prefilled pens.

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

MICHIGAN MEDICINE

Summary of newer insulins

- Ultra LA insulins helpful
  - Hypoglycemia reduction (nocturnal)
  - Can be given at different time of the day; atleast 8 hours apart
- Fast and concentrated meal insulins help
  - improve postprandial excursions and
  - have some quality of life improvement
- Insulin and GLP-1RA combinations
  - May become 1st injectable combination after failing NIA
  - Address both basal and prandial needs
  - Weight reduction

Table 8.4—Median cost of insulin products in the U.S. calculated as AWP (39) and NADAC (40) per 1,000 units of specified dosage form/product

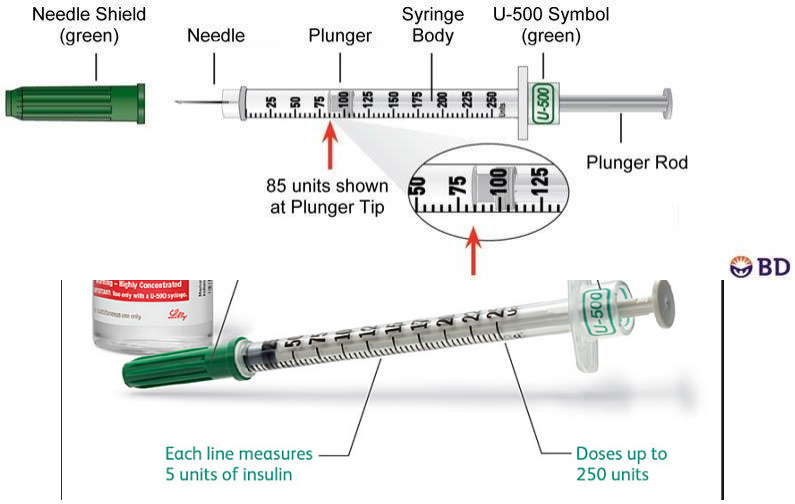
Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC (min, max)*
Rapid-acting analogs	• Lispro	U-100 vial;	$330	$264
		U-100 3 mL cartridges;	$408	$326
		U-100 prefilled pen; U-200 prefilled pen	$424	$339
	• Aspart	U-100 vial;	$331	$265
		U-100 3 mL cartridges;	$410	$330
		U-100 prefilled pen	$426	$341
	• Glulisine	U-100 vial;	$306	$245
		U-100 prefilled pen	$394	$315
	• Inhaled insulin	Inhalation cartridges	$725 ($544, $911)	N/A†
Short-acting analogs	• Human Regular	U-100 vial	$165 ($165, $178)	$135 ($135, $145)
Intermediate-acting analogs	• Human NPH	U-100 vial;	$165 ($165, $178)	$135 ($135, $145)
		U-100 prefilled pen	$377	$305
Concentrated Human Regular insulin	• U-500 Human Regular insulin	U-500 vial;	$178	$143
		U-500 prefilled pen	$230	$184
Basal analogs	• Glargine	U-100 vial; U-100 prefilled pen; U-300 prefilled pen	$298	$239 ($239, $241)
	• Glargine biosimilar	U-100 prefilled pen	$253	$203
	• Detemir	U-100 vial; U-100 prefilled pen	$323	$259
	• Degludec	U-100 prefilled pen; U-200 prefilled pen	$355	$285
Premixed insulin products	• NPH/Regular 70/30	U-100 vial;	$165 ($165, $178)	$134 ($134, $146)
		U-100 prefilled pen	$377	$305
	• Lispro 50/50	U-100 vial;	$342	$278
		U-100 prefilled pen	$424	$339
	• Lispro 75/25	U-100 vial;	$342	$273
		U-100 prefilled pen	$424	$340
	• Aspart 70/30	U-100 vial;	$343	$275
		U-100 prefilled pen	$426	$341
Premixed insulin/GLP-1 receptor agonist products	• Degludec/Liraglutide	100/3.6 prefilled pen	$763	N/A†
	• Glargine/Lixisenatide	100/33 prefilled pen	$508	$404

*AWP or NADAC calculated as in **Table 8.3**; median listed alone when only one product and/or price. †Not applicable; data not available.

THANK YOU
Questions?

Acknowledge Dr Umpierrez for sharing slides with me

U-500



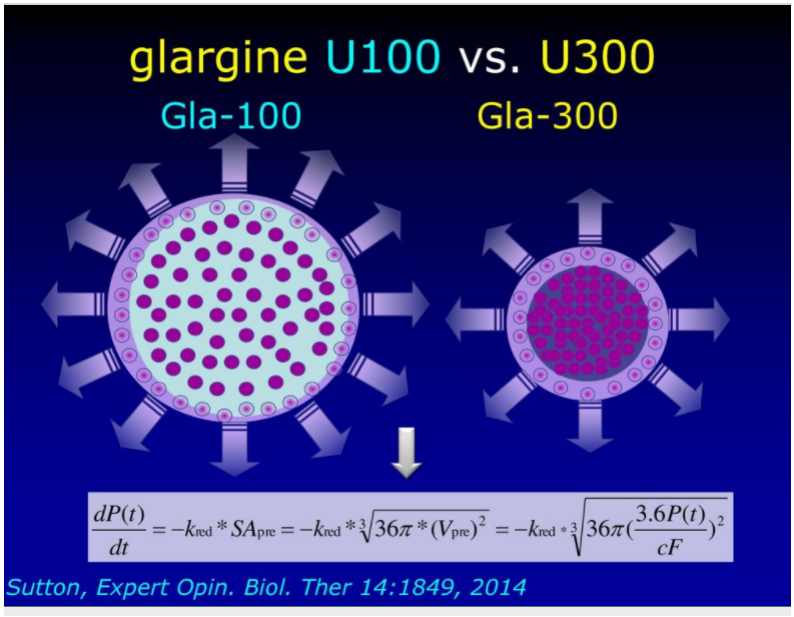
Algorithm for U500 Regular Insulin Therapy

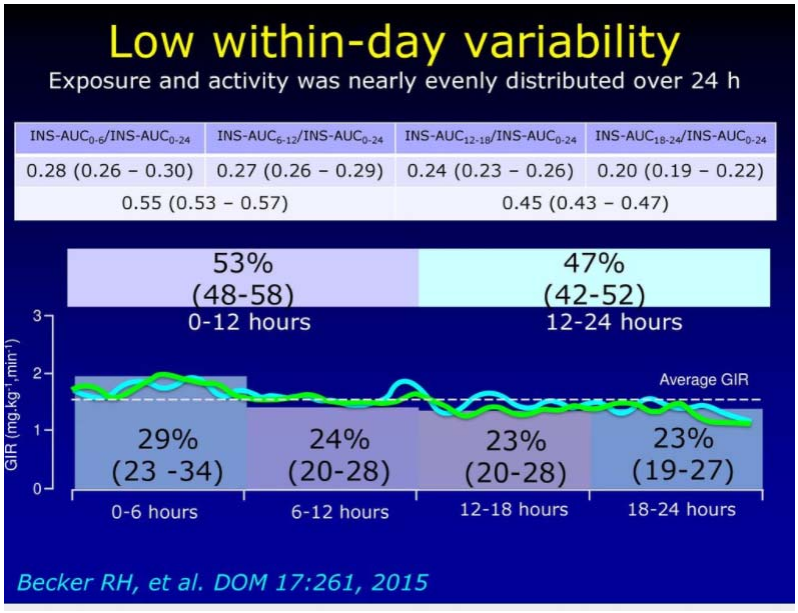
TDI Dose (U/d)	Injection Frequency/ Delivery Method*	Dosage Distribution (% of TDD)†
150-300	2 injections/d (AM & PM) with or without basal insulin	AM injection - 60% TDD PM injection = 40% TDD (ie, 60/40)
150-300	3 injections/d (AM, noon, and PM) with or without basal insulin	40/30/30 ***or*** 45/35/20 ***or*** 40/40/20
150-300	CSII‡	24-hour basal insulin infusion + 3 mealtime boluses (eg, 50% TDD for basal rate and 20/15/15 for mealtime boluses ***or*** 20% TDD for basal rate and 30/25/25 for mealtime boluses)

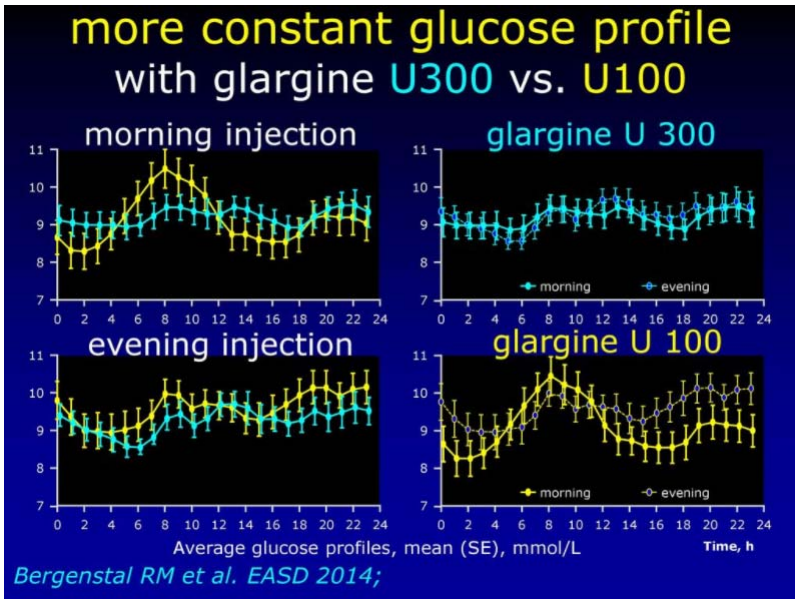
AM refers to pre-breakfast; noon refers to pre-lunch; PM refers to pre-evening meal.
*U500 regular boluses recommended at least 30 minutes premeal; dosage titration is according to frequent SMBG.
†Empirically reduce the conversion dose from U100 insulins by 10% to 20% if baseline HbA_{1c} is ≤ 8%, and increase the dose by 10% to 20% if HbA_{1c} ≥ 10%.
‡Off-label use.

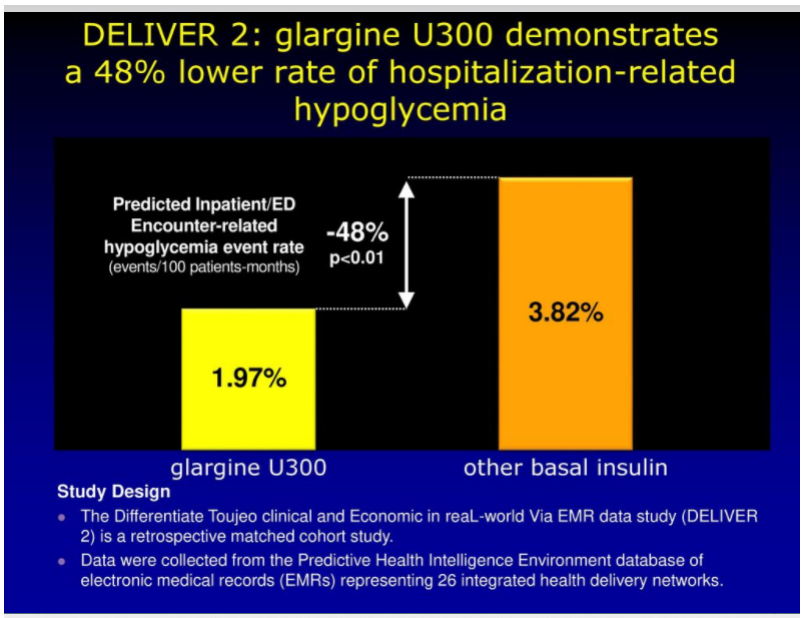
Medscape EDUCATION

Lane WS, et al. *Endocr Pract.* 2009;15:71-79.

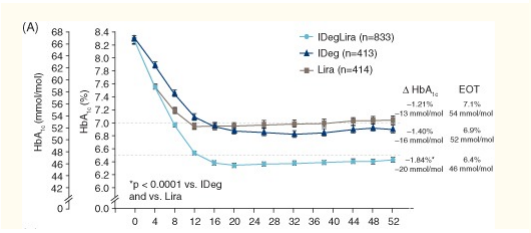

glargine U100 vs. U300
Gla-100
Gla-300
$\frac{dP(t)}{dt} = -k_{red} * SA_{pre} = -k_{red} * \sqrt[3]{36\pi * (V_{pre})^2} = -k_{red} * \sqrt[3]{36\pi (\frac{3.6P(t)}{cF})^2}$
Sutton, Expert Opin. Biol. Ther 14:1849, 2014


Low within-day variability
Exposure and activity was nearly evenly distributed over 24 h
INS-AUC0-6/INS-AUC0-24
INS-AUC6-12/INS-AUC0-24
INS-AUC12-18/INS-AUC0-24
INS-AUC18-24/INS-AUC0-24
0.28 (0.26 – 0.30)
0.27 (0.26 – 0.29)
0.24 (0.23 – 0.26)
0.20 (0.19 – 0.22)
0.55 (0.53 – 0.57)
0.45 (0.43 – 0.47)
53% (48-58)
0-12 hours
47% (42-52)
12-24 hours
Average GIR
GIR (mg.kg-1.min-1)
29% (23 -34)
24% (20-28)
23% (20-28)
23% (19-27)
0-6 hours
6-12 hours
12-18 hours
18-24 hours
Becker RH, et al. DOM 17:261, 2015


more constant glucose profile
with glargine U300 vs. U100
morning injection
glargine U 300
evening injection
glargine U 100
morning
evening
Average glucose profiles, mean (SE), mmol/L
Time, h
Bergenstal RM et al. EASD 2014;


DELIVER 2: glargine U300 demonstrates a 48% lower rate of hospitalization-related hypoglycemia
Predicted Inpatient/ED Encounter-related hypoglycemia event rate
(events/100 patients-months)
-48%
p<0.01
1.97%
3.82%
glargine U300
other basal insulin
Study Design
The Differentiate Toujeo clinical and Economic in reaL-world Via EMR data study (DELIVER 2) is a retrospective matched cohort study.
Data were collected from the Predictive Health Intelligence Environment database of electronic medical records (EMRs) representing 26 integrated health delivery networks.

IDegLira, Degludec or Liragutide - DUAL 1 trial



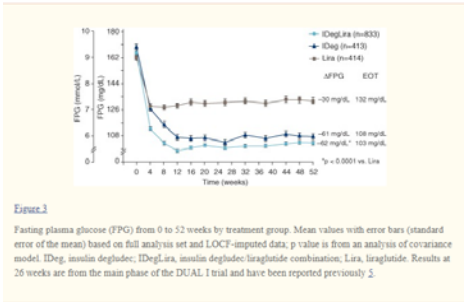
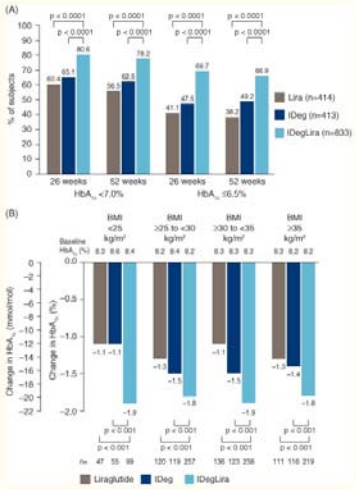


Figure 3

Fasting plasma glucose (FPG) from 0 to 52 weeks by treatment group. Mean values with error bars (standard error of the mean) based on full analysis set and LOCF-imputed data; p value is from an analysis of covariance model. IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide combination; Lira, liraglutide. Results at 26 weeks are from the main phase of the DUAL I trial and have been reported previously 5.



IDegLira

- Improved A1c
- Improved FPG
- Had greater % of patients reach A1c goals

Gough SCL. *Diabetes, Obesity & Metabolism*. 2015;17(10):965-973. doi:10.1111/dom.12498.

over 3700 patients already randomized in real life studies

achieve control

- Insulin-naïve T2DM (US)
- **Primary endpoint:** Patients (%) achieving individualized HbA1c target (HEDIS criteria) without hypoglycemia
- Target n=3324 (May 17), 77% randomized
- 6-month interim analysis n=1800 (Mar 2017)

reach control

- Insulin-naïve T2DM (EU, LATAM)
- **Primary endpoint:** Change in HbA1c
- Enrollment Completed n=703

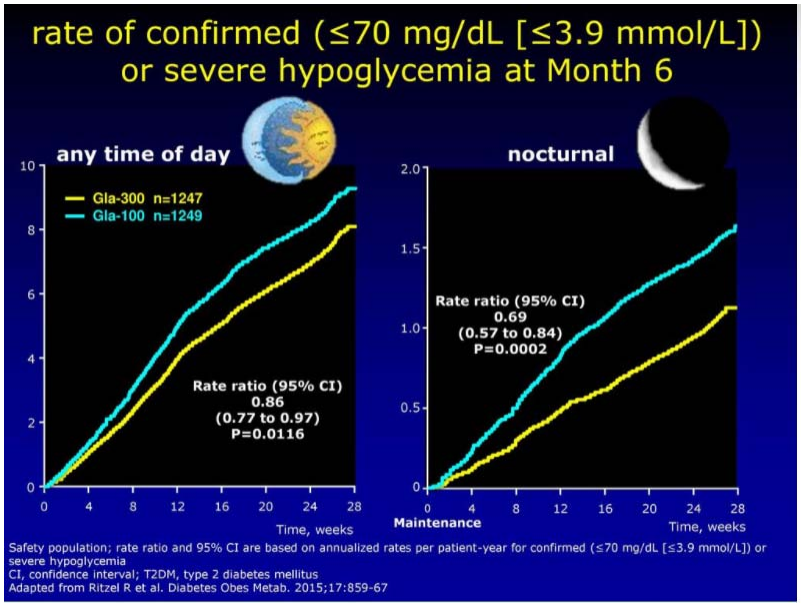
regain control

- T2DM uncontrolled on basal insulin (EU, LATAM)
- **Primary endpoint:** Change in HbA1c
- Enrollment Completed n=609

KEY SECONDARY OUTCOME MEASURES

Hypoglycemia, persistence to insulin treatment, HbA1c target achievement, weight, basal insulin dose, need for treatment intensification, patient-reported outcomes, healthcare utilization

rate of confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia at Month 6



Safety population; rate ratio and 95% CI are based on annualized rates per patient-year for confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia
CI, confidence interval; T2DM, type 2 diabetes mellitus
Adapted from Ritzel R et al. Diabetes Obes Metab. 2015;17:859-67

ITAS: Italian Titration Approach Study

- glargine U300 OD in the evening, starting dose: 0.2 U/kg
- Dose adjustement: target range for fasting SMPG 80-110 mg/dL
- glargine U300 dose will be adjusted based on two different approaches (Algorithm 1: managed by phy; Algorithm 2 managed by pt)

Median FBG 3 consecutive days	Algorithm phys (managed by phy)	Algorithm pat (managed by pt)
>180 mg/dL	+ 4	+ 4
>110-180 mg/dL	+ 2	+ 2
80–110 mg/dL	No change	No change
< 80 mg/dL	- 2	- 2
≤ 54 mg/dL*	At physician discretion	Contact physician

- * or occurrence of ≥2 symptomatic or 1 severe hypoglycemia episode(s) in the preceding week
- Patients randomised to algorithm 1 will have basal insulin dose adjusted during visits or telephone contacts
- Patients randomised to both algorithm 1 & 2 will adjust dose at least weekly, and no more frequently than every 3-4 days, as needed

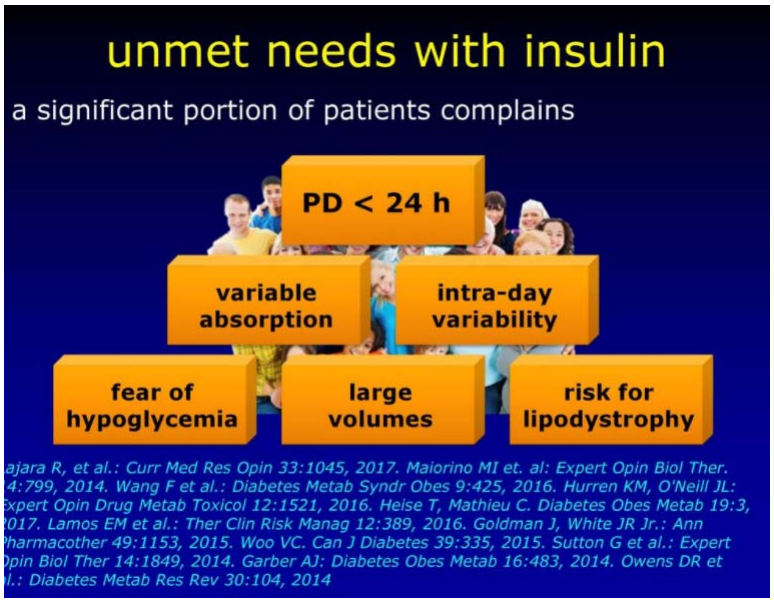
Cardiovascular Safety of Insulin Degludec: DEVOTE Study (cont)

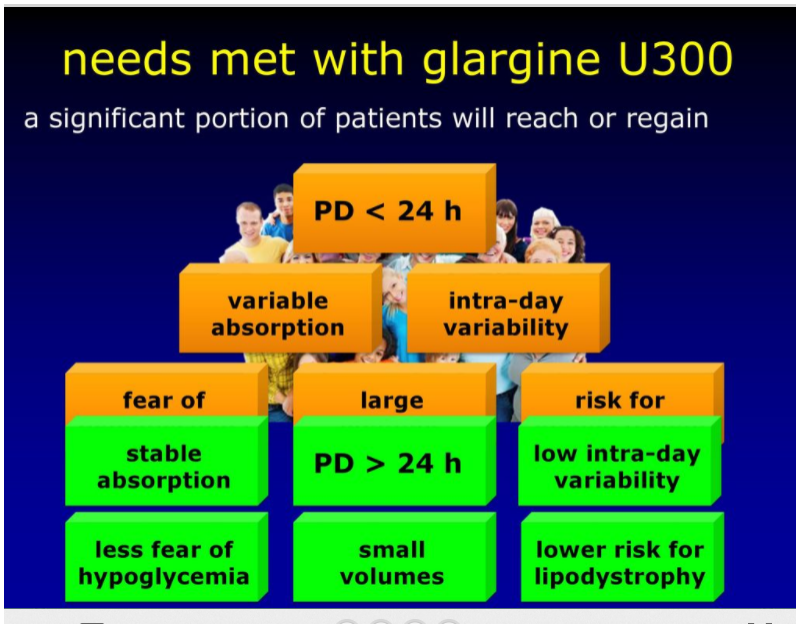
Outcome	Hazard Ratio	95% CI
Primary composite[1]	0.91	0.78-1.06
Expanded composite[2]	0.92	0.80-1.05
All-cause death	0.91	0.76-1.11
Non-CV death	0.84	0.60-1.16
CV death	0.96	0.76-1.21
Nonfatal MI	0.85	0.68-1.06
Nonfatal stroke	0.90	0.65-1.23
UA → hospitalization	0.95	0.68-1.31
Severe hypoglycemia	0.60	0.48-0.76
Nocturnal severe hypoglycemia	0.47	0.31-0.73

→ Degludec non-Inferior to glargine for major CV events

[1]CV death, nonfatal MI, nonfatal stroke
[2]CV death, nonfatal MI, nonfatal stroke, unstable angina leading to hospitalization

Marso SP, et al. *N Engl J Med*. 2017;doi:10.1056/NEJMoa1615692.


unmet needs with insulin
a significant portion of patients complains
PD < 24 h
variable absorption
intra-day variability
fear of hypoglycemia
large volumes
risk for lipodystrophy
ajara R, et al.: Curr Med Res Opin 33:1045, 2017. Maiorino MI et. al: Expert Opin Biol Ther. 4:799, 2014. Wang F et al.: Diabetes Metab Syndr Obes 9:425, 2016. Hurren KM, O'Neill JL: Expert Opin Drug Metab Toxicol 12:1521, 2016. Heise T, Mathieu C. Diabetes Obes Metab 19:3, 017. Lamos EM et al.: Ther Clin Risk Manag 12:389, 2016. Goldman J, White JR Jr.: Ann harmacother 49:1153, 2015. Woo VC. Can J Diabetes 39:335, 2015. Sutton G et al.: Expert pin Biol Ther 14:1849, 2014. Garber AJ: Diabetes Obes Metab 16:483, 2014. Owens DR et l.: Diabetes Metab Res Rev 30:104, 2014


needs met with glargine U300
a significant portion of patients will reach or regain
PD < 24 h
variable absorption
intra-day variability
fear of
large
risk for
stable absorption
PD > 24 h
low intra-day variability
less fear of hypoglycemia
small volumes
lower risk for lipodystrophy

Summary of new Ultralong-Acting Basal Insulins

	Glargine U-300	Degludec
Insulin Type	Analogue; ultralong-acting	Analogue; ultra long-acting
Onset	6 hours	1 hour
Peak	Flat	Flat
Half-Life	~23 hours	~ 25 hours
Steady State	4 days	2-3 days
Effective Duration	≤ 36 hours	Up to 42 hours

Lucidi D, et al. *Diabetes Care.* 2011;34:1312-1314.
Niswender K, et al. *Clin Diabetes*. 2009;27:60-68.

Date: Patient:

4 Steps to Managing Your Meal-Time Insulin

Getting started: Your Endocrinologist will determine your starting dose of meal-time insulin.

Step 1: Check your sugar
Check your blood sugar before breakfast, lunch, and dinner, and check at bedtime.

Step 2: Average your sugar
Take the averages for each meal over 3 days, and use this to change your insulin dose below.

Step 3: Change your dose

Meal	Glucose Range	What Do I Change?
Lunch	Less than 80	Decrease breakfast insulin by 2 units
	80 – 120	No change to breakfast insulin dose
	121 – 150	Increase breakfast insulin by 2 units
	151 – 180	Increase breakfast insulin by 3 units
	More than 181	Increase breakfast insulin by 4 units
Dinner	Less than 80	Decrease lunch insulin by 2 units
	80 – 120	No change to lunch insulin dose
	121 – 150	Increase lunch insulin by 2 units
	151 – 180	Increase lunch insulin by 3 units
	More than 181	Increase lunch insulin by 4 units
Bedtime	Less than 80	Decrease dinner insulin by 2 units
	80 – 120	No change to dinner insulin dose
	121 – 150	Increase dinner insulin by 2 units
	151 – 180	Increase dinner insulin by 3 units
	More than 181	Increase dinner insulin by 4 units

Step 4: Repeat
Continue checking your fasting blood sugar, and repeat steps 1 through 3.

SMART-D clinic- R. Iyengar/R. Gianch

How to Counsel and Manage Your Patients Before and During Pregnancy for Optimal Outcomes

Health Delivery and Technology in Today's
Diabetes Care
Applying Evidence Based Treatments to Personalize Care

April 28, 2018
Jennifer Wyckoff, MD

M | HEALTH SYSTEM UNIVERSITY OF MICHIGAN

Disclosures

- No relevant financial disclosures.

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Objectives

- Prevent congenital malformations and other poor pregnancy outcomes caused by diabetes

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Case 1:

24 yo Chinese PhD student
Established primary care with you for routine care
No PMH/PSH
Medication: OCPs x 8 years for menstrual irregularity
FH: Father- Type 2 diabetes, diagnosed at age 50
SH: no tob, rare ETOH, no IVDA,
Very busy with school, but also works a part time job in the evenings as a personal health assistant for an elderly woman
Recently got married, but planning pregnancy in the next year when she has finished her PhD
Vitals: 5'0" 126 lbs BP 126/74 P 70
Few skin tags on neck, otherwise normal

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Case 1: How many reasons are there for her to be screened for diabetes?

24 yo Chinese PhD student
Established primary care with you for routine care
No PMH/PSH
Medication: OCPs x 8 years for menstrual irregularity
FH: Father- Type 2 diabetes, diagnosed at age 50
SH: no tob, rare ETOH, no IVDA,
Very busy with school, but also works a part time job in the evenings as a personal health assistant for an elderly woman, no exercise
Recently got married, but planning pregnancy in the next year when she has finished her PhD
Vitals: 5'0" 126 lbs BP 126/74 P 70 BMI 24
Few skin tags on neck, otherwise normal

6

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Prevention, Step 1: SCREENING

Testing for Diabetes or Prediabetes in Asymptomatic Adults

Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

Classification and Diagnosis of Diabetes:
Standards of Medical Care in Diabetes - 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S13-S27

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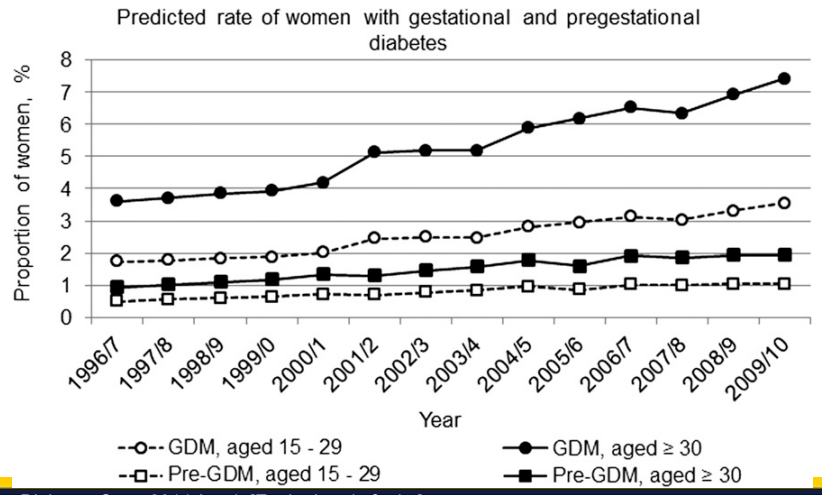
Why screening for diabetes is important



Feig, Diabetes Care. 2014 Apr 4. [Epub ahead of print]

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Prevention, Step 1: SCREENING

Truven database:

839,792 pregnancies- 0.23% had undiagnosed pre-existing diabetes
(1.44% had known preexisting diabetes.)

1931 women had diabetes and didn't know it. (Roughly 1 in 84)

9.5% **(183)** of infants born to mothers with **undiagnosed diabetes** had a major congenital malformation
(3.1% (60) of those infants had a heart defect)

Jovanovic Diabetes Metab Res Rev 31:707-716, 2015

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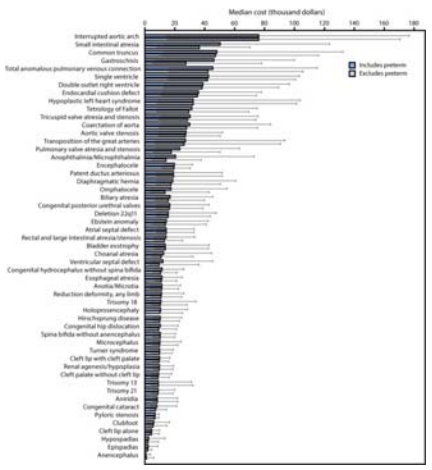
Prevention, Step 1: SCREENING

- 3% of pregnancies in the US are complicated by congenital malformations. (120,000 babies)
- $22.9 Billion in hospital costs alone in 2013
- Impact on families



MMWR Morb Mortal Wkly Rep. 2017 Jan 20;66(2):41-46. doi: 10.15585/mmwr.mm6602a1.

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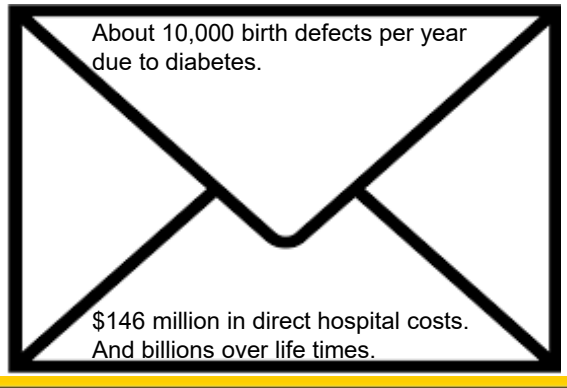
Prevention, Step 1: SCREENING

7.3% of birth defects were attributed to maternal diabetes.

American Journal of Obstetrics and Gynecology
Volume 199, Issue 3, September 2008, Pages 237.e1-237.e9



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Why screening for diabetes is important

Testing for Diabetes or Prediabetes in Asymptomatic Adults

How do you incorporate screening for diabetes into your practice?

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Case 2:

37 yo G0P0 with newly diagnosed Type 2 DM based on A1C of 9.3%
Establishing primary care with you after DM picked up on employment physical
PMH: PCOS, Infertility, Migraines, Palpitations, HTN dx'd 3 yrs ago, during divorce
PSH: s/p ccy
Medication: Atenolol, Excedrin prn
FH: Father and Mother- both deceased late 60's from CHF, Type 2 diabetes,
SH: + tob, no ETOH, no IVDA,
Office job
ROS: Nocturia
Vitals: 5'6" 226 lbs BP 140/86 P 60
Mild acanthosis, Mild hirsutism, Trace LE edema- otherwise normal
A1C- 9.3%; Normal CBC, Creatinine 0.8, Total cholesterol-240, Trigs 320, HDL 32

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Case 2:

Wrote Prescription for Metformin
Stopped Atenolol and started ACE
Counselled on Smoking Cessation
Order UMA (which was undetectable)

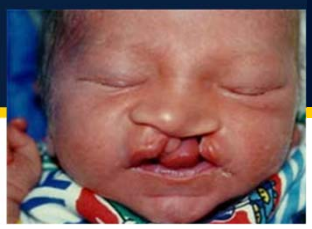
Returned 8 weeks later:
Nocturia has resolved; Feeling better
Smoking less
Wt 216; BP 130/78
A1C 8.3%

Case 2:

4 months later:
Receive a call from Risk management.
A few weeks after her last PCP visit, she had a + home pregnancy test.
Called her gynecologist- US confirmed pregnancy at 10 weeks- Referred to endocrinologist next day.
She stopped smoking.
A1C 8.0% Wt 213
ACE stopped. Metformin Stopped. Insulin started. Followed weekly.
At 18 weeks, A1C was 5.8%.
US revealed multiple congenital anomalies- (not renal)
Pregnancy Terminated.
Patient didn't pursue lawsuit.

- Didn't take a sexual history
- Didn't check a pregnancy test
- Didn't counsel on Metformin's effect on fertility
- Didn't refer to Comprehensive Diabetes Education classes
- Didn't counsel on risks of diabetes and pregnancy.
- No documented contraception plan

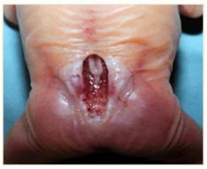
Prevention, Step 2: Preconception Counseling



In 2015….in the TRUVEN database

18.5-19%

of infants of mothers with pre-existing diabetes were born with a congenital malformation.



Even if you look at only MAJOR malformations,

10.9-11.4%

of infants of mothers with pre-existing diabetes were born with a MAJOR congenital malformation.

Jovanovic Diabetes Metab Res Rev 31:707-716, 2015

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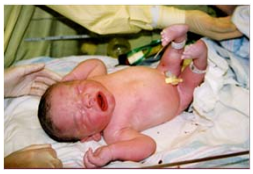
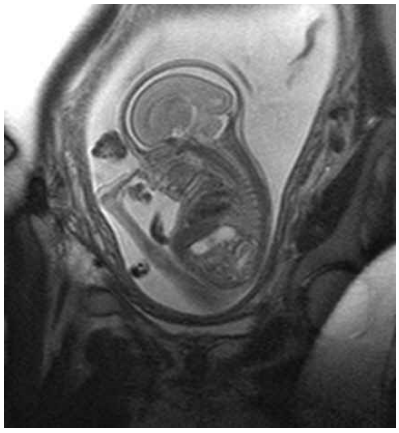
Prevention, Step 2: Preconception Counseling

Caudal Regression Syndrome





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Prevention, Step 2: Preconception Counseling

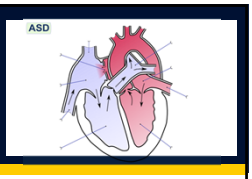


Table 4. Major Congenital Anomalies in Infants Born of Mothers With and Without Diabetes, 1988–2002

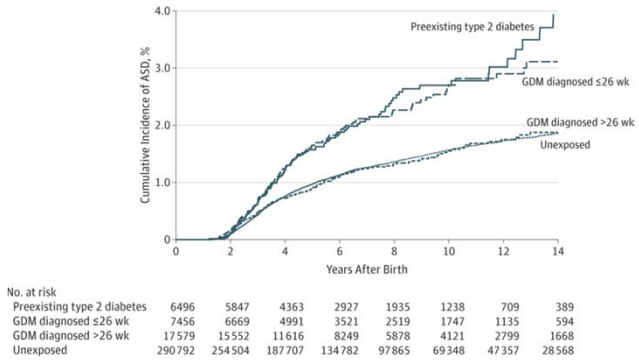
Type of Congenital Anomaly	IDM (n=516)	Non-IDM (n=150,589)	IDM Compared With non-IDM	P
Total	47 (9.1)	4,625 (3.1)	2.97 (2.25–3.90)	<.001
Adjusted total*			3.10 (2.28–4.22)*	<.001
Cardiac	25 (4.8)	1,147 (0.8)	6.36 (4.32–9.36)	<.001
Dextrocardia	2 (0.4)	31 (0.0)	18.83 (4.52–78.47)	.010
Patent ductus arteriosis	4 (0.8)	135 (0.1)	8.65 (3.21–23.29)	.010
Ventricular septal defect	10 (1.9)	511 (0.3)	5.71 (3.07–10.61)	<.001
Musculoskeletal	14 (2.7)	1,609 (1.1)	2.54 (1.51–4.27)	<.001
Caudal regression	3 (0.6)	4 (0.0)	218.88 (49.11–975.55)	<.001
Central nervous system	7 (1.4)	275 (0.2)	7.43 (3.54–15.65)	<.001
Spina bifida	1 (0.2)	17 (0.0)	17.17 (2.29–128.76)	.060
Ear, nose, and throat	5 (1.0)	368 (0.2)	3.97 (1.65–9.54)	.010
Genitourinary	3 (0.6)	659 (0.4)	1.33 (0.43–4.12)	.500
Hypospadias complex	6 (1.2)	626 (0.4)	2.80 (1.26–6.22)	.020

IDM, infants born of mothers with diabetes mellitus.
Data are n (%) or relative risk (95% confidence interval) unless otherwise specified.
* Major congenital anomaly was adjusted for maternal smoking and age and expressed as an odds ratio.

Fetal and Neonatal Outcomes of Diabetic Pregnancies.
Yang, Joanne; Cummings, Elizabeth; OConnell, Colleen; Jangaard, Krista
DOI: 10.1097/01.AOG.0000231688.08263.47

From: **Association of Maternal Diabetes With Autism in Offspring**

JAMA. 2015;313(14):1425-1434. doi:10.1001/jama.2015.2707



No. at risk

Preexisting type 2 diabetes	6496	5847	4363	2927	1935	1238	709	389
GDM diagnosed ≤26 wk	7456	6669	4991	3521	2519	1747	1135	594
GDM diagnosed >26 wk	17579	15552	11616	8249	5878	4121	2799	1668
Unexposed	290792	254504	187707	134782	97865	69348	47357	28568

Figure Legend:

Unadjusted Cumulative Incidence of ASD by In Utero Exposure to Maternal DiabetesASD indicates autism spectrum disorder; GDM, gestational diabetes mellitus.

Why Preconception Care is Essential

A Metanalysis of Preconception Care

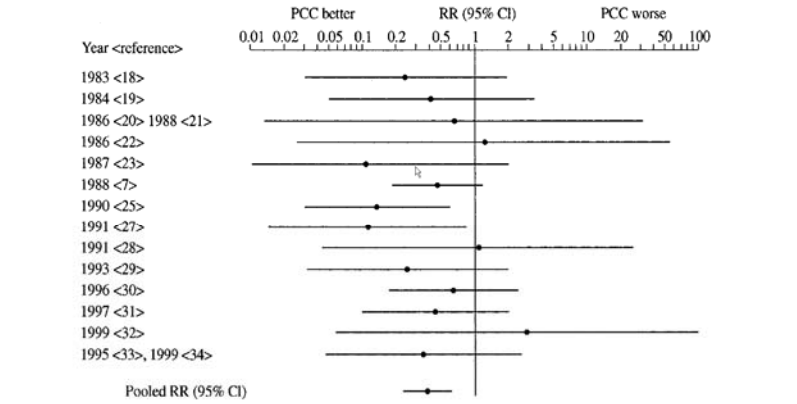


Figure 1. Relative risk (RR) for major congenital abnormalities from 14 studies of women with diabetes mellitus who did or did not receive preconception care (PCC).

Ray et al QJMED 2001 94:435-444

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Prevention, Step 2: Preconception Counseling

Preconception Counseling- Initial Conversation

- **Counseling on Risks to Fetus**
  - Miscarriage/ Stillbirth
  - Congenital Malformations
  - Macrosomia
  - Neonatal Hypoglycemia
  - Metabolic Imprinting/Epigenetic Modification
  - Genetic Counseling
  - Autism
  - DKA
- **Counseling on Risks to Mother**
  - C section
  - Exacerbation of Retinopathy
  - Preeclampsia/Preterm Delivery
  - Effect on Renal Function
  - Hypoglycemia

Document counseling and clearance status!!!

- **Key Components**
  - Patient Goals
  - Contraceptive Plan
  - Ensure Goal Prior to Conception
  - A1C < 6.5%
  - Insulin Pump/ CGM, if appropriate
  - Weight loss, if appropriate
  - Smoking Cessation

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Prevention, Step 2: Preconception Counseling

- Macrosomia >4000 g
  - T1DM 11%
  - T2DM 6.6%
  - Normal 4.6%

  Jovanovic Diabetes Metab Res Rev 31:707-716, 2015
- Neonatal Hypoglycemia
  - 48% Hypoglycemia
    - Glucose < 47mg/dl
  - 19% Severe hypoglycemia
    - Glucose < 36 mg/dl
- 15% recurrent
- 83% occurred in 24 hours
- J Pediatr. 2012 Nov;161(5):787-91. doi: 10.1016/j.jpeds.2012.05.022. Epub 2012 Jun 23.

Prevention, Step 2: Preconception Counseling

- 20% of women with pre-existing diabetes will develop preeclamspia.
- Sibai. AM J Obstet Gyn 2000 Feb; 182(2):364-9.

	Preeclamspia %
New	11
DM>10 yrs	22
Mild Disease	21
Proteinuria	36

Baseline Level of Kidney Damage Predicts Risk of Preclampsia

Relative Risk of Preeclampsia with first prenatal visit HbA1c Cut-Offs Among Diabetic Subjects

			Univariate		Multivariable	
HbA1c	% (n) <HbA1c	% (n) ≥HbA1c	RR (95% CI)	p-value	RR (95% CI)	p-value
≥ 6.5	48.1 (76)	51.9 (82)	4.63 (1.40, 15.38)	0.01*	4.42 (1.35, 14.47)	0.01*
≥ 7	67.1 (106)	32.9 (52)	5.30 (2.00, 14.07)	0.001*	5.26 (2.06, 13.41)	0.001*
≥ 7.5	78.5 (124)	21.5 (34)	5.73 (2.41, 13.66)	<0.0001*	5.60 (2.50, 12.56)	<0.0001*
≥ 8	85.4 (135)	14.6 (23)	4.70 (2.08, 10.64)	0.0002*	4.60 (2.18, 9.69)	<0.0001*

†Controlling for parity and body mass index
*Significant at <0.05 level
First prenatal visit A1c.

- Relative risk of preeclampsia was increased for every A1c 0.5 increment from 6.5 to 8.0 comparing < to ≥ the specified A1c

The Association of Circulating Angiogenic Factors and HbA1c with the Risk of Preeclampsia in Women with Preexisting Diabetes
Allison L Cohen, MD1,2, Julia B Wenger, MPH3, Tamarra James-Todd, PhD, MPH4, Brooke M Lamparello1, Elizabeth Halprin, MD1,2, Shanti Serdy, MD1,2, Shuling Liang, PhD2, Gary L Horowitz, MD2, Kee-Hak Lim, MD2, Sarosh Rana, MD2, Tamara C Takoudes, MD2, Jennifer A Wyckoff, MD6, Ravi Thadhani, MD, MPH3, S. Ananth Karumanchi, MD2,5, and Florence M Brown, MD1,2

Prevention, Step 2: Preconception Counseling

- 24% of 168 pregnancies in women with T1DM resulted in preterm delivery.
- 15% indicated (mostly for preeclampsia)
- 9% spontaneous
- Poor control was a factor in both.
- Approximately 32% of these infants had respiratory distress syndrome compared to 6% of IDM without preterm delivery.
- 69% of the spontaneous and 76%of the indicated pre term deliveries were admitted to the NICU, compared to 31% of controls.

Diabetes Care 27:2824–2828, 2004

Gestational Diabetes and Perinatal Outcomes among Women with and Those without a History of Bariatric Surgery.

Table 2. Gestational Diabetes and Perinatal Outcomes among Women with and Those without a History of Bariatric Surgery.

Variable	Bariatric-Surgery Group (N=596)	Matched Control Group (N=2356)	Risk Difference	Odds Ratio (95% CI)*	P Value
	no./total no. (%)		percentage points (95% CI)		
Gestational diabetes†					
Total	11/578 (1.9)	157/2294 (6.8)	−4.9 (−6.5 to −3.4)	0.25 (0.13 to 0.47)	<0.001
Insulin-treated	4/578 (0.7)	83/2294 (3.6)	−2.9 (−3.9 to −1.9)	0.17 (0.06 to 0.49)	<0.001
Large-for-gestational-age infant‡	51/590 (8.6)	523/2336 (22.4)	−13.8 (−16.6 to −11.0)	0.33 (0.24 to 0.44)	<0.001
Macrosomia‡	7/590 (1.2)	221/2336 (9.5)	−8.3 (−9.7 to −6.8)	0.11 (0.05 to 0.24)	<0.001
Small-for-gestational-age infant‡	92/590 (15.6)	178/2336 (7.6)	8.0 (4.8 to 11.1)	2.20 (1.64 to 2.95)	<0.001
Low-birth-weight infant‡	40/590 (6.8)	105/2336 (4.5)	2.3 (0.1 to 4.5)	1.34 (0.88 to 2.04)	0.17
Preterm birth§	59/590 (10.0)	176/2344 (7.5)	2.5 (−0.2 to 5.1)	1.28 (0.92 to 1.78)	0.15
Stillbirth¶	6/596 (1.0)	12/2356 (0.5)	0.5 (−0.4 to 1.3)	1.89 (0.59 to 6.05)	0.28
Neonatal death <28 days after live birth§	4/590 (0.7)	5/2344 (0.2)	0.5 (−0.2 to 1.2)	2.93 (0.57 to 15.14)	0.20
Stillbirth or neonatal death	10/596 (1.7)	17/2356 (0.7)	1.0 (−0.1 to 2.0)	2.39 (0.98 to 5.85)	0.06
Major congenital malformations§					
Total	14/590 (2.4)	83/2344 (3.5)	−1.2 (−2.6 to 0.3)	0.72 (0.40 to 1.29)	0.27
Excluding chromosomal abnormalities§	12/590 (2.0)	79/2344 (3.4)	−1.3 (−2.7 to 0.0)	0.63 (0.34 to 1.18)	0.16

* Odds ratios were conditioned on the matching set, including one pregnancy after bariatric surgery and up to five controls, with matching for maternal age, parity, presurgery BMI (with the use of early-pregnancy BMI in the controls), smoking, educational level, and delivery year; adjustments were made for history of coexisting conditions, history of substance abuse, and mother's country of birth.
† Analyses of gestational diabetes excluded women with prepregnancy diabetes (18 women [3%] in the bariatric-surgery cohort and 62 women [3%] in the matched control cohort).
‡ Analyses of large-for-gestational-age infants (>90th percentile), small-for-gestational-age infants (<10th percentile), macrosomia (birth weight >4500 g), and low birth weight (<2500 g) excluded stillbirths and births without data on birth weight. Analyses of large-for-gestational-age infants and small-for-gestational-age infants also excluded births without data on gestational age. There were 6 exclusions in the bariatric-surgery group (1.0%) and 20 in the matched-control group (0.9%).
§ Analyses of preterm birth, neonatal death, and congenital malformations excluded stillbirths and births without data on gestational age. There were 6 exclusions in the bariatric-surgery group (1.0%) and 12 in the matched-control group (0.5%).
¶ Stillbirth was defined as fetal death at 22 or more completed weeks of gestation on or after July 1, 2008 (97% of pregnancies), and at 28 or more weeks before July 1, 2008 (<3% of pregnancies).

- Bariatric surgery was associated with
  - Reduced risk of gestational diabetes
  - Reduced risk of excessive fetal growth
  - Shorter gestation
  - Increased risk of small-for-gestational-age infants
  - and <u>possibly</u> increased perinatal mortality.

Outcomes of Pregnancy after Bariatric Surgery
Johannsen NEJM 372;9 814-824

The NEW ENGLAND JOURNAL of MEDICINE

Prevention, Step 2: Preconception Counseling

How do you incorporate Preconception Counseling into your practice and documentation?

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Prevention, Step 3: Preconception **Care**

A Metanalysis of Preconception Care

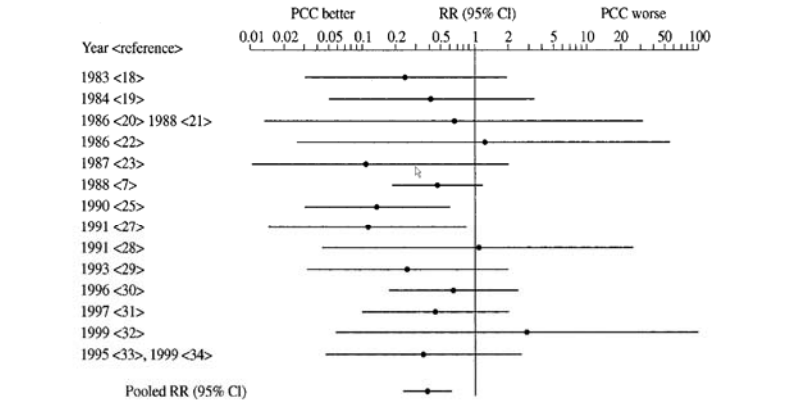

Figure 1. Relative risk (RR) for major congenital abnormalities from 14 studies of women with diabetes mellitus who did or did not receive preconception care (PCC).

Ray et al QJMED 2001 94:435-444

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Case 3 :

35 yo nurse with Type 1 since age 5, complicated by NPDR, Mild Microalbuminuria, Obesity (BMI 37) and Severe hypoglycemia.

Lantus 54 units at bedtime
I:C ratio of 1:5 before meals
CF of 1:20

A1C 8.5%, Mean glucose 220 Range (32-578)

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Prevention, Step 3: Preconception **Care**

Prevalence of achieving A1C < 7.0% in NHANES 1988-2010

% (SE)	1999-2002	2003-2006	2007-2010
Total	44.1 (2.4)	57.0 (2.3)	52.5 (2.5)
Age 20-49	36.5 (5.7)	49.7 (4.2)	48.9 (4.7)
50-64	45.6 (4.0)	49.6 (4.1)	48.8 (3.8)
65 or older	46.6 (3.7)	67.3 (3.3)	58.0 (2.7)
Male	41.9 (3.0)	54.9 (3.1)	50.8 (3.5)
Female	46.0 (3.6)	59.2 (2.8)	54.1 (2.5)
Insulin	25.8 (5.1)	28.4 (5.6)	30.3 (4.1)
Orals	43.8 (2.8)	58.6 (2.8)	59.2 (3.2.)
Both	22.5 (7.5)	37.7 (4.3)	24.2 (2.7)

Casgrande, Diabetes Care 2013; 1-9.

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Prevention, Step 3: Preconception **Care**

- Goals-
  - Fasting Glucose under 90 mg/dl
  - 1 hour postprandial under 130 mg/dl
  - 2 hour postprandial under 120 mg/dl
  - A1C < 6.5% preconception
  - A1C <6.0% during pregnancy

Managing Existing Diabetes and Pregnancy: ADA Technical Reviews and Consensus Recommendations for Care. Eds Kitzmiller et al. ADA 2008

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Prevention, Step 3: Preconception **Care**

Glycemic Targets in Pregnancies Affected by Diabetes

Table 2 Comparison of current international recommendations for glycemic targets in pregnancies affected by diabetes

Organization	Type 1/type 2 diabetes target	GDM target
American Diabetes Association [82]	Pre-meal, bedtime, overnight 60–99[a]	FBG ≤95
	Peak post-prandial 100–129[a]	1 h ≤140
		2 h ≤120
American College of Obstetricians and Gynecologists [83]		1 h <140
		2 h <120
Endocrine Society [84]	Pre-prandial ≤90 or[a]	Pre-prandial ≤90 or[a]
	Pre-prandial ≤95	Pre-prandial ≤95
	1 h ≤140	1 h ≤140
	2 h ≤120	2 h ≤120
Australian Diabetes in Pregnancy Society [85]		FBG ≤90
		1 h ≤133
		2 h ≤121
Canadian Diabetes Association [86]	FBG <95	FBG <95
	1 h <140	1 h <140
	2 h <120	2 h <120
National Institute for Health and Care Excellence [87]	FBG 63–106	FBG 63–106
	1 h <140	1 h <140

FBG fasting blood glucose
[a] If achievable without hypoglycemia

Springer

Curr Diab Rep (2015) 15:565 (Teri Hernandez)

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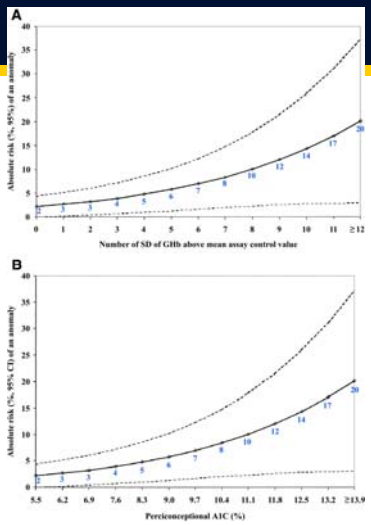
A: Risk of a major or minor congenital anomaly according to the number of SDs of GHb above normal, measured periconceptionally.

This is an underestimate!!!

Metanalysis of prospective cohort data



Andrea Guerin et al. Dia Care 2007;30:1920-1925

American Diabetes Association.

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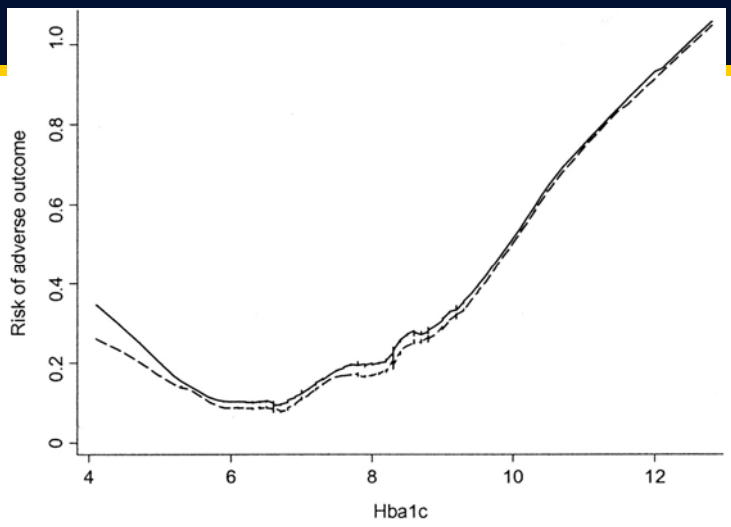
Relation between first-trimester A1C level and pregnancy outcome using the lowess model with bandwidth of 0.5.



Gunnar L. Nielsen et al. Dia Care 2006;29:2612-2616

American Diabetes Association.

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Prevention, Step 3: Preconception **Care**

- Contraception until A1C goal is achieved
  - Monthly visits with Multidisciplinary clinic- diabetes education/ nutrition, endocrinology, etc.
  - Insulin (only)
    - Metformin's use in pre-existing diabetes is controversial.
  - Insulin pump
  - CGM
- Comprehensive Review of Medications (including OTC)
  - No ACE, No ARB, No Atenolol, No diuretics
  - No statins
  - No oral hypoglycemic
  - No weight loss medications
  - Etc.
- Blood Pressure (goal < 140/90)
- Prenatal Vitamin for 3 months prior to conception
  - Folic acid 400 mcg
- Creatinine and Urine Microalbumin
  - Counsel on risk of preeclampsia, renal failure
  - For decreased GFR, refer to renal for preconception care/counseling.
- Exercise Echocardiogram, if indicated
- Ophthalmology referral
- Maternal-Fetal Medicine referral

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Case 3 :

37 yo nurse with Type 1 since age 5, complicated by history of PDR, HTN, Hypertriglyceridemia, Mild Microalbuminuria, Obesity (BMI 37), PCOS and Severe hypoglycemia. Wants to get her “diabetes in shape” before removing IUD.

Lantus 54 units at bedtime
I:C ratio of 1:5 before meals
CF of 1:20

A1C 8.5%, Mean glucose 220 Range (32-578)

Prevention, Step 3: Preconception **Care**

- Goals-
  - Fasting Glucose under 90 mg/dl
  - 1 hour postprandial under 130 mg/dl
  - 2 hour postprandial under 120 mg/dl
  - A1C < 6.5% preconception
  - A1C <6.0% during pregnancy

Managing Existing Diabetes and Pregnancy: ADA Technical Reviews and Consensus Recommendations for Care. Eds Kitzmiller et al. ADA 2008

Case 3 : Initial Visit

Counseled (a lot) on Risks
- •Miscarriage/ Stillbirth
- •Congenital Malformations
- •Macrosomia (>4000g)
- •Shoulder dystocia
- •Neonatal Hypoglycemia
- •Epigenetic Modification
- •Genetic Counseling
- •Autism
- •DKA
- •C section
- •Exacerbation of Retinopathy
- •Preeclampsia/Preterm Delivery
- •Effect on Renal Function
- •Hypoglycemia

- Reviewed medications
- Prenatal Vitamin
- Dietitian/ Diabetes Education
- Testing before and 2 hours after each meal; diet records
- Ordered A1C, Creatinine, UMA, Lipids, TSH
- Exercise Echocardiogram
- *2018- ADA guidelines- (Low dose aspirin from end of 1st trimester til delivery to prevent preeclampsia.)*
- Ophthalmology referral
  - Q trimester eye exams
- Maternal-Fetal Medicine referral

Case 3 : Follow up Visits

- Very disordered eating--- Dietitian
- Extreme Glucose variability
- Phobia of lows
- A1C- mid 8s
- Creatinine 0.7
- UMA 54
- Triglycerides 600
- TSH 1.2
- Exercise Echocardiogram- normal

- Next steps:
  - Pump
  - CGM
  - Strict food records
  - Monthly visits with weekly phone calls for over a year!
  - Relaxed her A1C goal to <7%

Prevention, Step 3: Preconception **Care**

- Goals-
  - Fasting Glucose under 90 mg/dl
  - 1 hour postprandial under 130 mg/dl
  - 2 hour postprandial under 120 mg/dl
  - A1C < 6.5% preconception
  - A1C <6.0% during pregnancy

Managing Existing Diabetes and Pregnancy: ADA Technical Reviews and Consensus Recommendations for Care. Eds Kitzmiller et al. ADA 2008

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Prevention, Step 3: Preconception **Care**

Preconception Care takes work!

How can you take care of your patients?

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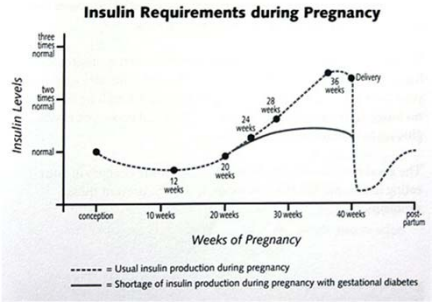
Prevention, Step 4: Prenatal Care

- Hypoglycemia- first trimester
  - Glucagon
  - Family involvement
  - Blood glucose awareness training
  - CGM
  - Medialert
  - Discuss Driving
  - Glucose tabs in purse
- Basal insulin needs increase ~ 50%
- I:C ratios decrease 4 fold.
- (Median of 12 to median of 3)
- J Matern Fetal Neonatal Med. 2013 Sep 27. [Epub ahead of print]



Sudden hypos- think placental insufficiency

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Case 3 :

37 yo nurse with Type 1 since age 5, …

-Laser surgery during pregnancy

-Preeclampsia and C section at 37 weeks

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Prevention, Step 4: Prenatal Care

- Hemoglobin A1C- q 4 weeks- < 6%
- Fetal Monitoring
  - First trimester dating ultrasound
  - Level II anatomy survey; Fetal Echocardiogram
  - Triple/quadruple screen or Amniocentesis or Fetal cells
  - For PDM: Ultrasounds for growth at 24,28,32,36 weeks
  - For PDM: Fetal monitoring with BPP and NST
    - Weekly from 28-36 weeks
    - Twice weekly from 36 weeks until delivery
- Insulin drip during labor and delivery
- Available NICU

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Preexisting Diabetes- Postpartum management

- Resume insulin at 1/3 to ½ of preconception dose.
- Titrate dose upward over the next few days as postpartum insulin sensitivity resolves.
- Breast feeding may increase insulin sensitivity. Keep snacks nearby.

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Summary

- Preconception Care can prevent congenital malformations (and other poor pregnancy outcomes)
- Consider screening for diabetes in reproductive age women
- Glycemic control is essential for reproductive age women with diabetes
- Contraception is needed until glycemic goals are met

POST TRANSPLANT DIABETES MELLITUS

Palak Choksi, MD
Assistant Professor
Metabolism, Endocrinology and Diabetes
University of Michigan

NOTHING TO DISCLOSE

CASE

- 61/W with history of T2DM c/b neuropathy, retinopathy and ESRD. She is s/p a deceased donor kidney transplant on 4/4/2018
- Currently on Prednisone 20 mg, just reduced from 40 mg
- Tacrolimus
- Mycophenolate Mofetil (MMF)
- Pre op HgA1c: 7.9%

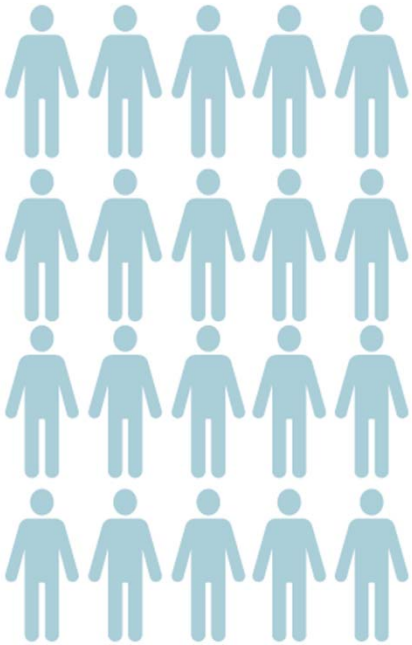
CASE

- 46/W with no PMH of DM s/p deceased donor kidney transplant (ESRD secondary to hypertension) on 09/25/2013. She was subsequently diagnosed with PTDM.
- 09/13-2/14: HgA1C normal, BG < 100

2/2014: HgA1c 6.0%

1/2015: 6.7%


10
min



HISTORY OF TRANSPLANT

1954: First kidney transplant

1960's: Liver, heart and pancreas

1980's: Lung and intestinal organs

34,770

28,588

6,182

http://optn.transplant.hrsa.gov

U.S. TRANSPLANT DATA 2017

Kidney: 19,849

Liver: 8,082

Heart: 3,244

INDICATIONS FOR TRANSPLANT

RENAL

- Diabetes Mellitus
- Polycystic kidney disease
- Hypertensive Nephropathy

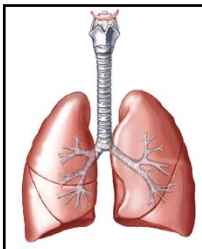
LIVER

- Cirrhosis (viral hepatitis, Alcohol)
- Primary liver tumors
- cholestatic disease (PBC or extra hepatic biliary atresia)

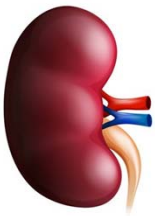
TERMINOLOGY

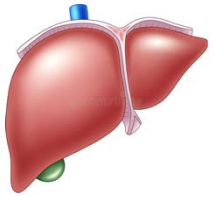
- Post transplant diabetes mellitus (PTDM)
- New Onset Diabetes After Transplant (NODAT)

Definitions were initially published in 2003 and revised in 2014



INCIDENCE



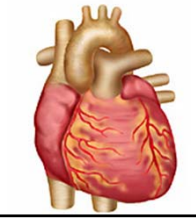


2-52% in renal transplant

2.5-25% in liver transplant

4-40% in heart transplant

30-35% in lung transplant



Usually seen within the first year

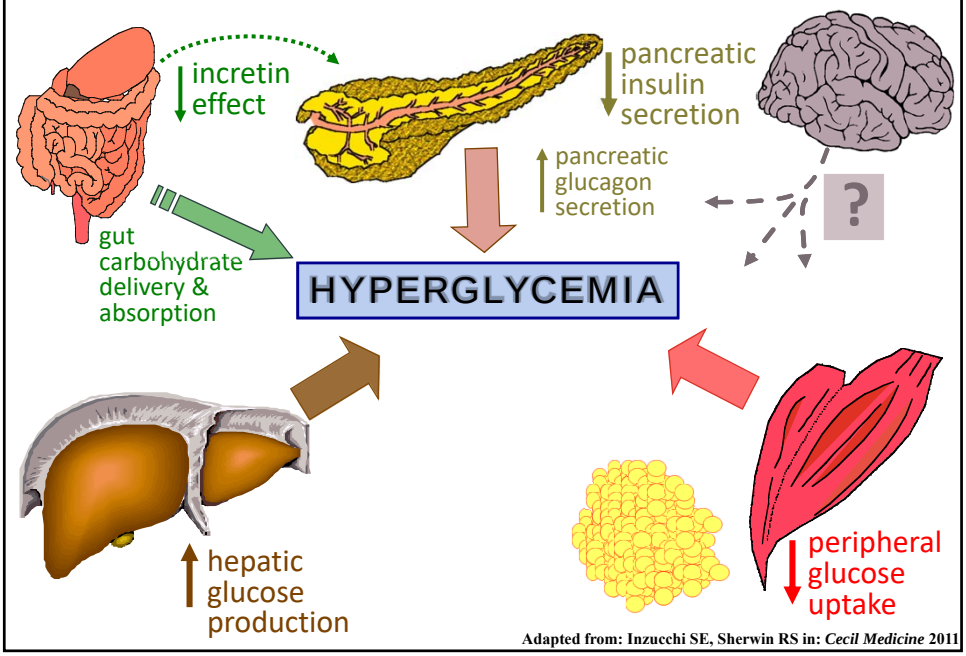
Woodward RS, Schnitzler MA, Baty J, Lowell JA, Lopez-Rocafort L, Haider S, Woodworth TG, Brennan DC Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients. Am J Transplant. 2003;3(5):590.

INCIDENCE

Based on organ procurement and transplant network data, prevalence of PTDM at one year following transplant has reduced from 12% in 2005 to 5% in 2012

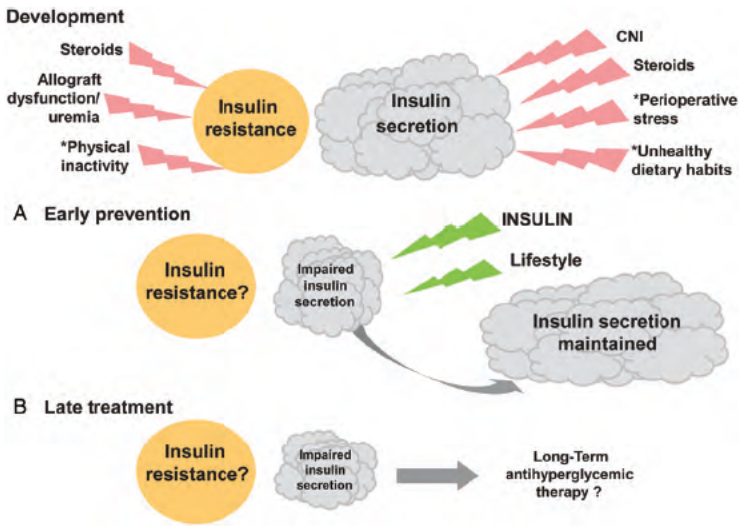
Boots JM, Christiaans MH, Van Duijnhoven EM, Van Suylen RJ, Van Hooff JP Early steroid withdrawal in renal transplantation with tacrolimus dual therapy: a pilot study. Transplantation. 2002;74(12):1703.
Hjelmesaeth J, Hartmann A, Kofstad J, Stenstrøm J, Leivestad T, Egeland T, Fauchald P Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. Transplantation. 1997;64(7):979.
Gunnarsson R, Arner P, Lundgren G, Magnusson G, Ostman J, Groth CG Diabetes mellitus--a more-common-than-believed complication of renal transplantation. Transplant Proc. 1979;11(2):1280.

PATHOPHYSIOLOGY OF DIABETES



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

MECHANISM OF PTDM



PTDM AFTER RENAL TRANSPLANT

Treatment of choice for RRT

- 40% patients reach a 17-year survival after transplant

- Liver: 88% at one year and 70% at 5 years
- 30% of deaths in liver transplant are caused by CV and cerebrovascular disease

PTDM AS A SOURCE FOR COMPLICATIONS

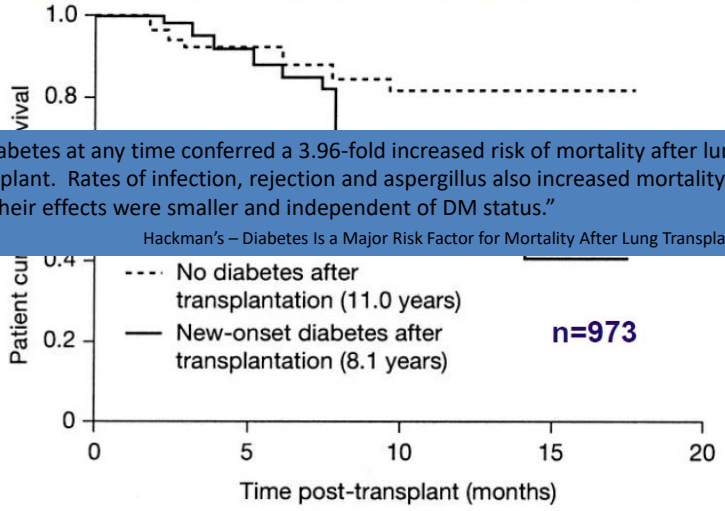
Increases risk of graft failure/ reduced graft function

Mortality

Susceptible to DM related complications:

Infection, metabolic syndrome, retinopathies, macroangiopathies

Decreased Patient Survival in PTDM

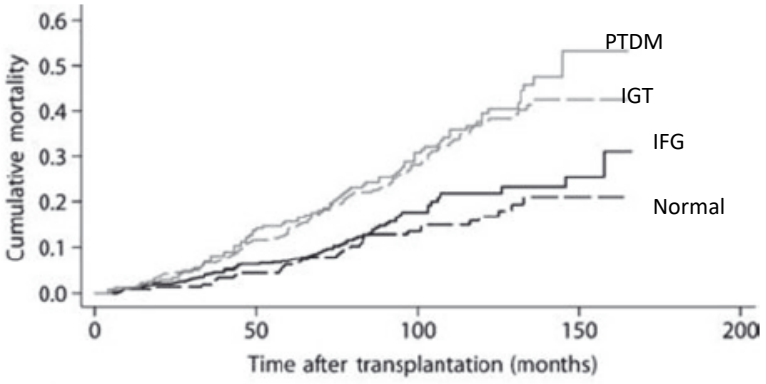


"…diabetes at any time conferred a 3.96-fold increased risk of mortality after lung transplant. Rates of infection, rejection and aspergillus also increased mortality risk but their effects were smaller and independent of DM status."

Hackman's – Diabetes Is a Major Risk Factor for Mortality After Lung Transplantation.

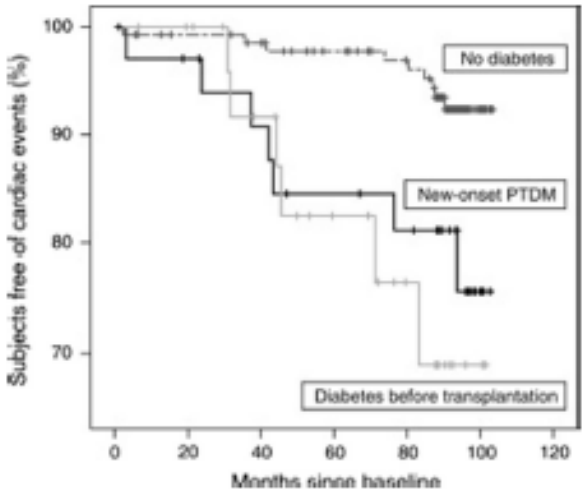
Jindal & Hjelmesaeth Transplantation 2000; 70: S58.

MORTALITY ASSOCIATED WITH PTDM



Valderhaug TG, Hjelmesaeth J, Hartmann A, Roislien J, Bergrem HA, Leivestad T, Line PD, Jenssen T (2011) The association of early post-transplant glucose levels with long-term mortality. Diabetologia 54(6):1341–1349.

CARDIAC EVENTS ASSOCIATED WITH PTDM



Hjelmesaeth J, Hartmann A, Leivestad T, Holdaas H, Sagedal S, Olstad M, Jenssen T (2006) The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. Kidney Int 69(3):588–595

COURSE OF PLTDM

Hyperglycemia may not be persistent

Of 17,184 adults – 29.2% developed at least one episode compatible with PTDM but at one year persistence was 4.9% (higher 7.6% for NASH)

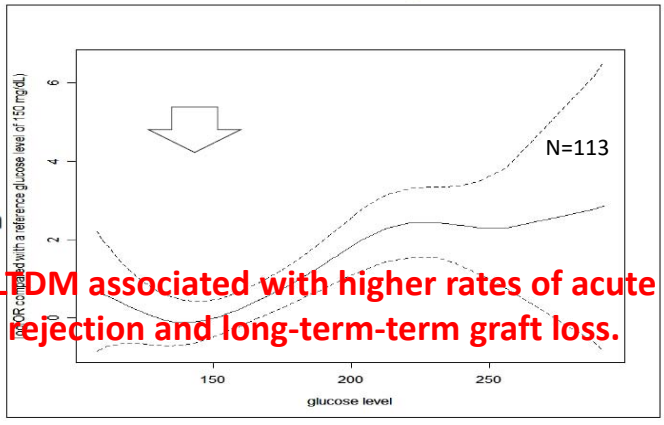
5 year follow up study of deceased donor transplants: mortality in those with persistent PLTDM was 36.5% compared to 13.9% in those with transient DM

COURSE OF PLTDM

CV mortality are a major cause of non-liver related mortality after LT 13-28%

Infections and infection-related complications

Post Liver Transplant Glucose Level and Increased Risk of Rejection



PLTDM associated with higher rates of acute rejection and long-term-term graft loss.

Wallia, et al.Transplantation. 2010 Jan 27;89(2):222-6.

RISK FACTORS (GENERAL)

- Classical
- Older age
- Male sex
- High BMI
- Pre-transplant impaired fasting glucose (RR 2.4 95% CI 1.1-5.3)
- Deceased donor
- Ethnicity (AA or Hispanics)
- Peri-operative hyperglycemia
- HLA mismatch

RISK FACTORS (RENAL)

- Immunosuppressants
- Ethnicity (high in AA and hispanics)
- Age
- Viral infections (CMV, HEP C, EBV)
- Sex
- Family history
- Genetic predisposition
- Parenteral Feeding (High Calorie feeds, TF, nutritional supplements)
- Polycystic kidney disease

PLTDM RISK FACTORS

NASH

Hepatitis C virus infection

Cytomegalovirus

Immunosuppressants (CNI and GC)

Deceased Donor

Parenteral Feeding (High Calorie feeds, TF, nutritional supplements)

HEPATITIS C

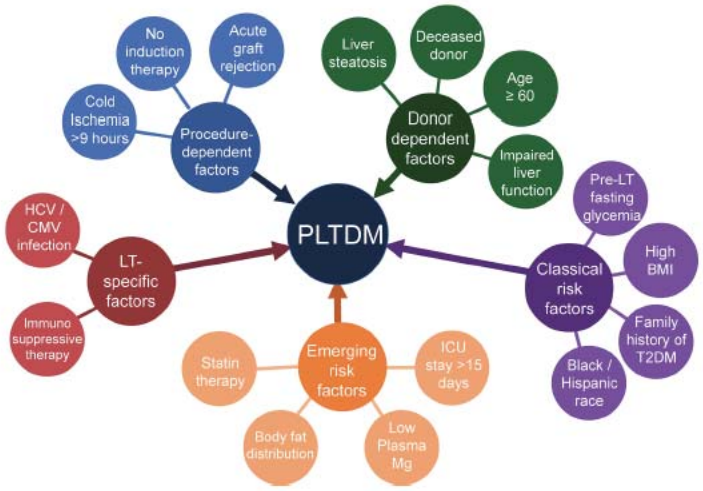
In a meta-analysis of 10 studies with 2502 patients, individuals with anti-HCV antibodies were nearly 4 times as likely to develop PTDM

HCV may induce islet cell dysfunction (impairment of insulin signaling in hepatocytes) and insulin resistance due to liver dysfunction

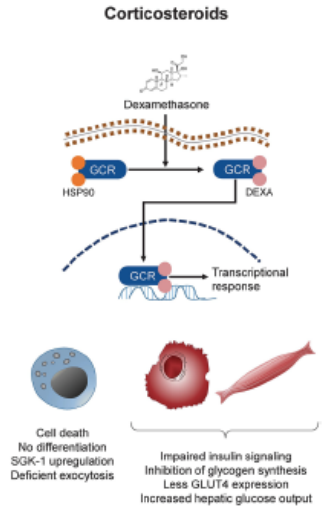
Treatment pretransplant is encouraged

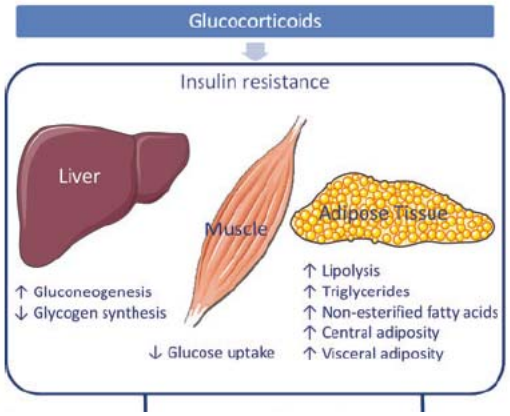
Fabrizi F, Martin P, Dixit V, Bunnapradist S, Kanwal F, Dulai G Post-transplant diabetes mellitus and HCV seropositive status after renal transplantation: meta-analysis of clinical studies. Am J Transplant. 2005;5(10):2433.

PLTDM RISK FACTORS



GLUCOCORTICOIDS





GLUCOCORTICOIDS

Induce insulin resistance in a dose-dependent manner

In a trial looking at GC withdrawal in kidney transplant patients, the overall incidence of PTDM was similar in both groups. However, the GC withdrawal arm lower proportion of patients required insulin.

Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P, Astellas Corticosteroid Withdrawal Study Group A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Ann Surg. 2008;248(4):564.

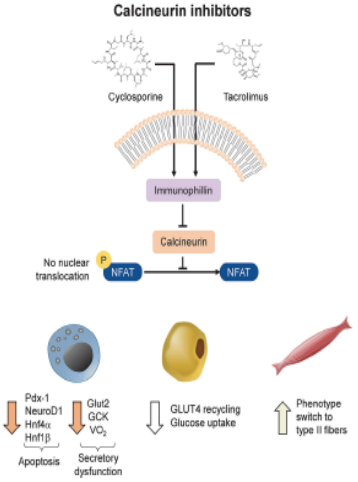
GLUCOCORTICOIDS

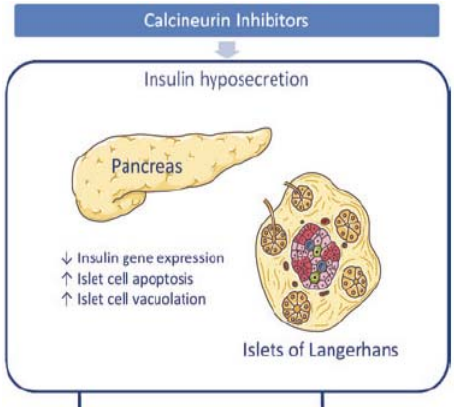
Table 4. Univariate Odds Ratios for the Initiation of Hypoglycemic Therapy According to Average Daily Glucocorticoid Dose

Dose, mg/d*	No. Cases (n=11 855)	No. Controls (n=11 855)	Odds Ratio	95% Confidence Interval
0	11 080	11 461	1.0	. . .
1-39	589	345	1.77	1.54-2.02
40-79	111	38	3.02	2.09-4.37
80-119	45	8	5.82	2.74-12.35
120+	30	3	10.34	3.16-33.90

Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J Glucocorticoids and the risk for initiation of hypoglycemic therapy. Arch Intern Med. 1994;154(1):97.

CALCINEURIN INHIBITORS





CALCINEURIN INHIBITORS

Tacrolimus reduces insulin secretion due to beta cell toxicity

Cyclosporine modifies insulin gene expression and is less diabetogenic than tacrolimus

Heisel O, Heisel R, Balshaw R, Keown P New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. Am J Transplant. 2004;4(4):583.

CALCINEURIN INHIBITORS

Higher levels of tacrolimus (> 15 ng/dl) confer a greater risk for the development of hyperglycemia

Maes BD, Kuypers D, Messiaen T, Evenepoel P, Mathieu C, Coosemans W, Pirenne J, Vanrenterghem YF Posttransplantation diabetes mellitus in FK-506-treated renal transplant recipients: analysis of incidence and risk factors. Transplantation. 2001;72(10):1655.

(mTOR) INHIBITORS

Inactivates the protein mTOR

Results in decreased cytokine-mediated T-cell activation and proliferation and inhibits antibody formation

Lower rates of use in liver transplant due to concerns for infection.

OTHER AGENTS?

Azathioprine

MMF

Bactrim

Statins

Not been proven to have a diabetogenic effect in this population

COMBINATION THERAPY

TABLE 9. Posttransplant diabetes mellitus

	Tacrolimus + AZA N = 57(%)	Cyclosporine + MMF N = 46(%)	Tacrolimus + MMF N = 42(%)
PTDM	8 (14.0)	3 (6.5)	3 (6.5)
On insulin at 1 yr posttransplant	7 (12.3)	3 (6.5)	1 (2.2)

RANDOMIZED TRIAL OF TACROLIMUS (PROGRAF) IN COMBINATION WITH AZATHIOPRINE OR MYCHOPHENOLATE MOFETIL VERSUS CYCLOSPORINE (NEORAL) WITH MYCOPHENOLATE MOFETIL AFTER CADAVERIC KIDNEY TRANSPLANTATION1, 2.

Johnson, Christopher; Ahsan, Nasimul; Gonwa, Thomas; Halloran, Philip; Stegall, Mark; Hardy, Mark; Metzger, Robert; Shield, Charles; Rocher, Leslie; Scandling, John; Sorensen, John; Mulloy, Laura; Light, Jimmy; Corwin, Claudia; Danovitch, Gabriel; Wachs, Michael; VanVeldhuisen, Paul; Salm, Kim; Tolzman, Diane; Fitzsimmons, William

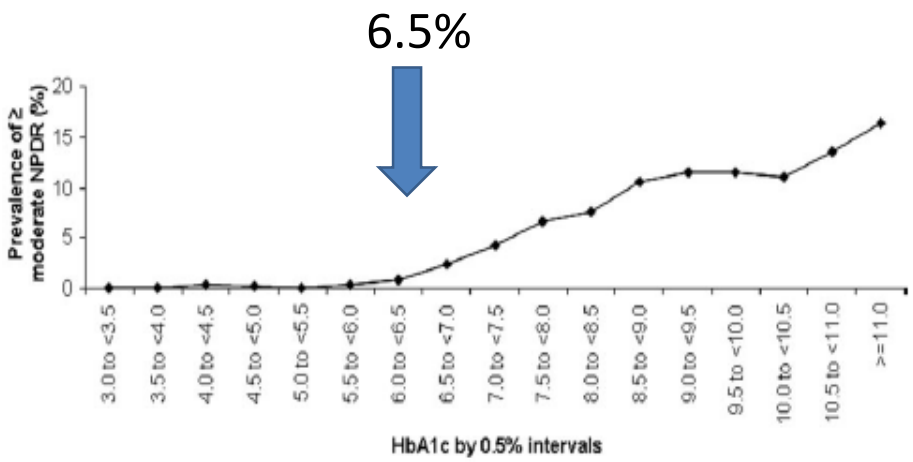
Transplantation. 69(5):834-841, March 15, 2000.

DIAGNOSIS OF DIABETES MELLITUS

- FPG≥126 mg/dl.
  - Prediabetes (IFG)≥100 mg/dl.
- 75 gram OGTT 2 hour-value≥200 mg/dl.
  - Prediabetes (IGT)≥140 mg/dl.
- Random blood glucose≥200 mg/dl + symptoms (polyuria, polydipsia, unexplained weight loss).

American Diabetes Association.
Cure • Care • Commitment®

International Expert Committee Report on the Role of A1C in the Diagnosis of Diabetes



THE INTERNATIONAL EXPERT COMMITTEE. Diabetes Care 2009;32:1327

CRITERIA FOR DIAGNOSIS PTDM

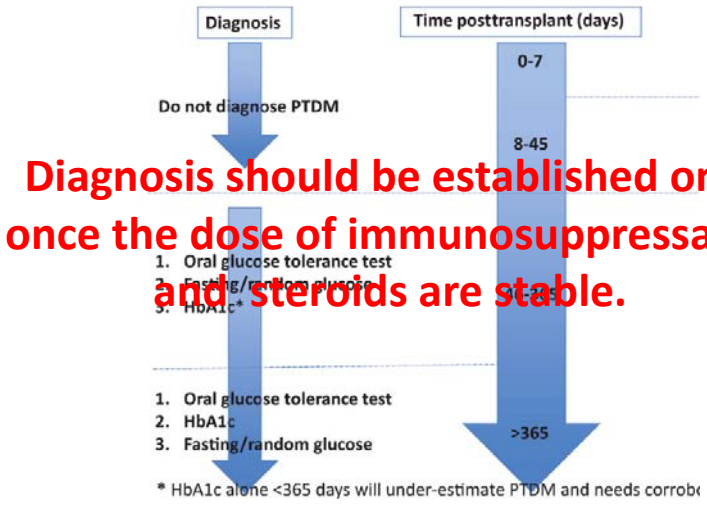
Requires one of the there

- Symptoms of hyperglycemia with random glucose > 200 mg/dL
- FBG ≥ 126 mg/dL
- 2hour post 75-g OGTT > 200 mg/dL
- HgA1c ≥ 6.5%

IMPAIRED GLUCOSE TOLERANCE IN THE POST TRANSPLANT PERIOD

- IFG: ≥ 100 mg/dl and < 126 mg/dL
- IGT: 2h post-75 g OGTT ≥ 140 and < 200 mg/dL

DIAGNOSING PTDM

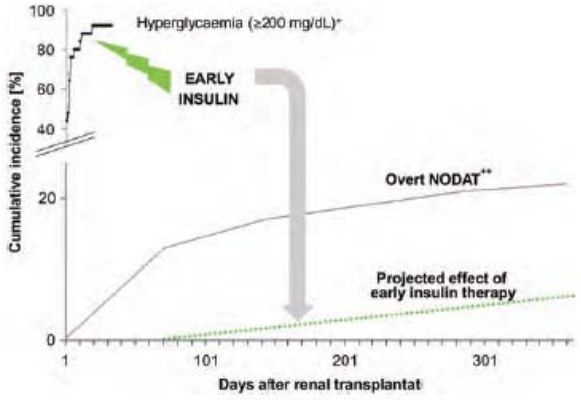


Diagnosis should be established only once the dose of immunosuppressants and steroids are stable.

ACCURACY OF HGA1C

- Uremia, hemolysis and erythropoietin use affect the levels of HgA1c
- Is not usually recommend until 3 months after transplant

EARLY INTERVENTION



Hecking M et al. European New Onset Diabetes After Transplantation Working Group. Novel View on New Onset Diabetes After Transplantation: Development, Prevention and treatment Nephrol Diab Transplant 2013

MANAGEMENT

- **Pretransplant screening**
- **Posttransplant:**

- Week 1-4: weekly FBG followed by at month 3,6 and 12
- HgA1c at 3 months
- If HgA1c < 6.0% recommend SMBG
- Until < 7.0% diet and lifestyle changes are recommended

MANAGEMENT

- Adjust immunosuppression if feasible

MANAGING PTDM

LIVER: PAUCITY OF LONG-TERM STUDIES

Strict glycemic control < 150 mg/dl in the FIRST year resulted in lower 1-year mortality, lower infection rates

Intraop hyperglycemia was an independent risk factor for post surgical site infections (OR 2.25 CI: 1.26-4.03)

Longer ICU stays

Prolonged ventilation

NON-GLYCEMIC GOALS

- Avoid smoking
- LDL < 100 in the absence of CVD and < 70 in the presence of CVD
- TG < 150 (difficult to maintain this on mTOR inhibitors)
- BP < 130/80 mmHg
- Routine eye and foot examinations

GLUCOSE GOALS

CBG: 140-180 for ICU patients

Non-ICU: < 140 premeals and < 180 mg/dl 2 hours post meal or random measurements.

Outpatient goals: 70-110 premeal

70-140 mg/dL for post meal measurements

HgA1c < 7% (tighter control around 6.5% in younger patients, few co-morbidities)

PHARMACOLOGIC THERAPIES

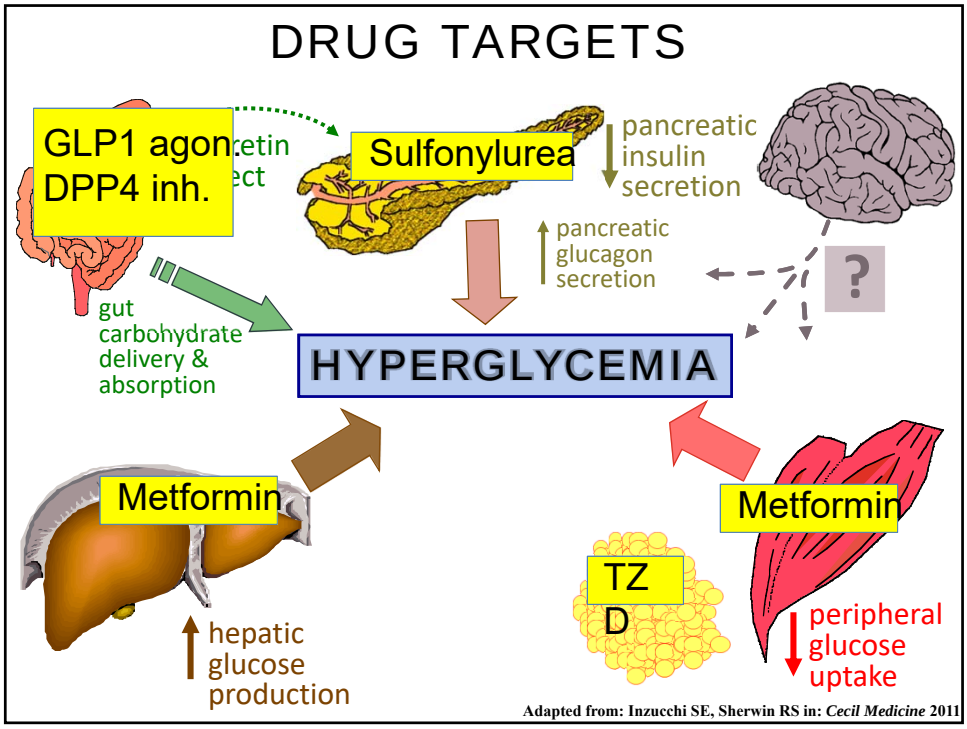
Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients (Review)

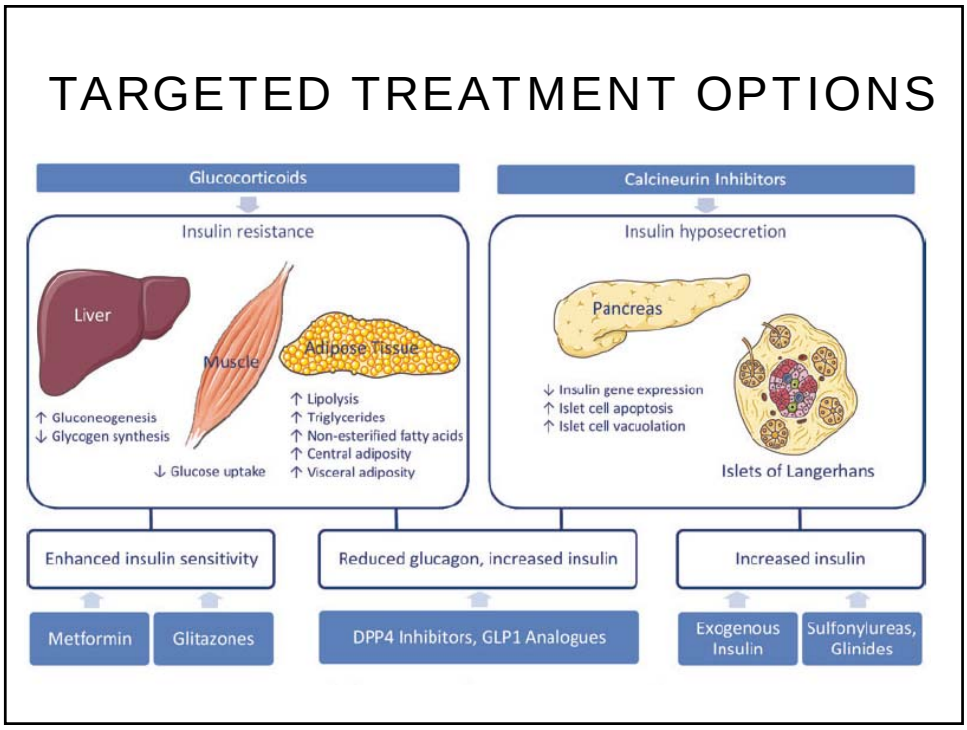
Lo C, Jun M, Badve SV, Pilmore H, White SL, Hawley C, Cass A, Perkovic V, Zoungas S

COCHRANE REVIEW 2017

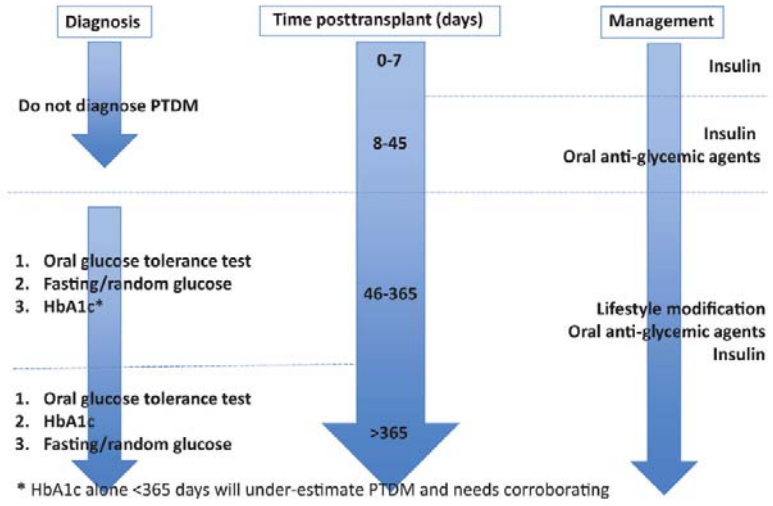
PHARMACOLOGIC THERAPIES

Commonly available classes include
Biguanides
Thiazolidinediones
Second generation sulphonylureas
Glucosidae inhibitors
DPP-IV inhibitors
GLP-1 analouges
Insulin


DRUG TARGETS
GLP1 agon
DPP4 inh.
Sulfonylurea
pancreatic
insulin
secretion
pancreatic
glucagon
secretion
?
gut
carbohydrate
delivery &
absorption
HYPERGLYCEMIA
Metformin
hepatic
glucose
production
Metformin
TZ
D
peripheral
glucose
uptake
Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011


TARGETED TREATMENT OPTIONS
Glucocorticoids
Calcineurin Inhibitors
Insulin resistance
Insulin hyposecretion
Liver
Muscle
Adipose Tissue
↑ Gluconeogenesis
↓ Glycogen synthesis
↓ Glucose uptake
↑ Lipolysis
↑ Triglycerides
↑ Non-esterified fatty acids
↑ Central adiposity
↑ Visceral adiposity
Pancreas
↓ Insulin gene expression
↑ Islet cell apoptosis
↑ Islet cell vacuolation
Islets of Langerhans
Enhanced insulin sensitivity
Reduced glucagon, increased insulin
Increased insulin
Metformin
Glitazones
DPP4 Inhibitors, GLP1 Analogues
Exogenous Insulin
Sulfonylureas, Glinides

TARGETED TREATMENT OPTIONS



Sharif A et al. Proceedings From an International Consensus Meeting on Posttransplantation Diabetes Mellitus: Recommendations and Future Directions. Am Journal of Transplantation 2014

TREATMENT OPTIONS

At this time there is inadequate data to recommend a hierarchy of anti-glycemic agents but rather treatment should be individualized.

Sharif A et al. Proceedings From an International Consensus Meeting on Posttransplantation Diabetes Mellitus: Recommendations and Future Directions. Am Journal of Transplantation 2014

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At this time there is inadequate data to recommend a hierarchy of anti-glycemic agents but rather treatment should be individualized.

Sharif A et al. Proceedings From an International Consensus Meeting on Posttransplantation Diabetes Mellitus: Recommendations and Future Directions. Am Journal of Transplantation 2014

TREATMENT BIGUANIDES

- Metformin
- Not contraindicated
- Use with caution in kidney transplant
- Can be used with EGFR between 30-59
- Large retrospective studies did not show worsening patient or graft survival
- Small studies (retrospective) did not show an HgA1c change
- Concomitant use with MMF may cause GI upset

European Medicines Agency (2016) Use of metformin to treat diabetes now expanded to patients with moderately reduced kidney function.
Stephen J, Anderson-Haag TL, Gustafson S, Snyder JJ, Kasiske BL, Israni AK (2014) Metformin use in kidney transplant recipients in the United States: an observational study. Am J Nephrol 40(6):546–553.
Kurian B, Joshi R, Helmuth A (2008) Effectiveness and longterm safety of thiazolidinediones and metformin in renal transplant recipients. Endocr Pract 14(8):979–984.

TREATMENT SULPHONYLUREAS

- glimepiride, glipizide, glyburide

-evaluated in the presence of glucocorticoids. Monitor renal function.

Can lower HgA1c 0.8-2.0%

Weight gain

Kasayama S, Tanaka T, Hashimoto K, Koga M, Kawase I Efficacy of glimepiride for the treatment of diabetes occurring during glucocorticoid therapy. Diabetes Care. 2002;25(12):2359.

TREATMENT MEGLITINIDES

- Repaglinide
- No dose adjustment in renal disease
- Undergoes hepatic metabolism, caution in liver disease
- Targets post prandial hyperglycemia
- expensive

Türk T, Pietruck F, Dolff S, Kribben A, Janssen OE, Mann K, Philipp T, Heemann U, Witzke O Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. Am J Transplant. 2006;6(4):842.

TREATMENT
DPP-IV INHIBITORS

- Sitagliptin, Vildagliptin
- Inhibits dipeptidyl peptidase 4 (increased insulin synthesis and release and decreased glucagon levels)
- Adjust dose for renal insufficiency
- Does not cause hypoglycemia
- Weight neutral

Lane JT, Odegaard DE, Haire CE, Collier DS, Wrenshall LE, Stevens RB Sitagliptin therapy in kidney transplant recipients with new-onset diabetes after transplantation. Transplantation. 2011 Nov;92(10):e56-7.
Strøm Halden TA,Åsberg A, Vik K, Hartmann A, Jenssen T Short-term efficacy and safety of sitagliptin treatment in long-term stable renal recipients with new-onset diabetes after transplantation. Nephrol Dial Transplant. 2014;29(4):926. Epub 2014 Jan 22.
Haidinger M, Werzowa J, Hecking M, Antlanger M, Stemer G, Pleiner J, Kopecky C, Kovarik JJ, Döller D, Pacini G, Säemann MD Efficacy and safety of vildagliptin in new-onset diabetes after kidney transplantation--a randomized, double-blind, placebo-controlled trial. Am J Transplant. 2014 Jan;14(1):115-23. Epub 2013 Nov 26.

TREATMENT

- GLP-1 AGONIST

Limited data in animal models focusing on graft failure

- Case series using liraglutide in KTR (no DM)

- SGLT-2 INHIBITORS

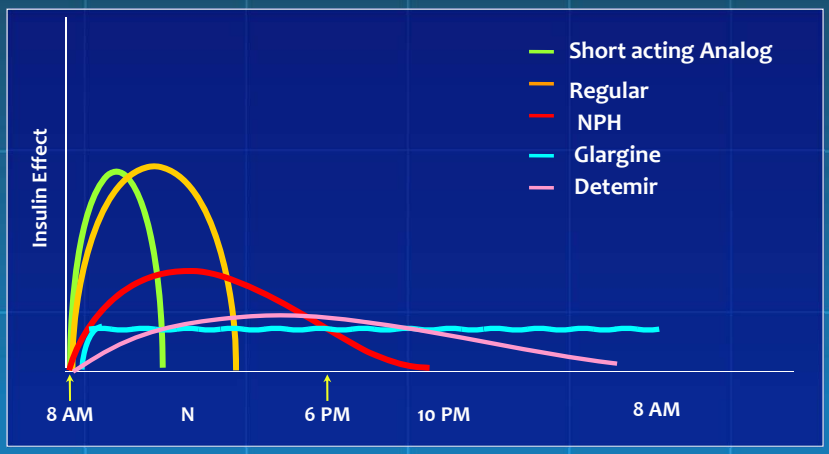
- No data

- TZD's

- Limited data

TREATMENT
INSULIN

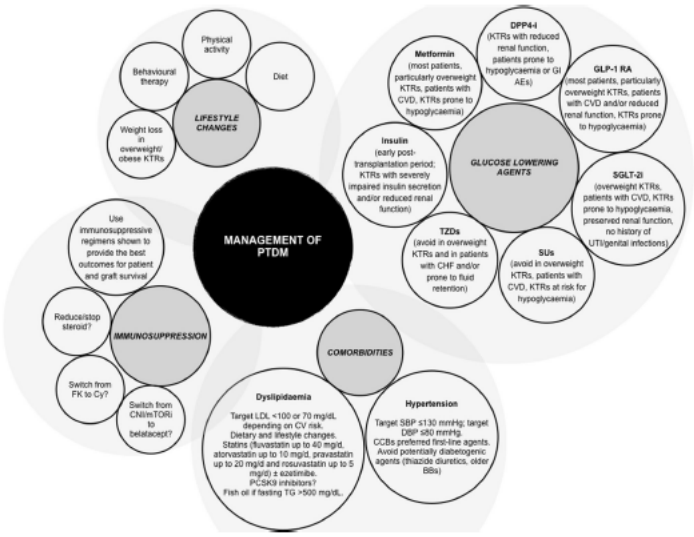
Pharmacokinetics of Insulin Preparations



AACE Inpatient Glycemic Control Resource Center

6-23

MANAGEMENT



KEY TAKEAWAYS

- Hyperglycemia is deleterious

  -PTDM affects survival of graft and patient

- Glucose Control Improves Outcomes (targets controversial)
- - Aim for tighter BG control in the immediate post-transplant phase and even as an outpatient

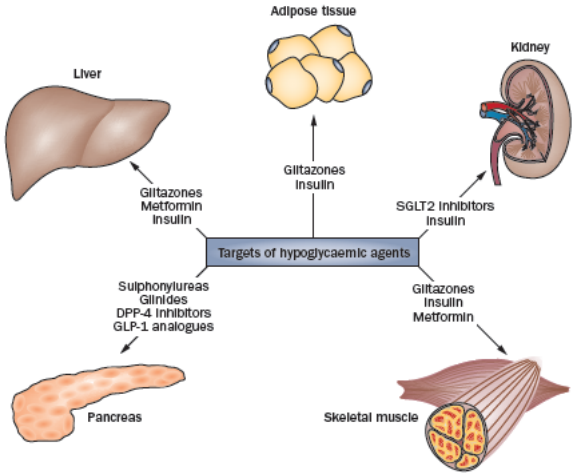
  - While certain oral agents can be used, the studies are small and with short term follow up.

  - Insulin therapy is a safe and effective way of managing PTDM

- Remember to adjust the doses (oral or insulin) as GC and CNI doses are reduced.

THANK YOU

Roma Gianchandani, MD



Trond Jenssens, Andres Hartmann. Emerging treatments for post transplant diabetes. Nature Reviews Nephrology August 2015

Table 2 | Approved hypoglycaemic drugs for use in PTDM

Drug class	Drugs	Main mechanisms of action	Risk of hypoglycaemia
Sulphonylureas	Glimepiride, glipizide, glibenclamide	Increases insulin secretion by blocking β-cell K^+–ATPase	Yes
Glinides	Repaglinide, nateglinide	Similar action to sulphonylureas but exhibit a shorter half-life	Yes
Biguanides	Metformin	Decreases glucose production in liver and increases glucose uptake in muscle	No
Glitazones (PPAR-γ activators)	Pioglitazone	Increases insulin sensitivity in muscle, fat and liver cells	No
DPP-4 inhibitors	Sitagliptin, vildagliptin	Inhibits degradation and increases endogenous levels of GLP-1 and GIP	No
Insulin	Insulin NPH, glargine, detemir, short-acting insulin and analogues	Insulin-receptor-stimulated glucose disposal and reduced glucose production	Yes

Abbreviations: DPP-4, dipeptidyl peptidase-4; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; NPH, neutral protamine hagedorn; PPAR, peroxisome proliferator-activated receptor; PTDM, post-transplantation diabetes mellitus.

Trond Jenssens, Andres Hartmann. Emerging treatments for post transplant diabetes. Nature Reviews Nephrology August 2015

Table 3 | Use of hypoglycaemic drugs in patients with PTDM and impaired renal function

Drug class	eGFR 60–90 ml/min/1.73 m²	eGFR 30–59 ml/min/1.73 m²	eGFR 15–30 ml/min/1.73 m²	eGFR <15 ml/min/1.73 m²
Sulphonylureas	Used without dose adjustment	Used with or without dose adjustment; caution for hypoglycaemia	Not generally recommended due to risk of hypoglycaemia	Not generally recommended due to risk of hypoglycaemia
Glinides	Used without dose adjustment	Used without dose adjustment	Should not be used	Should not be used
Biguanides	Used without dose adjustment	Used with or without dose adjustment*	Should not be used	Should not be used
Glitazones (PPAR-γ activators)	Used without dose adjustment	Used without dose adjustment	Used with or without dose adjustment	Should not be used
DPP-4 inhibitors	Used without dose adjustment	Used with or without dose adjustment	Used with or without dose adjustment	Used with or without dose adjustment
GLP-1 analogues[‡]	Not studied in PTDM	Not studied in PTDM	Not studied in PTDM	Not studied in PTDM
SGLT2 inhibitors[§]	Not studied in PTDM	Not studied in PTDM	Not studied in PTDM	Not studied in PTDM
Insulin	Used without dose adjustment	Used with or without dose adjustment; caution for hypoglycaemia	Used with or without dose adjustment; caution for hypoglycaemia	Used with or without dose adjustment; caution for hypoglycaemia

*Not approved in the USA for patients with GFR <60 ml/min/1.73 m². ‡Have been used safely in patients with type 2 diabetes and GFR >30 ml/min/1.73 m²; no documentation in PTDM. §Reduced glucose-lowering effect at GFRs <60 ml/min/1.73 m²; no documentation in PTDM. Abbreviations: DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; PPAR, peroxisome proliferator-activated receptors; PTDM, post-transplant diabetes mellitus; SGLT2, sodium-glucose linked transporter 2.

Trond Jenssens, Andres Hartmann. Emerging treatments for post transplant diabetes. Nature Reviews Nephrology August 2015

Table 2 Glucose-lowering agents

	Mechanism of action	Disadvantages	Advantages	Evidence in PTDM	Potential DDI
Metformin	↓ hepatic glucose production ↑ gut glucose utilisation and GLP-1 secretion	Contraindicated if eGFR < 30 mL/min/1.73 m² GI side effects Possible vitamin B 12 deficiency Caution if eGFR 30–59 mL/min/1.73 m²	No hypoglycaemia No weight gain Reduction in microvascular and macrovascular endpoints Low cost	Neutral effect on patient or graft survival [65] Efficacy in PTDM not demonstrated [66]	None known
Sulfonylureas/glinides	Stimulation of glucose-independent insulin secretion	Hypoglycaemia, weight gain, increased CV risk Dose adjustment in renal impairment	Rapid onset of action Low cost	SU not effective [73] Gliquidone and repaglinide effective in improving glucose control [74, 75]	Glibenclamide—cyclosporine (↑ glibenclamide) Repaglinide—cyclosporine (↑ repaglinide)
Thiazolidinediones	↑ insulin sensitivity and glucose uptake in muscle and adipose tissue	Water retention and weight gain; increased fracture risk; potential risk for CHF	No dose adjustment in renal impairment	TZDs effective in improving glucose control [66, 77–80]	None known (pioglitazone)
DPP-4-i	↑ glucose-dependent insulin secretion ↓glucose—dependent glucagon secretion	All but linagliptin require dose adjustment in moderate to severe renal impairment; potential risk for CHF (saxagliptin, alogliptin)	No hypoglycaemia No weight gain	Linagliptin, sitagliptin and vildagliptin have shown some efficacy and good tolerability [83–85]	Sitagliptin-cyclosporine (↑ Cy trough levels) Vildagliptin—tacrolimus (↓ FK trough levels)
Insulin	↑ tissue uptake of glucose ↓ Hepatic glucose production	Hypoglycaemia, weight gain, injectable	No dose adjustment in renal impairment	Conflicting results in terms of patient and graft survival [61]	None known
GLP-1 RA	↑ glucose-dependent insulin secretion ↓glucose-dependent glucagon secretion Slows gastric emptying ↑ satiety	GI side effects, high cost, injectable; dose adjustment in moderate renal impairment (exenatide), not recommended in severe renal impairment (exenatide, lixisenatide, dulaglutide); not recommended in ESRD (liraglutide)	Weight reduction, BP reduction, reduction in MACE and CV mortality (liraglutide) No dose adjustment in moderate to severe renal impairment (liraglutide, albiglutide) nor ESRD (semaglutide)	Good tolerability (liraglutide) [89]	None known
SGLT2-i	Blocks glucose reabsorption by the kidney, increasing glucose excretion in the urine	Not effective in renal impairment (eGFR <45 for empagliflorin, canagliflorin and <60 mL/min/1.73 m² for dapagliflorin); polyuria, increased risk for UTIs, genital infections (all); increased risk for amputations and fractures (canagliflorin)	Reduction in MACE (empagliflorin, canagliflorin) and CV mortality (empagliflorin)	N/A	Canagliflorin—cyclosporine (↑ canagliflorin)

DDI drug–drug interaction, *GLP-1* glucagon-like peptide-1, *eGFR* estimated glomerular filtration rate, *GI* gastrointestinal, *PTDM* post-transplantation diabetes mellitus, *CV* cardiovascular, *SU* sulfonylureas, *TZDs* thiazolidinediones, *CHF* congestive heart failure, *DPP4-i* dipeptidyl peptidase-4 inhibitors, *Cy* cyclosporine, *FK* tacrolimus, *GLP-1 RA* glucagon-like peptide-1 receptor agonists, *GI* gastrointestinal, *ESRD* end-stage renal disease, *BP* blood pressure, *MACE* major adverse cardiovascular events, *SGLT2-i* sodium-glucose co-transporter 2 inhibitors, *UTIs* urinary tract infections

Trond Jenssens, Andres Hartmann. Emerging treatments for post transplant diabetes. Nature Reviews Nephrology August 2015

67/F BMI 27 without diabetes, no FH, no Hep C, with h/o Li induced nephropathy on HD for 18 months now s/p DDRT.

HgA1c 5.0% at baseline

Plot BG 1,2,3 weeks post suregry

1 month

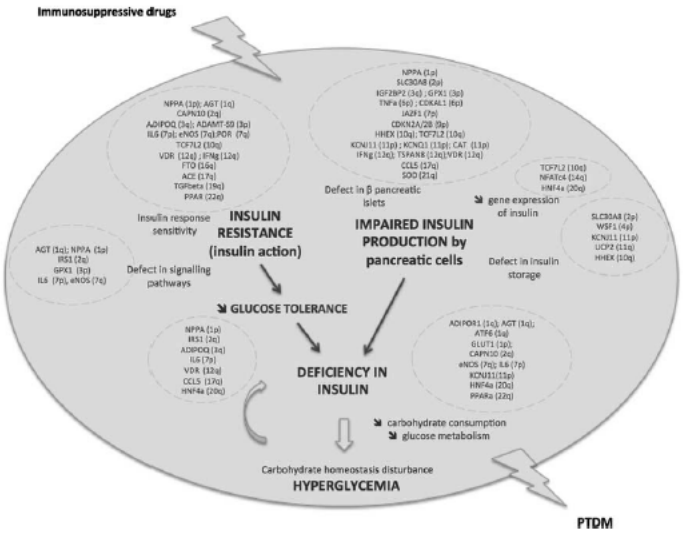
3 month

HgA1c at first follow up visit

KEY TAKEAWAYS

- Caused by side effects of immunosuppressive therapies
- Can use HgA1c, OGTT, RBG for diagnosis
- Aim for tighter BG control in the immediate post-transplant phase and even as an outpatient
- While certain oral agents can be used, the studies are small and with short term follow up.
- Insulin therapy is a safe and effective way of managing PTDM
- Remember to adjust the doses (oral or insulin) as GC and CNI doses are reduced.

PHYSIOLOGY OF PTDM



ACCURACY OF HGA1C

- Uremia, hemolysis and erythropoietin use affect the levels of HgA1c
- Meta-analysis conducted on 6 studies

PHARMACOLOGIC THERAPIES

SULFONYLUREAS

PHARMACOLOGIC THERAPIES

Meglitinides

Induce insulin secretion in a dose dependent manner.

Undergo extensive hepatic metabolism and therefore cautious use is warranted in PTLDM.

PHARMACOLOGIC THERAPIES

TZD- agonist of PPAR-γ

Two small studies in solid organ transplant (rosiglitazone)

PHARMACOLOGIC THERAPIES

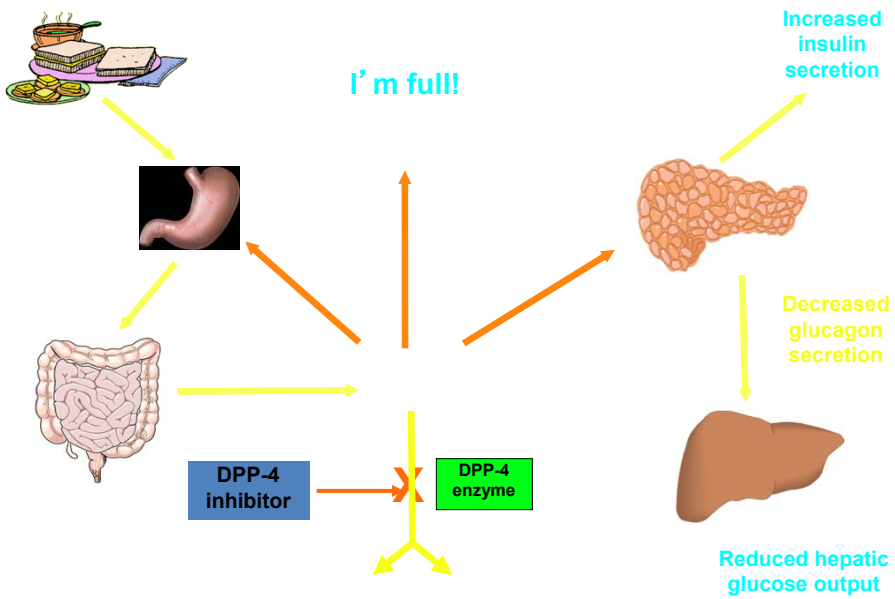
DPP-IV inhibitors

PHARMACOLOGIC THERAPIES

GLP-1 Analogues

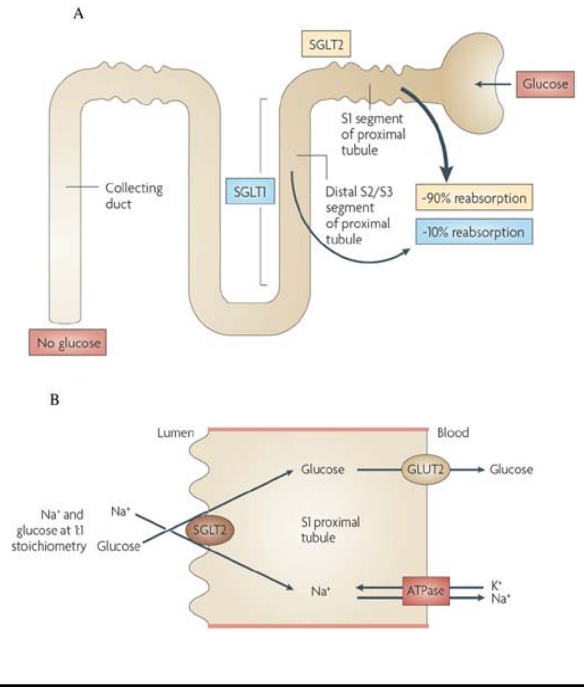
No data in LT

One case series of 5KT recipients.



PHARMACOLOGIC THERAPIES

SGLT-2 inhibitors



PHARMACOLOGIC THERAPIES

- RENAL
- Metformin
- Sulfonylureas
- Meglitinides
- TZD's
- GLP-1 agonist
- DPP-IV inhibitors
- SGLT-2 inhibitors

✓

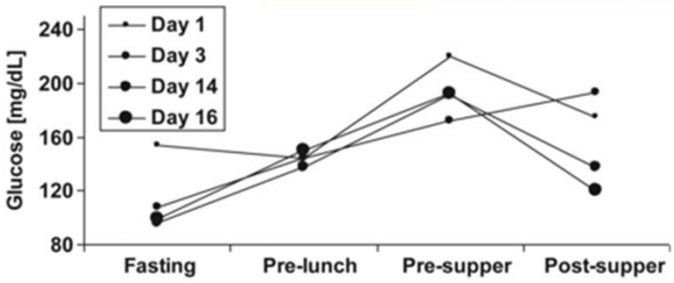
☑

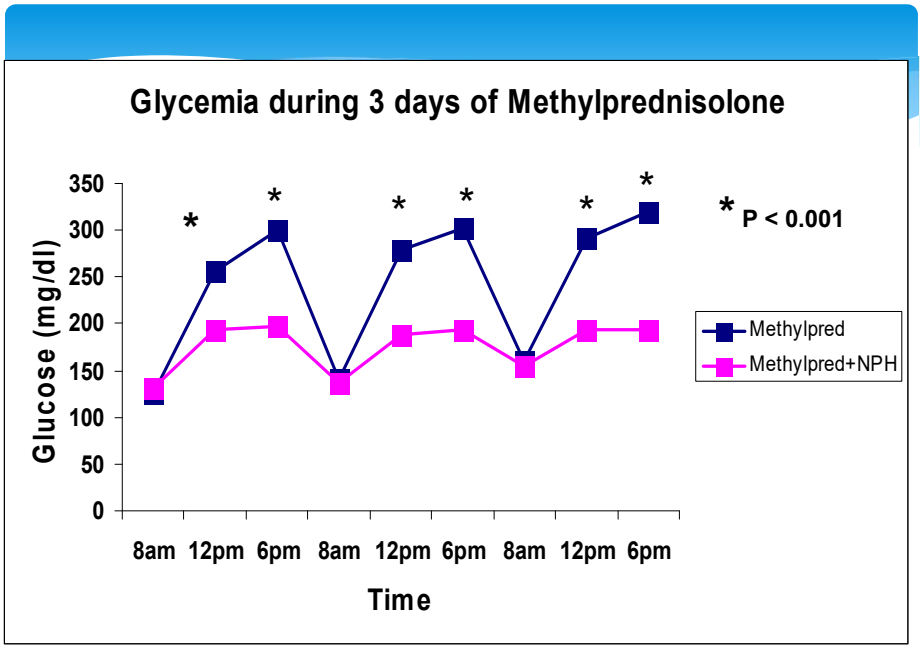
- LIVER
- Metformin
- Sulfonylureas
- Meglitinides
- TZD's
- GLP-1 agonist
- DPP-IV inhibitors
- SGLT-2 inhibitors

✓

☑

Glucose pattern with PTDM





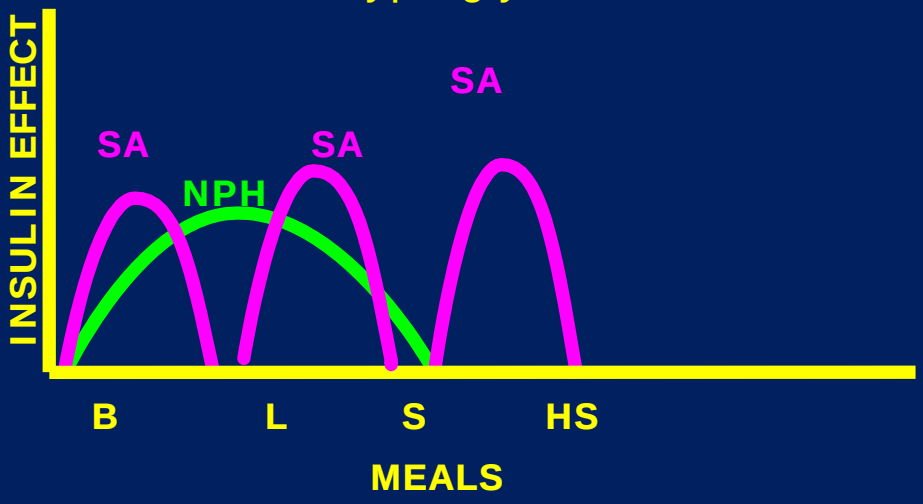
Diagnosing Diabetes Outpatient Setting – after discharge

Blood Test Levels for Diagnosis of Diabetes and Prediabetes

	A1C (percent)	Fasting Plasma Glucose (mg/dL)	Oral Glucose Tolerance Test (mg/dL)
Diabetes	6.5 or above	126 or above	200 or above
Prediabetes	5.7 to 6.4	100 to 125	140 to 199
Normal	About 5	99 or below	139 or below

Definitions: mg = milligram, dL = deciliter
For all three tests, within the prediabetes range, the higher the test result, the greater the risk of diabetes.

NPH for Glucocorticoid induced Hyperglycemia



NPH provides best coverage for afternoon when glucocorticoid induced hyperglycemia is greatest
Best if am BG is acceptable

NEUROLOGIC COMPLICATIONS OF SOLID ORGAN TRANSPLANT

NEUROLOGIC COMPLICATIONS OF SOLID ORGAN TRANSPLANT

- Seizures
- Encephalopathy
- CVA
- Opportunistic infections
- Posttransplant lymphoproliferative disorders
- Central Pontine Myelinosis
- Neurotoxicity of immunosuppressive agents

NEUROTOXICITY

- Corticosteroids: delirium, insomnia, depression, difficulty concentrating
- MMF: headaches
- CNI: PRES, encephalopathy, akinectic mutism, seizures, peripheral neurotoxicity
- Non-CNI: Tremors, confusion, paresthesias, hypoesthesia, headache

Management of Type 2 Diabetes in Patients with NAFLD

Nazanene H. Esfandiari, MD, FACE

April 28, 2018

- I have nothing to disclose

Objectives

- Prevalence of NAFLD
- Pathophysiology of NAFLD
- Risk factor for NAFLD
- Definition of NAFLD
- Diagnosis of NAFLD
  - Labs
  - Imaging studies
  - Liver biopsy
- Treatment of patients with diabetes and NAFLD

Case 1

- 57 year-old woman with type 2 diabetes, HTN and dyslipidemia, comes for follow up visit. She is on Metformin 1000 mg po bid, glipizide 5 mg bid, Januvia 100 mg daily and Lantus 40 units SQ at night. She also takes Lisinopril 20 mg daily, HCTZ 25 mg daily and Lipitor 40 mg daily.
- Family history: sister with rheumatoid Arthritis and hypothyroidism and father with hepatitis C after blood transfusion.
- PE: BP: 140/80 mmHg, HR:75, Weight: 180 pounds and Height: 5'3". BMI: 31.9 kg/m2. Heart, lung and abdominal exams were unremarkable. Monofilament test was 10/10 bilaterally and onychomycosis in both great toes.

Case 1

- Upon reviewing her meter download, her morning glucoses have ranged between 100-120 mg/dl and post prandial glucoses have ranged between 190-320 mg/dl.

- Labs:
  - Glucose: 160 mg/dl and A1C of 8.6%
  - Creatinine; 1 mg/dl and EGFR >60
  - ALT: 50 (15-40), AST: 57 (15-40), Alkaline phosphatase: 100 (30-120)
  - Negative hepatitis serology
  - Cholesterol: 195 mg/dl, triglycerides: 220 mg/dl, HDL: 39 mg/dl, LDL:90 mg/dl

Case 1

- What is the best explanation for elevated liver enzymes?

a) Statin use
b) Hepatitis C
c) NAFLD
d) Primary biliary cirrhosis

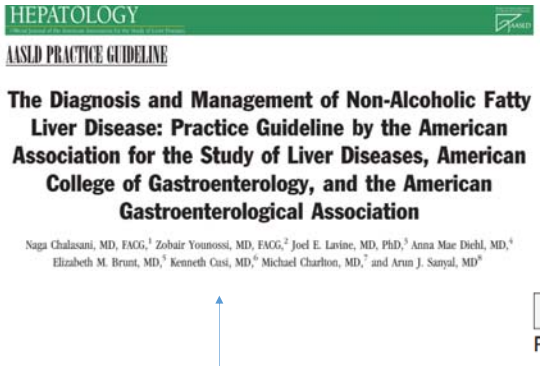
Case 2

- 64 year-old man with type 2 diabetes, obesity, hypertension, dyslipidemia and prior stent placement for CAD, comes for follow up visit.
- He is on metformin 1000 mg po bid, Lisinopril 30 mg daily and Lipitor 40 mg daily.
- Vital signs: BMI of 30 kg/m2, BP of 110/70 mmHg and heart rate of 70. Abdomen was obese but the rest of the exam was unremarkable.
- Labs: CBC: normal, A1C: 7.0%, creatinine: 0.9 mg/dl, ALT: 76 (15-40), AST: 50 (15-40), LDL: 130 mg/dl, HDL:38 mg/dl and triglycerides: 200 mg/dl.

Case 2

- What is the best next step in the management of this patient?

A) Consider liraglutide therapy
B) Consider bariatric surgery referral
C) Consider Actos therapy
D) Consider Fibroscan
E) Consider excluding other causes for liver diseases


HEPATOLOGY

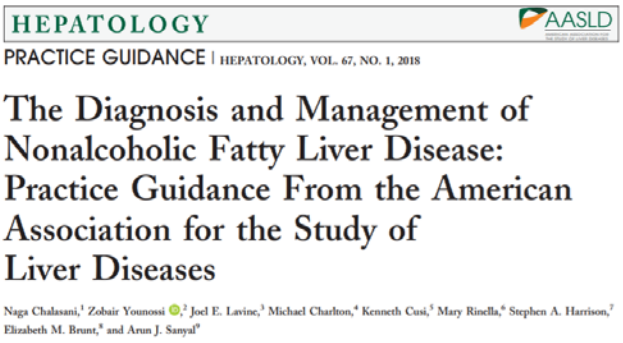
AASLD PRACTICE GUIDELINE

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

Naga Chalasani, MD, FACG,[1] Zobair Younossi, MD, FACG,[2] Joel E. Lavine, MD, PhD,[3] Anna Mae Diehl, MD,[4] Elizabeth M. Brunt, MD,[5] Kenneth Cusi, MD,[6] Michael Charlton, MD,[7] and Arun J. Sanyal, MD[8]

2012

2018


HEPATOLOGY

AASLD

PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 1, 2018

The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases

Naga Chalasani,[1] Zobair Younossi,[2] Joel E. Lavine,[3] Michael Charlton,[4] Kenneth Cusi,[5] Mary Rinella,[6] Stephen A. Harrison,[7] Elizabeth M. Brunt,[8] and Arun J. Sanyal[9]

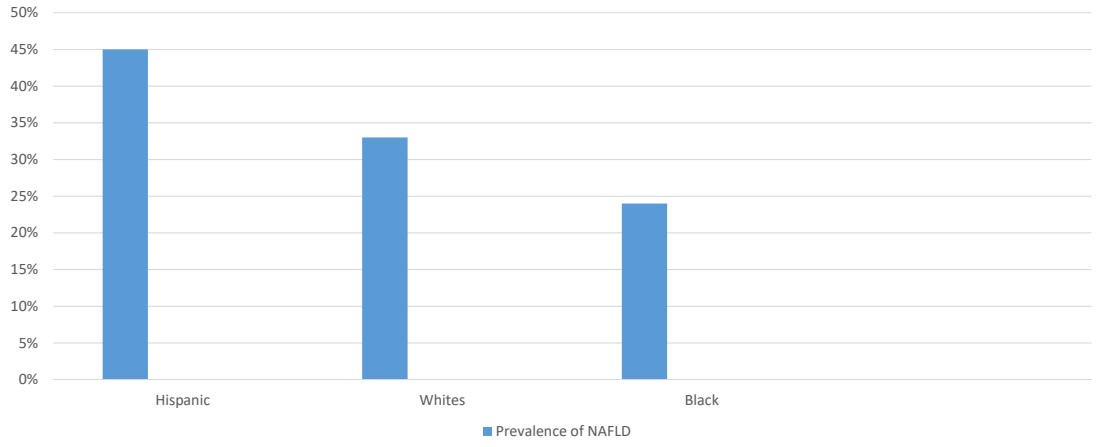
Prevalence of NAFLD

United States	30%
Middle East	32%
South America	30%
Asia	27%
Europe	24%
Africa	13%

Furthermore, the prevalence of NAFLD in men is 2 times higher than in women.

Carr RM, et al. Gastroenterol Clin North Am. 2016;45:639–652.

Ethnic Differences in the Prevalence of NAFLD



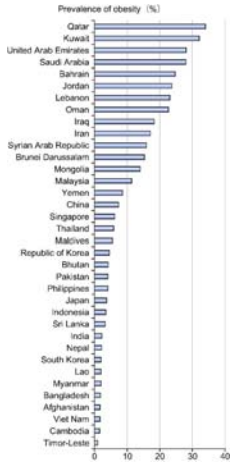
Browning et al. Hepatology 2004;40:1387

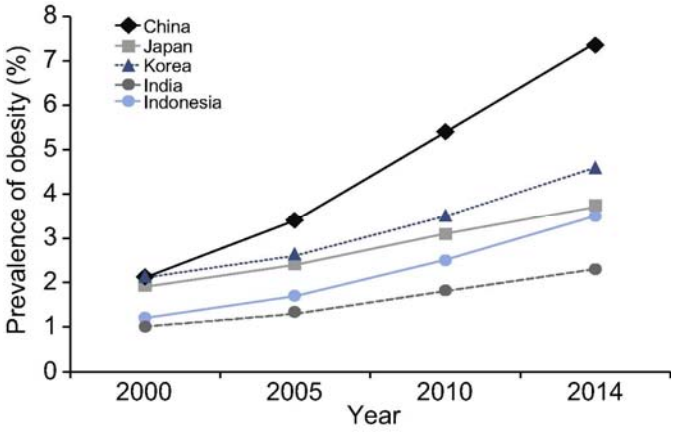
Clinical and Histologic Characterization of Nonalcoholic Steatohepatitis in African American Patients

- Although African Americans have lower intrahepatic triglyceride accumulation, once NAFLD develops, NASH occurs as frequently, and as severe, as in Caucasian patients. Therefore, African Americans with NAFLD should be screened for NASH with the same degree of clinical resolve as in Caucasian patients.

Bril et al. Diabetes Care 2018 Jan; 41(1): 187-192

New trends on obesity and NAFLD in Asia





Fan JG et al. Journal of Hepatology 2017 67, 862-873

BMI Classification

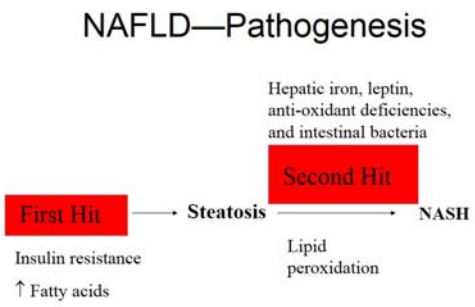
International classification of adult underweight, overweight and obesity according to body mass index.[7]

Classification	International	Asian*
Underweight	<18.5	<18.5
Normal range	18.5–24.9	18.5–22.9
Overweight	25.0–29.9	23.0–24.9
Obese class I	30.0–34.9	25.0–29.9
Obese class II	35.0–39.9	≥30.0
Obese class III	≥40.0	

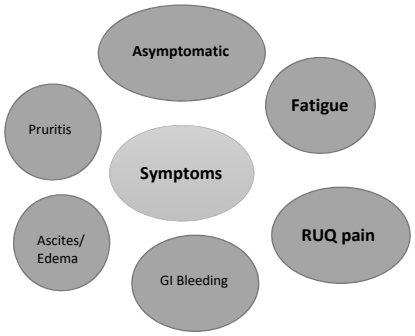
Fan JG et al. Journal of Hepatology 2017 67, 862-873

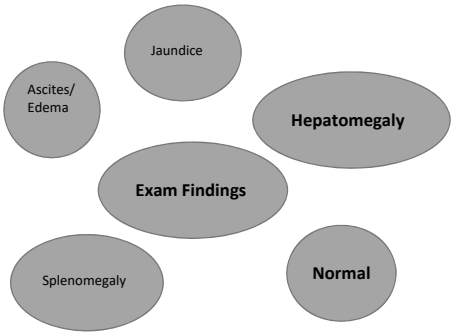
Pathogenesis of NAFLD

- Complex and multifactorial
- First Hit: accumulation of triglycerides in hepatocytes
- Second Hit; production of free radicals which damage hepatic cells by inflammation, fibrosis, and cellular death characteristics of NASH. The second hit can be a variety of factors, such as oxidative stress, endoplasmic reticulum stress, proinflammatory cytokines, and gut-derived bacterial endotoxin.
- It has been believed that many "hit" factors may act simultaneously leading to the development of NAFLD, which supports the multihit model proposed in 2010. Indeed, among the proposed hit factors, many can interact with each other, forming a vicious circle.

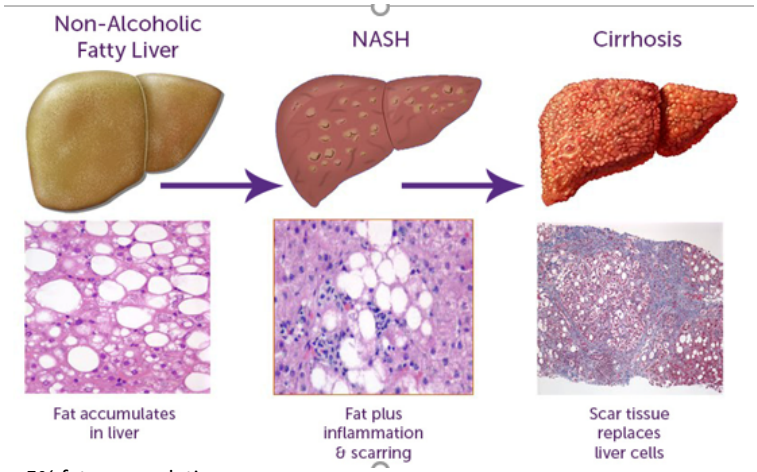


Clinical Symptoms and Physical Exam Findings in patients with NAFLD





Definition



>5% fat accumulation

Definition

- ALD: Alcoholic Liver Disease: Significant alcohol consumption*
  - > 21 drinks/week for males
  - > 14 drinks/weeks for females
- NAFLD: Non-Alcoholic Fatty Liver Disease

  steatosis without hepatocyte injury
- NASH: Non-Alcoholic Steatohepatitis

  steatosis with inflammation, hepatocyte injury with or without fibrosis

Sanyal et al. hepatology 2011

Spectrum of Liver Disease in Type 2 Diabetes

- Abnormal liver enzymes
- NAFLD®
- NASH ®
- Cirrhosis ®
- Liver cancer
- Acute liver failure
- Hepatitis C

- Keith G. Tolman, MD, Vivian Fonseca, MD, Anthony Dalpiaz, PHARMD and Meng H. Tan, MD. Diabetes Care 2007 Mar; 30(3): 734-743.

Risk Factors

TABLE 3. Risk Factors Associated With NAFLD

Common Conditions With Established Association	Other Conditions Associated With NAFLD
Obesity	Hypothyroidism
T2DM	Obstructive sleep apnea
Dyslipidemia	Hypopituitarism
MetS*	Hypogonadism
Polycystic ovary syndrome	Pancreatoduodenal resection
	Psoriasis

Chalasani N, et al. Practice Guidance. Hepatology. 2018.

Metabolic Syndrome Definition

- (1) waist circumference greater than 102 cm in men or greater than 88 cm in women;
- (2) TG level 150 mg/dL or greater;
- (3) HDL cholesterol level less than 40 mg/dL in men and less than 50 mg/dL in women;
- (4) systolic blood pressure 130 mm Hg or greater or diastolic pressure 85 mm Hg or greater;
- (5) fasting plasma glucose level 110 mg/dL or greater

TABLE 1. Common Causes of Secondary HS

Macrovesicular steatosis
- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- WD
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g., mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids)

Microvesicular steatosis
- Reye's syndrome
- Medications (valproate, antiretroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g., lecithin-cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman's disease)

Screening for NAFLD in Primary Care, Diabetes, and Obesity Clinics

- Biochemistries can be normal in NAFLD. So, liver US or TE (fibroscan) are more sensitive tests.
- Some experts recently have called for "vigilance" for chronic liver disease (CLD) in patients with type 2 diabetes, but routine screening is not recommended in high-risk groups attending primary care, diabetes, or obesity clinics.
- Systematic screening of family members for NAFLD is not recommended currently.

Chalasani et al. Hepatology 2018

Requirements for the Diagnosis of NAFLD

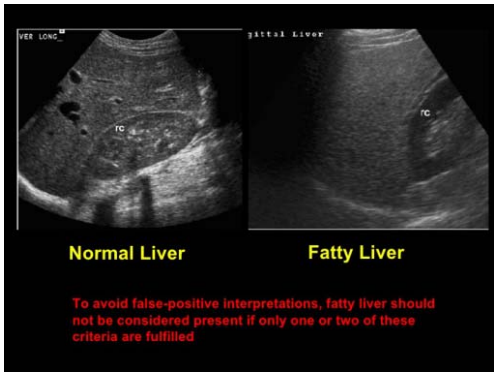
(1) There is hepatic steatosis by imaging or histology
(2) There is no significant Alcohol consumption
(3) There are no competing etiologies for hepatic steatosis
(4) There are no coexisting causes of chronic liver disease

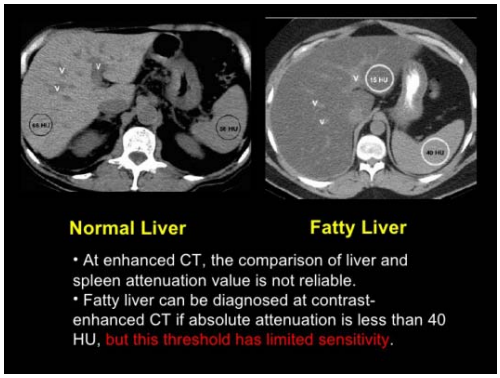
Chalasani et al. Hepatology 2018

Diagnosis of NAFLD

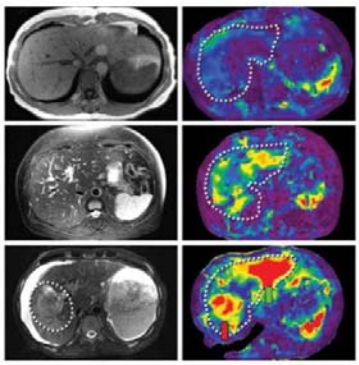
- Labs
  - Hepatic function tests: Most patients have normal LFTs or Elevated ALT and AST and occasionally alkaline phosphatases
  - Elevated Ferritin(x1.5 ULN)
- Order other labs to exclude other causes of liver disease:
  - Viral hepatitis
  - Autoimmune hepatitis
  - Iron and copper overload
  - Drugs (amiodarone, tamoxifen, steroids,..)
  - Alpha 1 antitrypsin deficiency
- Evaluate for steatosis by imaging: Liver US or CT or MRI
- Evaluate for Fibrosis : Fibroscan or MR Elastography
- Liver biopsy

Imaging Studies Detecting Fat



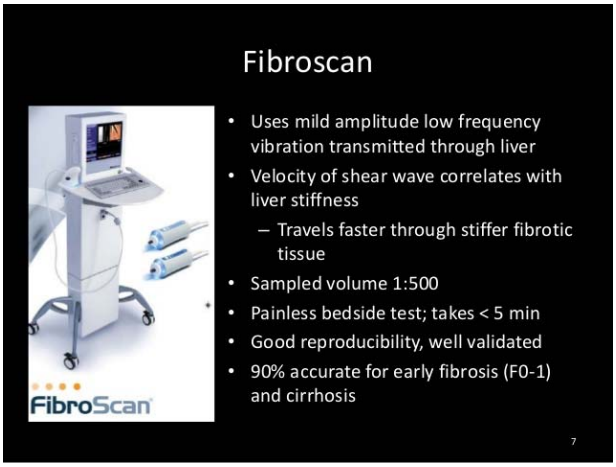


Imaging Studies Detecting Fibrosis



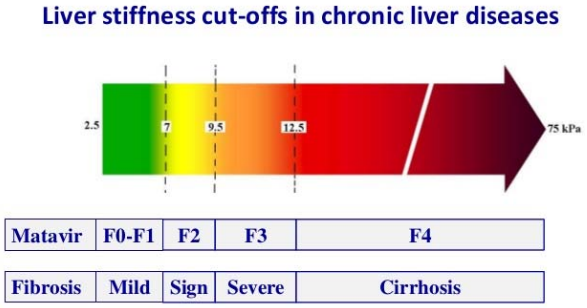
Traditional MR images (left column) convey anatomy, while MR elastograms (right column) demonstrate varying degrees of tissue stiffness in liver (dotted line). These range from softest (purple) to hardest (red). Images of healthy tissue (top row) taken with conventional MR and GE's MR Touch elastography product contrast with images from 61-year-old patient with nonalcoholic fatty liver disease (second row) and those from 61-year-old with hepatitis C, cirrhosis, and cancer (third row). Stiff liver tissue is apparent in right lobe (red arrow) and in left lobe (green arrow) of liver. (Provided by GE Healthcare)

MR Elastography



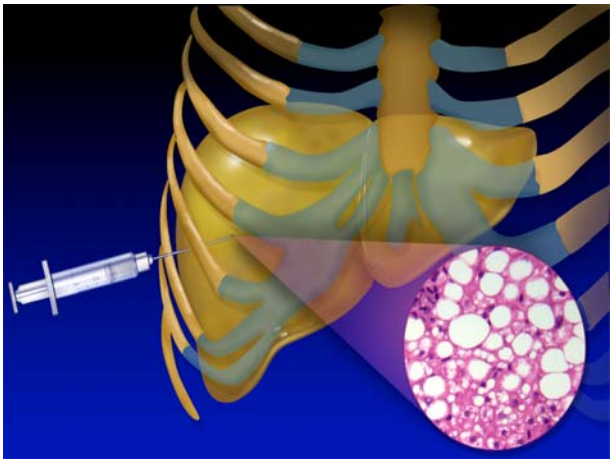
Fibroscan

Liver Stiffness Cut-offs in Chronic Liver Diseases



Castéra L et al. J Hepatol 2008 ; 48 : 835 – 847.

NAFLD Diagnosis
Role for Liver Biopsy?



-Gold Standard test

-expensive, requires expertise for interpretation, some morbidity and very rare mortality risk.

-Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatosteatitis (HS) and the presence and/or severity of coexisting Chronic liver diseases(CLDs) cannot be excluded without a liver biopsy.

NAFLD Fibrosis Score: http://nafldscore.com

NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

Age (years)
BMI (kg/m²)
IGF/diabetes
AST
ALT
Platelets (x10⁹/l)
Albumin (g/l)
calculate score

BMI: body mass index
IGF: impaired fasting glucose

NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

Age (years) 50
BMI (kg/m²) 29
IGF/diabetes ☑
AST 50
ALT 52
Platelets (x10⁹/l) 170000
Albumin (g/l) 4
Score -2,205.281

< -1.455: predictor of **absence** of significant fibrosis (F0-F2 fibrosis)
≤ -1.455 to ≤ 0.675: indeterminate score
> 0.675: predictor of **presence** of significant fibrosis (F3-F4 fibrosis)

BMI: body mass index
IGF: impaired fasting glucose

<-1.455: 90% sensitivity and 60% specificity to exclude advanced fibrosis
> 0.675: 67% sensitivity and 97% specificity to identify the presence of advanced fibrosis

Management of Diabetes in Patients with Concomitant Liver Disease

- Lifestyle Modification
- Pharmacologic Therapy
  - Insulin sensitizers
  - GLP-1 analogues and DPP-VI inhibitors
  - Vit E
  - SGLT2 inhibitors
  - Ursodeoxycholic acid
  - Omega-3 fatty acid
  - Bariatric Surgery

Lifestyle Modification
Diet, Exercise and Weight loss

- A combination of a hypocaloric diet (daily reduction by 500-1,000 kcal) and moderate-intensity exercise is likely to provide the best likelihood of sustaining weight loss over time.
  - Weight loss of at least 3%-5% of body weight appears necessary to improve steatosis, but a greater weight loss (7%-10%) is needed to improve the majority of the histopathological features of NASH, including fibrosis.
  - Exercise alone in adults with NAFLD may prevent or reduce HS, but its ability to improve other aspects of liver histology remains unknown.

Lifestyle Modification

- Wong WW et al. Int J Hepatol 2013: 352-342.
  - Lifestyle modification in 154 patients with NAFLD in 12-month RCT
  - 5.6 kg reduction in total body weight was associated with 55% decrease in liver triglycerides content.
  - Liver biopsy was not done(impact on histology??
- Promrat et al. Hepatology 2010: 121-129.
  - Reduction of a total body weight of >9% is associated with histological improvement in steatosis, necrosis, and inflammation in patients with NASH.

Pharmacologic Therapy

- Insulin Sensitizers
  - Metformin:
    - Metformin is not metabolized by liver but largely eliminated by renal clearance and can be use safely in the vast majority of patients with NASH except advanced cirrhosis.
    - Two published meta-analyses conclude that metformin therapy did not improve liver histology in patients with NAFLD and NASH. (Musso et al. Hepatology 2010: 79-104; Ratziu et al. Hepatology 2010: 2206-2215)

Metformin is good for diabetes but is not effective for the treatment of NASH (does not significantly improve liver histology).

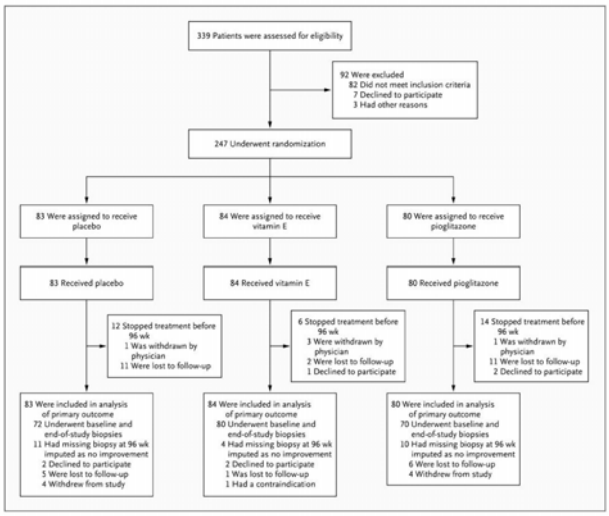
Pharmacologic Therapy

- Insulin Sensitizers:
  - Thiazolinediones (TZDs): are ligands for the transcription factor PPAR- ɣ that plays a major role in the regulation of glucose and lipid metabolism and inflammation.
  - We review three studies:
    - Sanyal et al. NEJM 2010:1675-1685.
    - Cusi et al. Ann Intern Med 2017.
    - Bril et al. Clin Gastroenterol Hepatol Feb 2018.

ORIGINAL ARTICLE

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., et al., for the



<u>PIVENS trial</u>

96 weeks
247 patients with NASH,
(No diabetes, cirrhosis, Hep C, CHF and limited alcohol 5 years prior to study)
Three arms:
-Placebo
-Vit E 800 IU/d
-Actos 30 mg/d

Sanyal et al. NEJM 2010. 362: 1675-1685

Primary Outcome: histologic improvement

Vitamin E *vs* placebo

43% improvement vs 19%: (P=0.001)

significant (steatosis, lobular inflammation, hepatocellular ballooning and fibrosis)

Pioglitazone vs Placebo

- 34% improvement vs 19% (P=0.04) not significant

Secondary Outcome

Vitamin E vs placebo

Also reduction in SGOT/SGPT

Pioglitazone vs Placebo

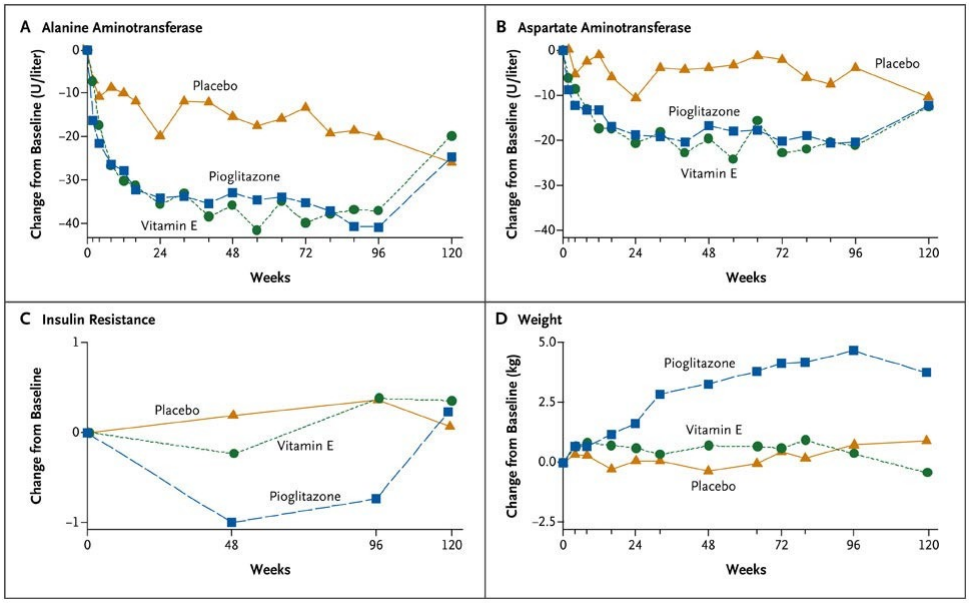
-Reduction in SGOT/SGPT

-Reduction in steatosis, lobular inflammation

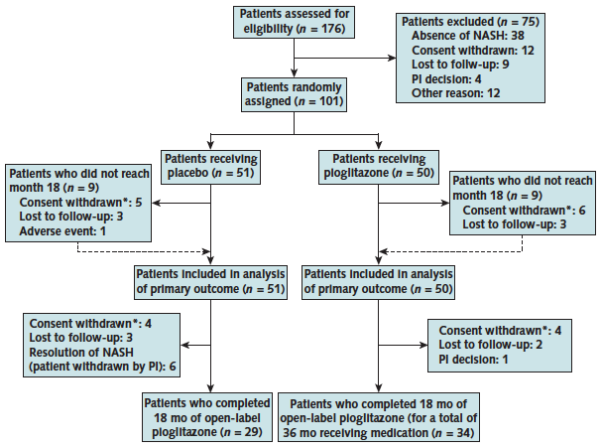
-Improvement in insulin resistance

-Increase in weight that did not resolve after discontinuation of Pioglitazone

In Conclusion: Vitamin E was superior to placebo in adults with NASH and without diabetes



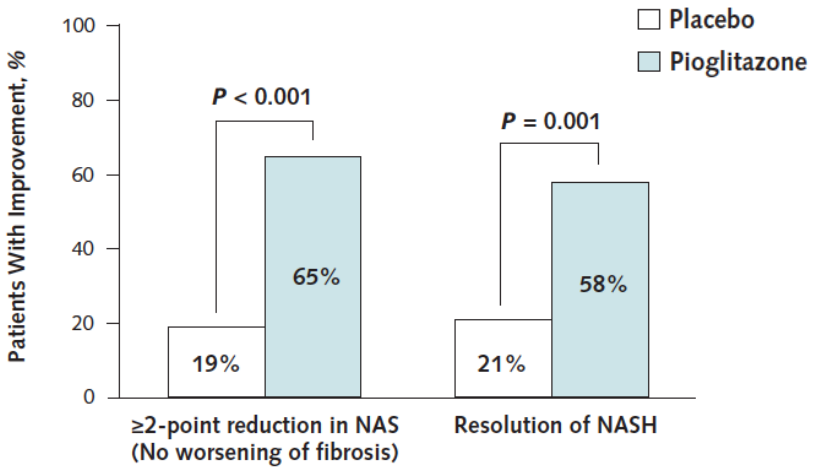
Long-Term Pioglitazone Treatment for Patients with Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus. A Randomized, Controlled Trial



Randomized, double blinded,
101 with prediabetes or T2DM and biopsy-proven NASH
Actos 45 mg daily and diet (-500 calories) vs placebo for 18 m
Primary outcome: >2 points reduction in NAS score
Secondary Outcome: Resolution of NASH
Other histologic outcomes,
metabolic parameters and hepatic TG content

Cusi et al, Ann Intern Med 2017

Effect of Pioglitazone on Primary and Secondary Liver Histologic Outcomes at 18 months*

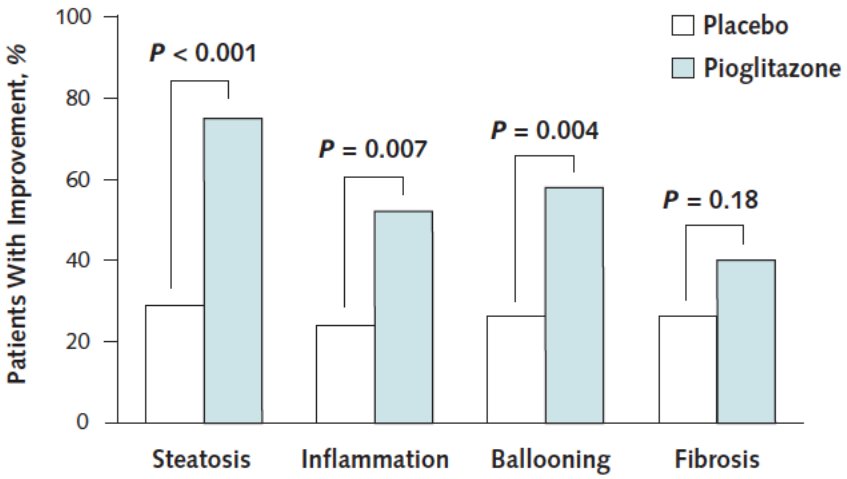


* In patients with paired biopsies (n = 82)

Resolution of NASH defined as absence of NASH after 18 mo of therapy with definite NASH at baseline

Cusi et al, Ann Intern Med 2017.

Effect of Pioglitazone on Primary and Secondary Liver Histologic Outcomes at 18 months*



* In patients with paired biopsies (n = 82)

Cusi et al, Ann Intern Med 2017.

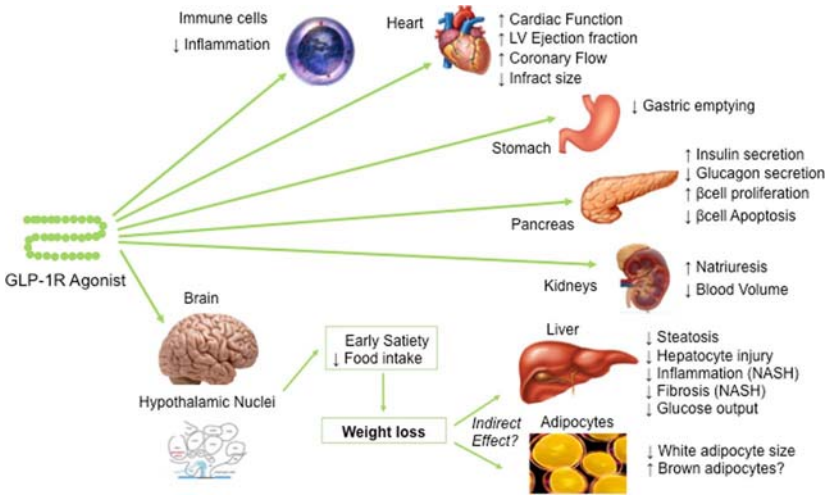
Response to Pioglitazone in Patients With Nonalcoholic Steatohepatitis With vs Without Type 2 Diabetes

- Prospective Study
- 52 patients had type 2 diabetes biopsy-confirmed NASH
- 49 patients with prediabetes
- Either Actos 45 mg daily or placebo for 18 months and decreased diet by 500 calories

- NASH resolved completely in 44% with type 2 diabetes and 26% of patients without it, respectively, perhaps indicating that pioglitazone acts slightly differently when patients with NASH have type 2 diabetes.

Bril et al. Clin Gastroenterol Hepatol Feb 2018

Physiological effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in humans.



Gauri Dhir, and Kenneth Cusi J Investig Med 2018;66:7-10

JIM

Pharmacologic Therapy

- Glucagon Like Peptide-1 Analogues:
  - The LEAN trial (Liraglutide Efficacy and Action in NASH)was the first RCT that as a proof of concept (n=52) reported on the true efficacy of a GLP-1RA in patients with biopsy-proven NASH. After 48 weeks of treatment with liraglutide (1.8 mg per day), resolution of NASH occurred in 9/23 (39%) compared with 2/22 (9%) participants in the placebo group.
  - These results have created a new treatment paradigm in the field. This study is being followed up by a large multicenter trial testing three doses of semaglutide once daily versus placebo in patients with biopsy-proven NASH (ClinicalTrials.gov NCT 02970942).*
- DDP-4 Inhibitors:
  - These medications decrease postprandial plasma glucose.
  - Animal studies have shown their ability to reduce liver triglyceride content and inflammation.

*D. Gauri and K Cusi. BMJ. J Invetig Med 2018;66:7-10.

Pharmacologic Therapy
Vit E

- Vitamin E (rrr a-tocopherol) administered at a daily dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH and therefore may be considered for this patient population. Risks and benefits should be discussed with each patient before starting therapy.
- Meta-analysis including 136,000 participants found taking Vitamin E supplements > 400 IU/day had a higher risk of all cause mortality (1).
- Vitamin E > 400 IU/day increases risk of prostate cancer in relatively healthy men (2)

1. Miller et al Annals of Internal Medicine 2005
2. Klein, et al, JAMA 2011

Pharmacologic Therapy
SGLT2 Inhibitors

- Study in rodents have shown that SGLT2 inhibitors, decrease hepatic triglycerides accumulation and other inflammatory biomarkers in addition to the reduction of plasma glucose concentration.
- Their impact on NAFLD remains to be determined.

Pharmacologic Therapy

- Ursodeoxycholic acid, Omega-3 fatty acids, and miscellaneous agents:
  - UCDA is not recommended for the treatment of NAFLD or NASH.
  - Omega-3 fatty acids should not be used as a specific treatment of NAFLD or NASH, but they may be considered to treat hypertriglyceridemia in patients with NAFLD.
  - Patients with NAFLD should not consume heavy amounts of alcohol.

- Management of CVD and Dyslipidemia
  - There is a strong association between NAFLD and increased risk of CVD events and mortality that withstands correction for traditional CVD risk factors. Thus, aggressive modification of CVD risk factors should be considered in all patients with NAFLD.
  - Patients with NAFLD or NASH are not at higher risk for serious liver injury from statins. Thus, statins can be used to treat dyslipidemia in patients with NAFLD and NASH. While statins may be used in patients with NASH cirrhosis, they should be avoided in patients with decompensated cirrhosis.

Table 1
Therapeutic agents for T2DM and their effect NAFLD/NASH in clinical trials

Treatment	Mechanism of action	AST/ALT	Liver fat by imaging	Liver histology	
Oral					
Metformin [38,45-48]	Insulin-sensitizer	↓	↓*,↔^	Unchanged	
Pioglitazone [52, 53, 55]	PPARγ agonist	↓	↓^	Improved	***
Sitagliptin [72, 80, 81]	DPP-4 inhibitor	↓	n/a	n/a	
Vildagliptin [82]	DPP-4 inhibitor	↓	↓^	n/a	
Canagliflozin [90]	Inhibits renal glucose reabsortion	↓	n/a	n/a	
Dapagliflozin [91, 92]	Inhibits renal glucose reabsortion	↓	n/a	n/a	
Injectable					
Exenatide [70]	GLP-1 receptor agonist	↓	↓^	n/a	
Liraglutide [69-75]	GLP-1 receptor agonist	↓	↓**,^	Improved	***

*NAFLD assessed by ultrasound, **NAFLD assessed by CT, ^NAFLD assessed by MRI/^{1}H-MRS, n/a: data not available

Portillo-Sanchez et al. Clinical Diabetes and Endocrinology 2016:1-9

Bariatric Surgery

- Sustained weight loss is difficult to achieve with non-surgical weight loss and harder yet to sustain. Bariatric surgery improves or eliminates comorbid disease in most patients and improves long-term survival and death from CVD and malignancy, the two most common causes of death in NAFLD.
- It can be considered in otherwise eligible obese individuals with NAFLD or NASH.

Chalasani et al. Practice Guidance. Hepatology 2018

NASH, Obesity, and Liver Transplantation

- NASH is on a trajectory to become the most common indication for liver transplantation in the United States.
- Patients with NASH cirrhosis have high prevalence of CVD. Thus, careful attention should be paid to identifying CVD, whether clinically apparent or occult, during the transplant evaluation process.

Summary

Hepatitis A and B vaccination
No alcohol

- NAFLD and NASH are alarmingly increasing in prevalence.
- You need to exclude other causes for liver diseases before diagnosing NAFLD.
- The underlying mechanism is insulin resistance in patients with obesity.
- Most patients with NASH succumb to CV disease, malignancy, liver disease respectively.
- Statin can be used to treat dyslipidemia in NAFLD patients.
- Individuals who have steatosis without diabetes have 5-10% risk of fibrosis and individuals who have steatosis and diabetes have 15-20% risk of fibrosis.
- Having fibrosis increases the risk of cirrhosis and liver cancer.
- Recommend 7-10% weight loss.
- Actos will be to NASH what metformin has been to type 2 diabetes. (Dr. Cusi)
- Another medication which might be useful in future is Liraglutide or other GLP-1 analogues.

Case 1

- 57 year-old woman with type 2 diabetes, HTN and dyslipidemia, comes for follow up visit. She is on Metformin 1000 mg po bid, glipizide 5 mg bid, Januvia 100 mg daily and Lantus 40 units SQ at night. She also takes Lisinopril 20 mg daily, HCTZ 25 mg daily and Lipitor 40 mg daily.
- Family history: sister with rheumatoid Arthritis and hypothyroidism and father with hepatitis C after blood transfusion.
- PE: BP: 140/80 mmHg, HR:75, Weight: 180 pounds and Height: 5'3". BMI: 31.9 kg/m2. Heart, lung and abdominal exams were unremarkable. Monofilament test was 10/10 bilaterally and onychomycosis in both great toes.

Case 1

- Upon reviewing her meter download, her morning glucoses have ranged between 100-120 mg/dl and post prandial glucoses have ranged between 190-320 mg/dl.

- Labs:
  - Glucose: 160 mg/dl and A1C of 8.6%
  - Creatinine; 1 mg/dl and EGFR >60
  - ALT: 50 (15-40), AST: 57 (15-40), Alkaline phosphatase: 100 (30-120)
  - Negative hepatitis serology
  - Cholesterol: 195 mg/dl, triglycerides: 220 mg/dl, HDL: 39 mg/dl, LDL:90 mg/dl

Case 1

- What is the best explanation for elevated liver enzymes?

a) Statin use
b) Hepatitis C
c) NAFLD
d) Primary biliary cirrhosis

Case 2

- 64 year-old man with type 2 diabetes, obesity, hypertension, dyslipidemia and prior stent placement for CAD, comes for follow up visit.
- He is on metformin 1000 mg po bid, Lisinopril 30 mg daily and Lipitor 40 mg daily.
- Vital signs: BMI of 30 kg/m2, BP of 110/70 mmHg and heart rate of 70. Abdomen was obese but the rest of the exam was unremarkable.
- Labs: CBC: normal, A1C: 7.0%, creatinine: 0.9 mg/dl, ALT: 76 (15-40), AST: 50 (15-40), LDL: 130 mg/dl, HDL:38 mg/dl and triglycerides: 200 mg/dl.

Case 2

- What is the best next step in the management of this patient?

A) Consider liraglutide therapy
B) Consider bariatric surgery referral
C) Consider Actos therapy
D) Consider Fibroscan
E) Consider excluding other causes for liver diseases


Thank
you!!

Case-Based Interactive Lessons: Treat the Infected Diabetes Foot

Brian M. Schmidt DPM
Assistant Professor
Metabolism, Endocrinology, and Diabetes – Podiatry
Department of Internal Medicine

Objectives:

- Evaluate and Review Cases pertinent to Diabetic Foot Infections (DFI)
  - Description of Wounds
  - Clinical Findings
  - Imaging and Micro
  - Laboratory Values
- Pearls from the Podiatrist
- Question and Answer

- But first ….

Why should we care?

In 2017, estimated to be 425 million diabetics worldwide
IDF Diabetes Atlas, 8th ed

→ Lifetime risk of a diabetic to develop foot ulcer is: 34%
Amstrong, NEJM 2007

→ More than 50% of DFUs become infected
Armstrong, NEJM 2007

↓

50% of people who suffer a proximal amputation, lose the other limb in ≤ 2 years

← 80% of 120,000 non-traumatic amputations are from diabetes

← 20% of DFU result in amputation
Lipsky et al, Clin Infect Dis 2012

Why should we care?

The 5 year mortality rate after limb amputation is **68%**

Why else we should care?

$$$$

- **850 billion USD** is worldwide expenditure of diabetes in 2017
- Approximately **60 billion** USD spent annually in U.S. on lower extremity complications

Driver et al, J Vasc Surg

What can we do?

Standardize your approach to diabetic foot infections

Early identification is key to limb salvage

1. Understand Diabetic foot risk categories
2. Know a DFI classification system
3. Assess and identify barriers to healing
4. Microbiology exam
5. Imaging considerations
6. Diabetic foot osteomyelitis
7. Antimicrobial therapy and referral to foot specialist

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Understand Diabetic Foot Risk Categories

Adapted from IDF Clinical Practice Recommendations on the Diabetic Foot 2017

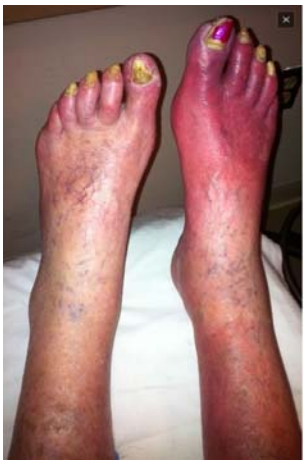
Annual Diabetic Foot Exam

- American Diabetes Association recommends:
  - Perform complete foot exam at least once a year
    - Consists of:
      - History
      - General Inspection
      - Dermatological Assessment
      - Musculoskeletal Assessment
      - Neurological Assessment
      - Vascular Assessment
      - Risk classification and follow up

Understand Diabetic Foot Risk Categories

- How often would you recommend this person be seen by a podiatrist?

A.) Annual
B.) every 3 – 6 months
C.) every 1-2 months
D.) Once a week
E.) Every 2-3 months



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Description	Severity grade	Score
a. No signs or symptoms of infection	Non infected	0 → No Abx, but wound care
b. Erythema between 0.5 mm to 2 cm, induration, tenderness, warmth, and purulent discharge.	Mild	1
c. Erythema > 2 cm, muscle, tendon, orbone or joint infection.	Moderate	2
d. Any local infection with systemic inflammatory response (SIRS) manifested by at least 2 of following: • Temperature > 38 or < 36 • Heart rate > 90 beats/min, • Respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg, • White blood cell count > 12000 or < 4000 cells/μL or 10% immature (band) forms; or severe metabolic disturbances (hyperglycemia or hypoglycemia)	Severe	3

For severe infection and some moderate grade infection, hospitalization is needed for limb preservation.

4/28/2018 - Schmidt

Adapted from IDSA 2012

SB1

Description	Severity grade	Score
a. No signs or symptoms of infection	Non infected	0
b. Erythema between 0.5 mm to 2 cm, induration, tenderness, warmth, and purulent discharge.	Mild	1 → PO Abx and wound care
c. Erythema > 2 cm, muscle, tendon, orbone or joint infection.	Moderate	2
d. Any local infection with systemic inflammatory response (SIRS) manifested by at least 2 of following: • Temperature > 38 or < 36 • Heart rate > 90 beats/min, • Respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg, • White blood cell count > 12000 or < 4000 cells/μL or 10% immature (band) forms; or severe metabolic disturbances (hyperglycemia or hypoglycemia)	Severe	3

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4/28/2018 - Schmidt

Adapted from IDSA 2012

Slide 14

SB1 Schmidt, Brian, 3/28/2018

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Probe to bone testing

For severe infection and some moderate grade infection, hospitalization is needed for limb preservation.

Adapted from IDSA 2012

Probe-to-Bone testing (PTB)

Use 'blunt metal probe'

Can assist in diagnosis of diabetic foot osteomyelitis, but is largely setting dependent

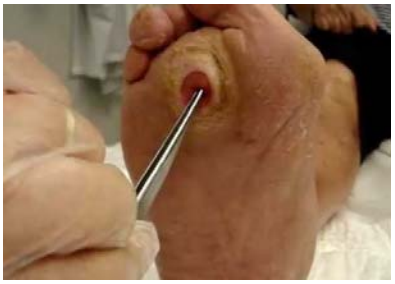

Table 1. Descriptive characteristics of studies describing the probe-to-bone test.

Study (year)	N	Sens (%)	Spec (%)	PPV (%)	NPV (%)	LR(+)	LR(–)	Prev (%)	Method of diagnosis
Outpatient									
Shone et al (2006)	81	38	91	53	85	4.22	0.68	23.5	Clinical
Lavery et al (2007)	247[f] / 217[†]	87	91	57	98	9.4[f] / 6.5[†]	6.81[f] / 6.5[†]	20	Microbiology
Infected outpatient									
Morales Lozano et al (2010)	132	98	78	95	91	4.5	0.02	79.5	Clinical and microbiology
Inpatient									
Grayson et al (1995)	75	66	85	89	56	4.4	0.15	66	Histology
Mutluoglu et al (2012)	65	66	84	87	62	4.13	0.24	60	Imaging and clinical
Aragón-Sánchez et al (2011)	338	95	93	97	83	14.34	0.06	72.4	Histology and microbiology

Key: N – number of participants/ulcers; Sens – sensitivity; Spec – specificity; PPV – positive predictive value; NPV – negative predictive value; LR(+) – positive likelihood ratio; LR(–) – negative likelihood value; Prev – prevalence; [f] – total; † – infected

Wrobel J, Schmidt B (2016) Probe-to-bone testing for osteomyelitis in the diabetic foot: a literature review. The Diabetic Foot Journal

SB1

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c. Erythema > 2 cm, muscle, tendon, orbone or joint infection.	Moderate	2 → Abx, urgent consult & hospitalization
d. Any local infection with systemic inflammatory response (SIRS) manifested by at least 2 of following: • Temperature > 38 or < 36 • Heart rate > 90 beats/min, • Respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg, • White blood cell count > 12000 or < 4000 cells/μL or 10% immature (band) forms; or severe metabolic disturbances (hyperglycemia or hypoglycemia)	Severe	3

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4/28/2018 - Schmidt

Adapted from IDSA 2012

Slide 17

SB1 Schmidt, Brian, 3/28/2018

Slide 18

SB1 Schmidt, Brian, 3/28/2018

Classification Practice

Classify wound based on clinical appearance

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B.) 1 – Mild
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D.) 3 – Severe

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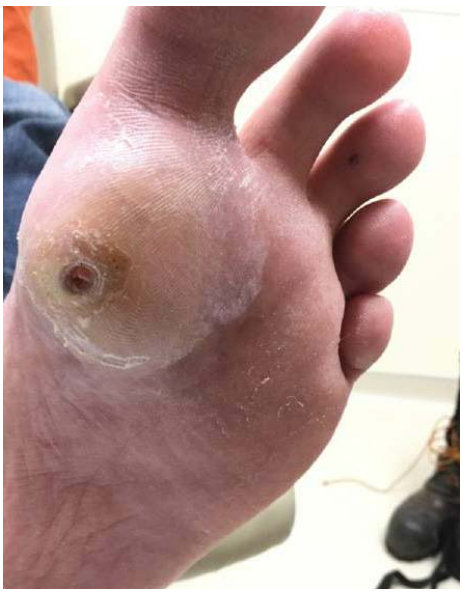

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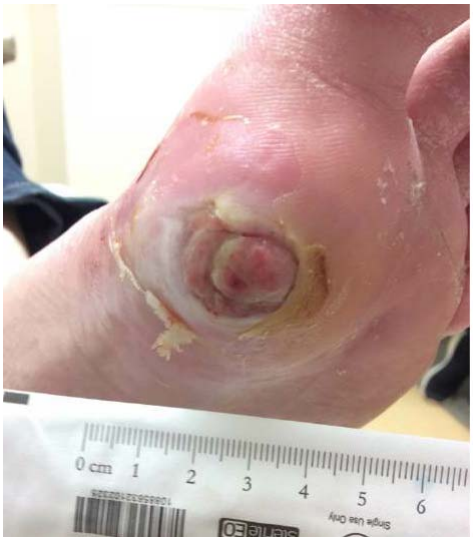

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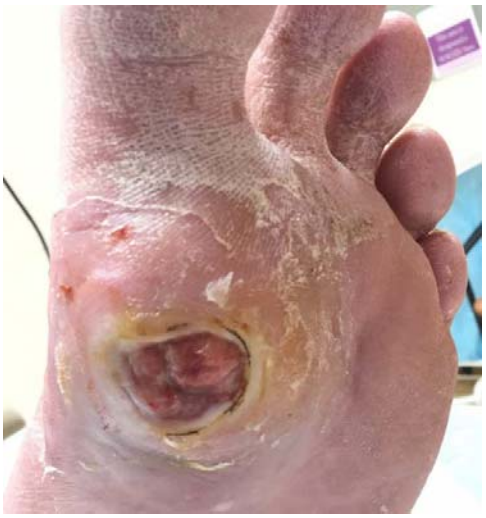

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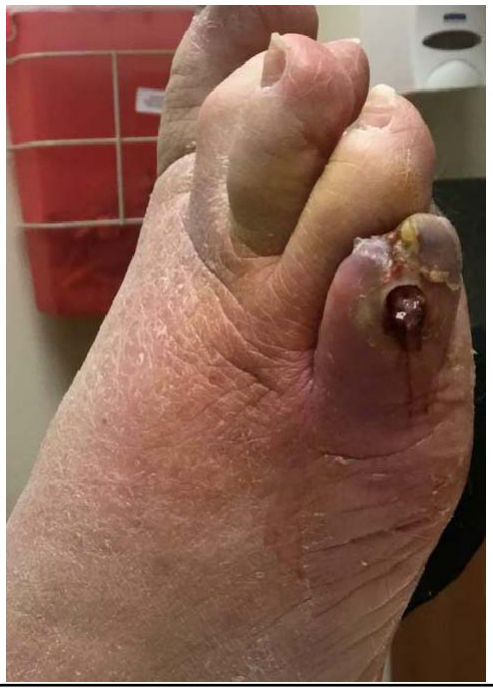

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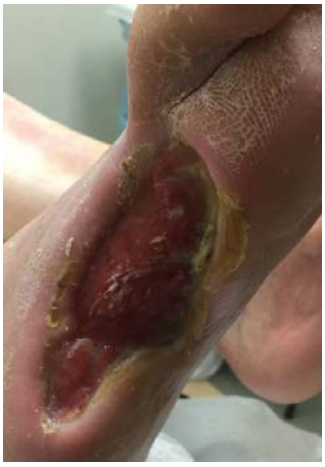
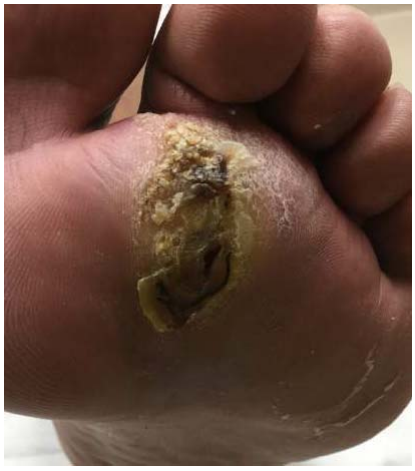
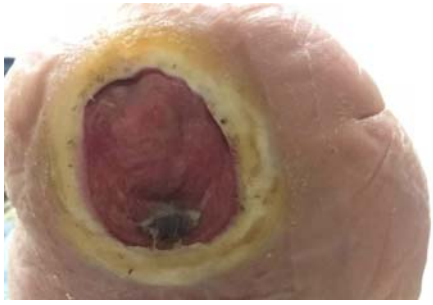
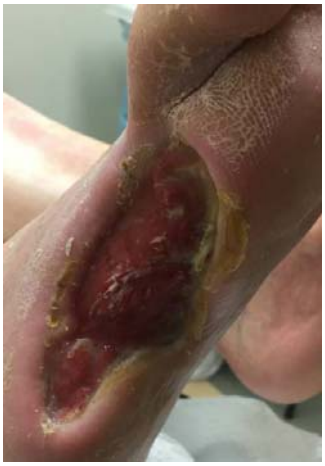
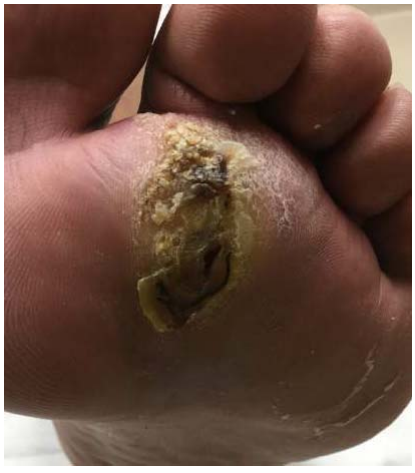
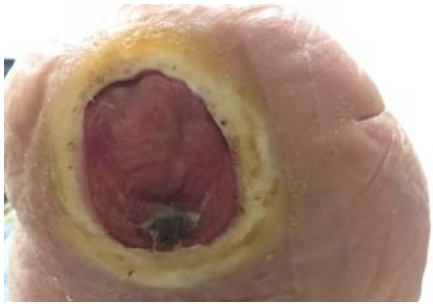
Assessing the Diabetic Foot

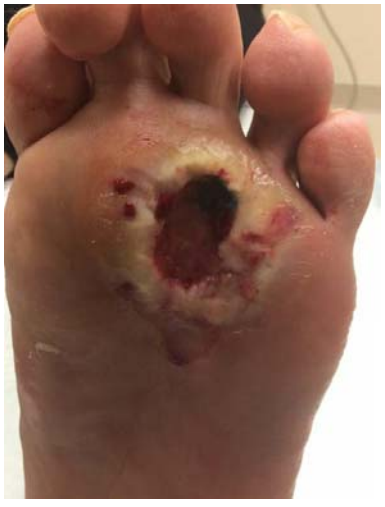
What can you do at this point?

CASES

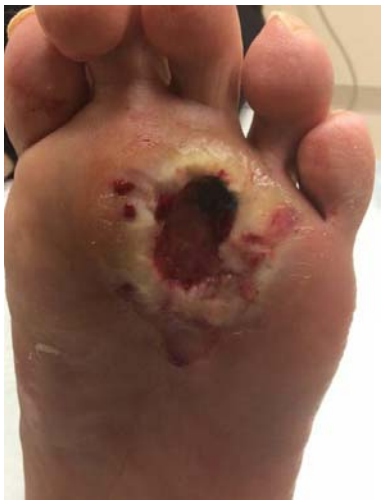
Describe that wound (MEASURE - MIT)

- **M- Measure**
  - Dimensions
    - Length x Width
- **E – Exudate**
  - Malodor?
  - Color?
  - Consistency?
    - Thick, thin, viscous
- **A – Appearance**
  - Does it look ‘angry’



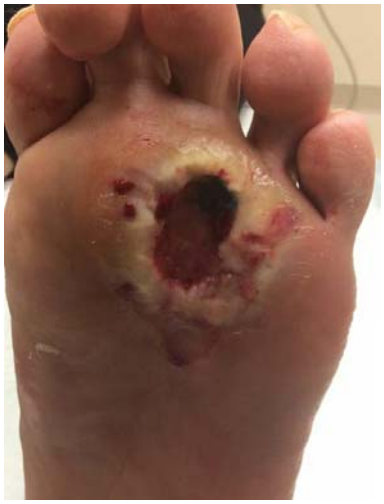
Describe that wound (MEASURE - MIT)

- **S-Suffering**
  - Painful to palpation?
  - Fluctuant / Soft tissue Crepitus
- **U - Undermining**
  - Are the edges of the wound contiguous?
  - Can you place an object under wound margins
- **R – Realm**
  - Location
- **E - Edge**



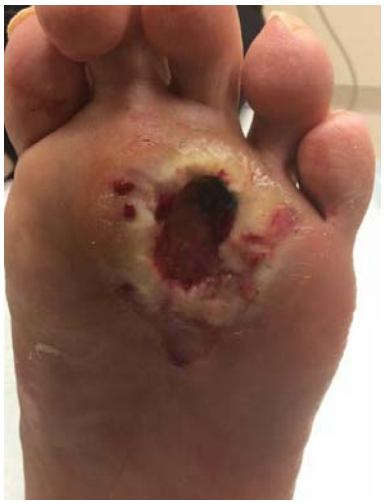
Describe that wound (MEASURE - MIT)

- **M – Moisture**
  - Color surrounding wound
  - Macerated
  - Dry, cracking, flaking
- **I - Infection**
  - Red
  - Hot
  - Swollen
- T - Tissue
  - Granular, Fibrotic, Necrotic, Slough,Punctate



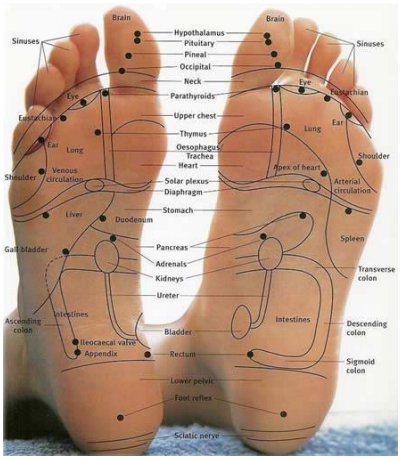
Describe that wound (MEASURE - MIT)

- M:
- E:
- A:
- S:
- U:
- R:
- E:
- M:
- I:
- T:



Case #1

- CC: New onset foot pain
  - PMHx: T2DM (last A1c ~10%), HTN, CKD, h/o CHF, DPN, pre-ulcerative callus
  - Social Hx: Factory worker
  - Meds: Many
  - PSHx: Left hallux amputation in June (well healed)
  - Allergies: NKDA
  - ROS: Negative



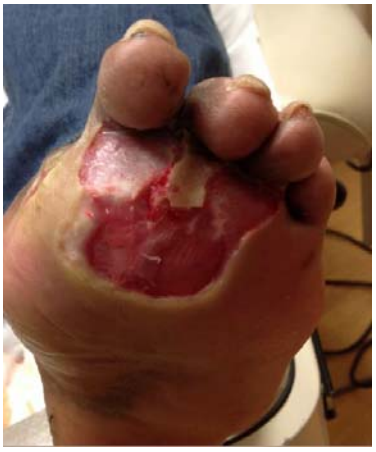
4/28/2018 - Schmidt

Case #1 / Week 1

- CC: New onset foot pain

- Focused LE Exam:
  - Vitals: BP: 177/75
  - Pulse: 78
  - Temp: 36.7 °C (98 °F)
  - NAD and AA0x 3
  - Palpable DP and PT, foot is well perfused with brisk CFT
  - Gross sensation noted
  - Protective sensation diminished via SMWF testing per ADA CPG
  - Blistered skin sub 2/3 metatarsal head region without POP or SOIs

Describe the wound



MEASURE - MIT

- M:
- E:
- A:
- S:
- U:
- R:
- E:
- M:
- I:
- T:

Hallmarks of Treatment in DFI

Debridement ⟷ **Infection Control** ⟷ **Offload**

- Removes non-viable tissue
- Stimulates healing
- Facilitates drainage

Antibiotics
(more later…)

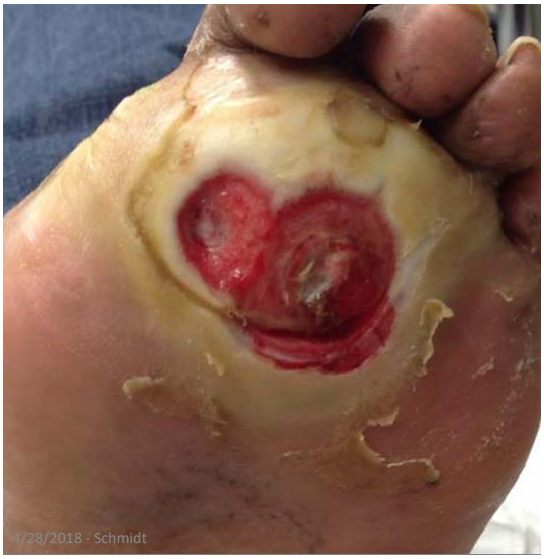
- Redistributes plantar pressure
- Many, many devices

Treatment (Case 1 / Week 1)

Case #1/ Week 2

- Patient RTC in one week
  - Completed Augmentin as prescribed
  - Continues working full-time
  - Wearing 'Nike +' sneakers
    - No diabetic insoles or post-op shoe
  - Has been applying Restore qod
  - Denies pain
  - Denies N/V/F/C/SOB/CP

Describe the wound



MEASURE - MIT

- M:
- E:
- A:
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- R:
- E:
- M:
- I:
- T:

Percent Change in Wound Area of Diabetic Foot Ulcers Over a 4-Week Period Is a Robust Predictor of Complete Healing in a 12-Week Prospective Trial

PETER SHEEHAN, MD[1]
PETER JONES, MSC[2]
ANTONELLA CASELLI, MD[3]
JOHN M. GIURINI, DPM[3]
ARISTIDIS VEVES, MD[3]

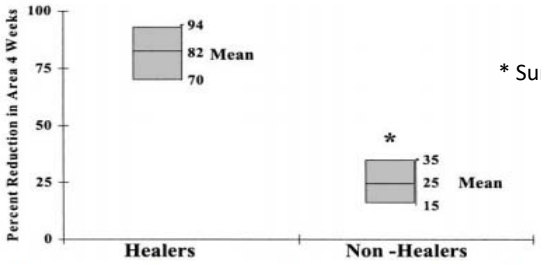
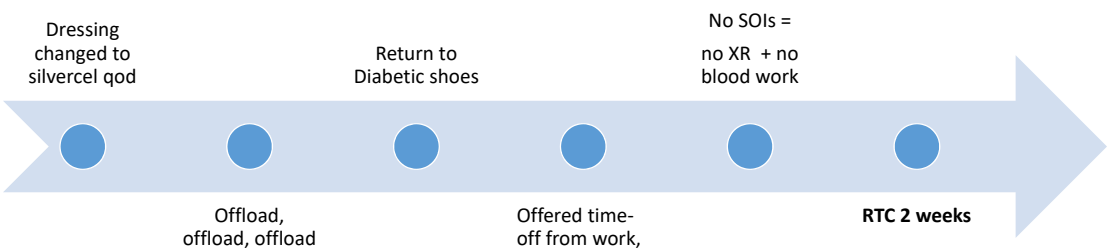


Figure 2— *Mean percent reduction in ulcer area during the first 4 weeks of the study in patients whose ulcers healed completed during the 12-week study period (healers) and those in whom ulcers failed to heal (nonhealers). The healers had a mean percent reduction in ulcer area of 82% (95% CI 70–94), which was significantly higher than that of the nonhealers, who had a reduction of 25% (15–35, P < 0.001).*

* Surface area (cm^2) not cubic area (cm^3)

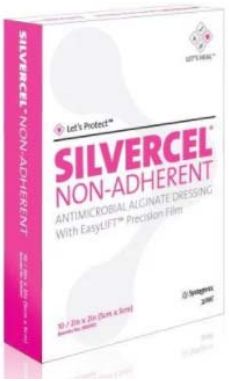
Diabetes Care, Volume 26, No 6, June 2003

Treatment (Case 1 / Week 2)

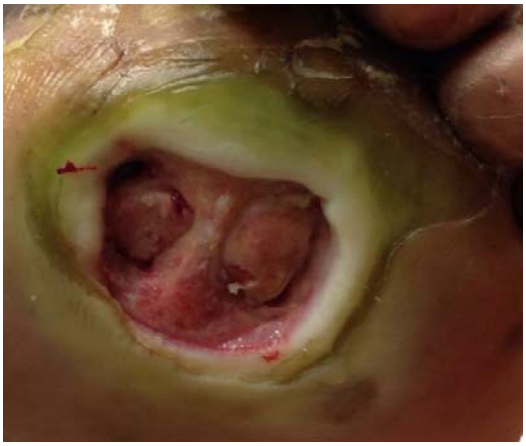


Case #1/ Week 4

- Patient RTC in two weeks
  - Continues to work full-time
  - Wearing 'Nike +' sneakers
    - No diabetic insoles AGAIN
  - Has been applying Silvercel qod
  - Reports more drainage
  - Reports increase in pain
  - Denies N/V/F/C/SOB/CP



Describe the wound



MEASURE - MIT

- M:
- E:
- A:
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- E:
- M:
- I:
- T:

Treatment (Case 1 / Weeks 4 - 12)

WTD applied

Referral to emergency department (IDSA 2+)

- Admitting for IV abx and worked-up for OM
- Diagnosed with OM of 2/3 MTH

At the hospital:
Transmetatarsal Amputation (TMA) rec

- Patient refused
- Elected for IV abx therapy and medical management

Ultimately, developed AIN and went into AKF

→ ESRD on HD 3d/wk x 3 months

Weekly ESR, CRP, and CBC after dialysis

Weekly wound care visits

Treatment (Case 1 / Week 13- 24)

After completion of Abx, started bioengineered skin alternative

- Dermagraft and Apligraf

Repeated application weekly

Offload, offload, offload

Case #2 / Week 1

- CC: “Black Foot”
  - PMHx: HLD, IDDM (~A1c 9.1%), DPN, CKD stage II, PAD
  - Social Hx: Unemployed
  - Meds: Many
  - PSHx:
    - s/p arteriogram/ocelot recannalization of R SFA/popliteal artery (2017)
    - arteriogram left leg contralateral approach, balloon angioplasty right external iliac artery, ocelot recanalization left SFA, stent graft assited angioplasty left SFA, drug eluting balloon angioplasty left popliteal artery, drug eluting balloon angioplasty left common femoral artery
  - Allergies: NKDA
  - ROS: 10/10 pain described as aching

Classification Practice

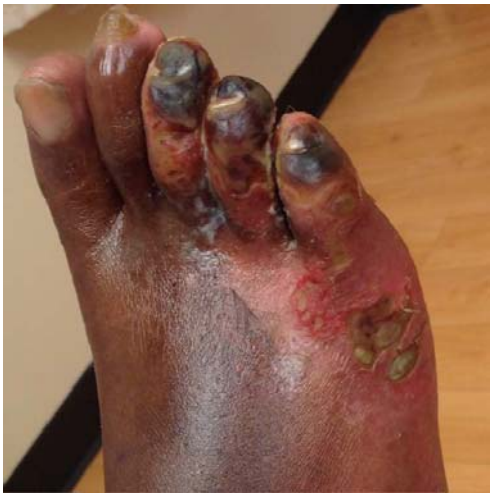
Classify this Foot based on appearance according to IDSA:

a.) 0

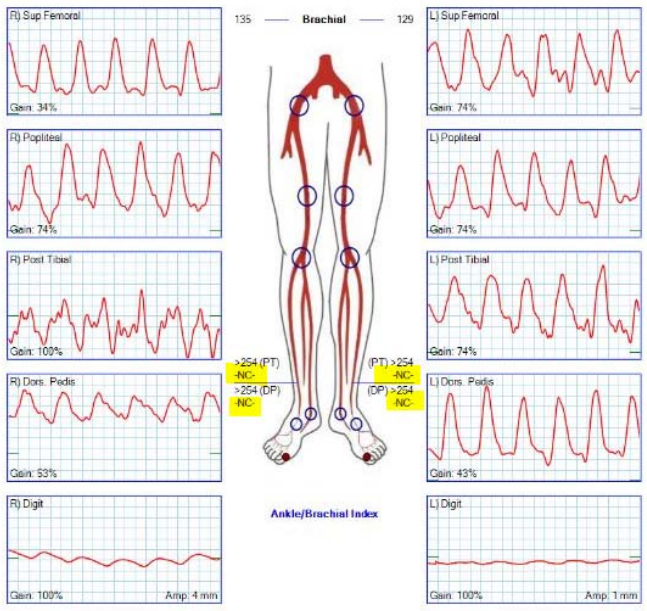
b.) 1

c.) 2

d.) 3



- The Non-invasive vascular studies demonstrate all “NC” arteries:
  - DP
  - PT



What’s Next?

- What is your next step?

a.) Emergency Department referral
b.) Foot is warm and perfused, RTC 1 week
c.) Antibiotics
d.) Look at Toe Brachial Index (TBIs)
e.) Vascular consultation

What amount of transcutaneous oxygen is required for wound healing?

A.) 20 mmHg
B.) 30 mmHg
C.) 40 mmHg
D.) 50mmHg
E.) 80mmHg

Refresher

ABPI	Toe Brachial Index	Toe Pressure	Waveforms	$TcP0_2$* (indicating perfusion)
> 0.9 – 1.3	> 0.6	> 80 mmHg	triphasic	> 40 mmHg
> 0.6	> 0.4	>50 mmHg	biphasic/mono	30–39 mmHg
> 0.4	> 0.2	> 30 mmHg	biphasic/mono	20–29 mmHg
< 0.4	< 0.2	< 30 mmHg	monophasic	< 20 mmHg
> 0.9			An audible hand-held Doppler of the dorsalis pedis or posterior tibial artery that is triphasic/biphasic is equivalent to an ABPI > 0.9. **Beware** of falsely elevated ABPI levels that may be due to calcified vessels in persons with diabetes.[24]	

*Transcutaneous oxygen pressure

Canadian Association of Wound Care. Advances for the Management of Diabetic Foot Complications. Session workbook. 2016.

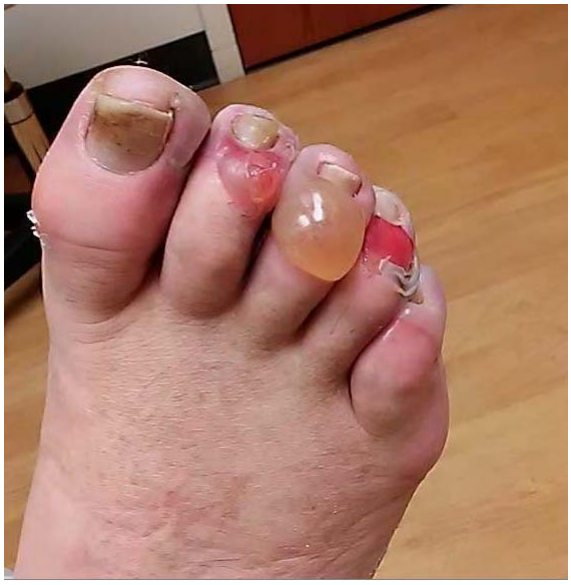
Case #3 / Week 1

- CC: Blisters
  - PMHx: Obesity, HTN, HLD, DM (A1c of 7%), DPN, calluses
  - Social Hx: Retired widower. No EtOH, no smoking hx
  - Meds:
    - ASA
    - Lipitor
    - Chlorthalidone
    - Novolog 2-12u at meal time
    - Lantus 40u bid
    - Metoprolol
    - Lisinopril
  - PSHx: THR
  - Allergies: PCN and Vancomycin
  - ROS: Negative

Case #3 / Week 1

Blisters after walking on treadmill

- Called same day
- Seen same date as CC
- IDSA classification?



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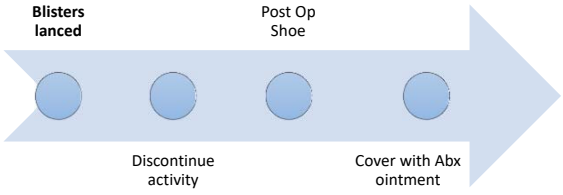
Treatment (Case #3 / Week 1)



4/28/2018 - Schmidt

What's Next?

What can we do?

Standardize your approach to diabetic foot infections

Early identification is key to limb salvage

1. Understand Diabetic foot risk categories
2. Know a DFI classification system
3. Assessing the Diabetic Foot
4. **Microbiology exam**
5. Imaging considerations
6. Diabetic foot osteomyelitis
7. Antimicrobial therapy and referral to foot specialist

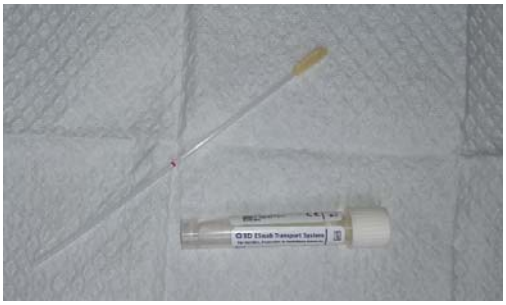
Microbiology Exam

<u>"Let infection be your guide"</u>

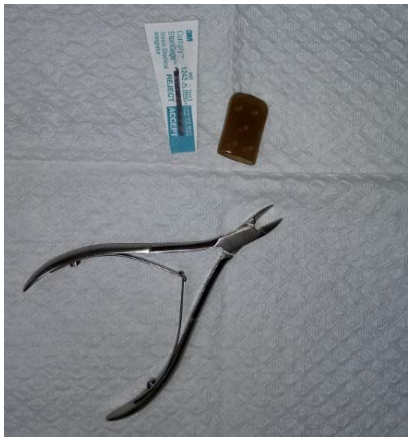
- Clinical Signs of infection
  IDSA grade
- Is there pus?
- Malodor?

Microbiology Exam

Swab



Tissue sample



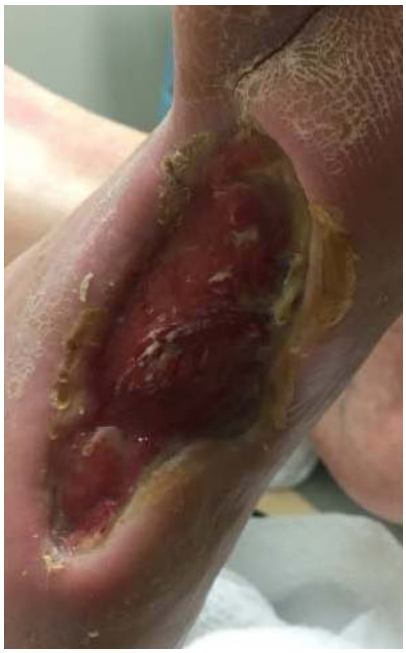
Microbiology Exam

Swabs and tissue samples are always concordant in DFI?

A.) True
B.) False

Microbiology Exam

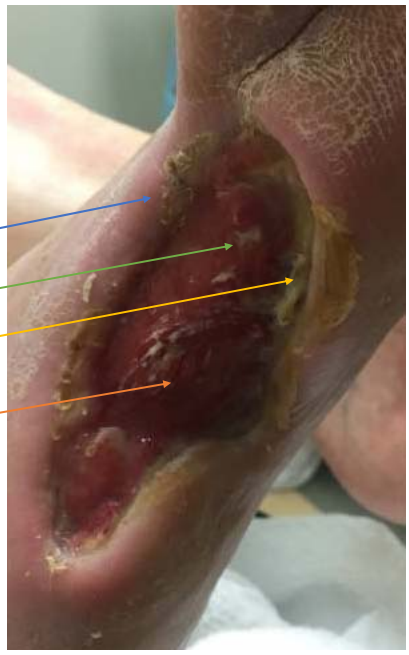
Where to culture?



Microbiology Exam

Where to culture?

A.) Here
B.) Over here
C.) There
D.) Everywhere
E.) No culture



What can we do?

Standardize your approach to diabetic foot infections

<u>Early identification is key to limb salvage</u>

1. Understand Diabetic foot risk categories
2. Know a DFI classification system
3. Assessing the Diabetic Foot
4. Microbiology exam
5. **Imaging considerations**
6. Diabetic foot osteomyelitis
7. Antimicrobial therapy and referral to foot specialist

Imaging

- Which is best when concerned for DFI?

  a.) CT
  b.) MRI
  c.) Bone scan
  d.) Ultrasound
  e.) XR

Case #4 / Day 1 → Inpatient

- CC: Sepsis
  - PMHx: Type 2 diabetes (A1c ~10.9%), CAD, HTN, depression, COPD
  - Social Hx:
  - Meds:
    - ASA
    - Furosemide
    - Gabapentin
    - Lisinopril
    - Metformin
  - PSHx: Right knee fusion
  - Allergies: Latex and Chlorhexadine
  - ROS: (+)Fever and (+)chills

Case #4 / Day 1

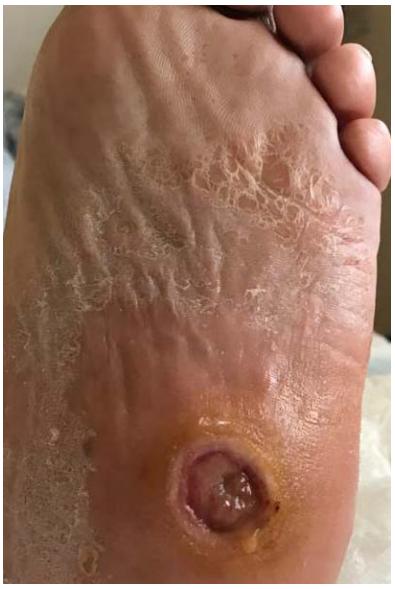
Ulceration plantar central midfoot left measures 2.0 x 1.5 x 0.3cm

Septic from foot?

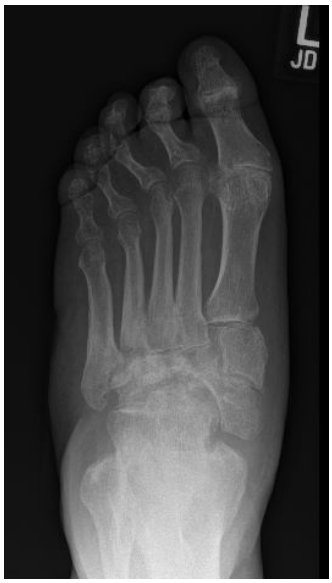
IDSA classification?

Does it look infected?

Plan: **???**



Case #4 / Week 1

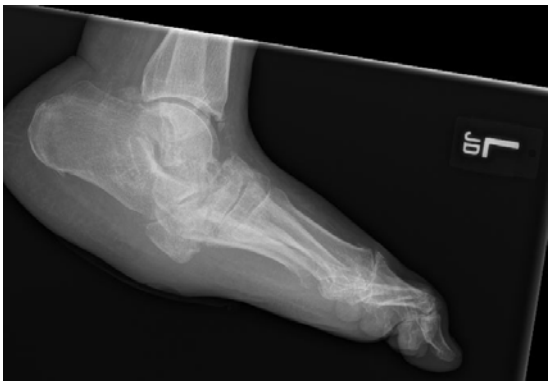


- **XR Left foot:**

What bone is missing?

A.) Cuboid
B.) Phalanx
C.) Navicular
D.) Medial Cuneiform

Case #4 / Week 1



- **XR Left foot:**

  Is this infection?

- **So, is this infected?**

What can we do?

Standardize your approach to diabetic foot infections

Early identification is key to limb salvage

1. Understand Diabetic foot risk categories
2. Know a DFI classification system
3. Assessing the Diabetic Foot
4. Microbiology exam
5. Imaging considerations
6. **Diabetic foot osteomyelitis**
7. Antimicrobial therapy and referral to foot specialist

Diabetic Foot Osteomyelitis (DFO)

- What is the threshold level of Western Sedimentation Rate (ESR) for DFO?

A.) 10 mm/h
B.) 30 mm/h
C.) 50 mm/h
D.) 70 mm/h
E.) 90 mm/h

Diabetic Foot Osteomyelitis (DFO)

- What is the threshold level of C-Reactive Protein(CRP) for DFO?

A.) 1.0 mg/dL
B.) 1.5 mg/dL
C.) 2.0 mg/dL
D.) 2.7 mg/dL
E.) 3.2 mg/dL

What can we do?

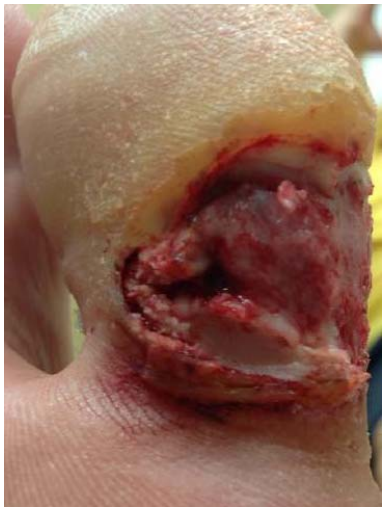
Standardize your approach to diabetic foot infections

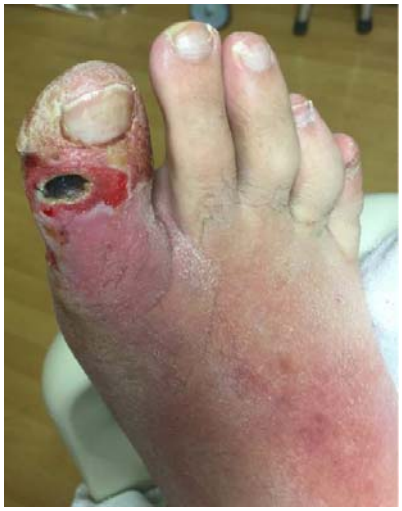
<u>Early identification is key to limb salvage</u>

1. Understand Diabetic foot risk categories
2. Know a DFI classification system
3. Assessing the Diabetic Foot
4. Microbiology exam
5. Imaging considerations
6. Diabetic foot osteomyelitis
7. **Antimicrobial therapy and referral to foot specialist**

Case #5 / Week 1

- CC: Cellulitis
  - PMHx: T2DM(~A1c 7.9%), DPN
  - Social Hx: Farmer, (-)smoking, (-)drinking, (-)illicits
  - Meds: Cymbalta, Lantus (40u qhs), oxycodone
  - PSHx: None
  - Allergies: NKDA
    - Sensitivity to Glucophage
  - ROS: Negative





What's Next?

Antimicrobial Selection

Which Antibiotic would you recommend?

Susceptibility

	Proteus mirabilis MIC	
Amikacin	<=4 mcg/mL	Sensitive
Amoxicillin + Clavulanate	<=8 mcg/mL	Sensitive
Ampicillin	<=8 mcg/mL	Sensitive
Ampicillin + Sulbactam	<=8 mcg/mL	Sensitive
Aztreonam	<=4 mcg/mL	Sensitive
Cefazolin	4 mcg/mL	Intermediate
Cefepime	<=1 mcg/mL	Sensitive
Ceftriaxone		Sensitive
Cefuroxime	<=4 mcg/mL	Sensitive
Ciprofloxacin	<=0.06 mcg/mL	Sensitive
Ertapenem	<=0.5 mcg/mL	Sensitive
Gentamicin	<=2 mcg/mL	Sensitive
Levofloxacin	<=1 mcg/mL	Sensitive
Meropenem	<=1 mcg/mL	Sensitive
Piperacillin/tazobactam	<=8 mcg/mL	Sensitive
Tobramycin	<=2 mcg/mL	Sensitive
Trimethoprim/Sulfa	<=2 mcg/mL	Sensitive

Antimicrobial Selection

How long would you recommend Abx therapy?

Susceptibility

	Proteus mirabilis MIC	
Amikacin	<=4 mcg/mL	Sensitive
Amoxicillin + Clavulanate	<=8 mcg/mL	Sensitive
Ampicillin	<=8 mcg/mL	Sensitive
Ampicillin + Sulbactam	<=8 mcg/mL	Sensitive
Aztreonam	<=4 mcg/mL	Sensitive
Cefazolin	4 mcg/mL	Intermediate
Cefepime	<=1 mcg/mL	Sensitive
Ceftriaxone		Sensitive
Cefuroxime	<=4 mcg/mL	Sensitive
Ciprofloxacin	<=0.06 mcg/mL	Sensitive
Ertapenem	<=0.5 mcg/mL	Sensitive
Gentamicin	<=2 mcg/mL	Sensitive
Levofloxacin	<=1 mcg/mL	Sensitive
Meropenem	<=1 mcg/mL	Sensitive
Piperacillin/tazobactam	<=8 mcg/mL	Sensitive
Tobramycin	<=2 mcg/mL	Sensitive
Trimethoprim/Sulfa	<=2 mcg/mL	Sensitive

Questions?

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