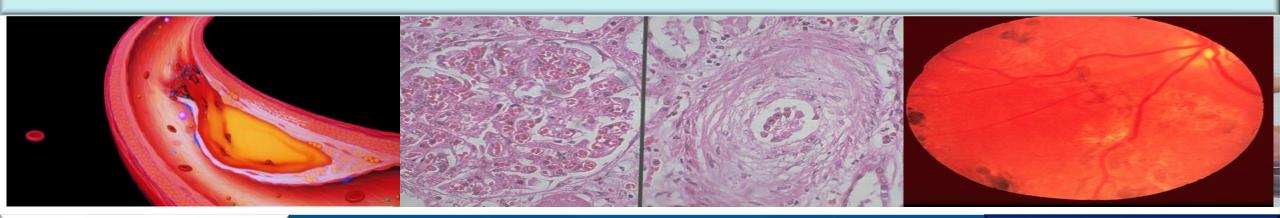
Time To Re - Think T2DM: Cardio-Renal-Metabolic Syndrome Let's Not Sugar Coat Diabetes

Tools for Professional Practice 2023 & Beyond: <u>Beyond Glycemia</u> '<u>Turning the Tides</u>' For the Future of Diabetes Care T2DM, CKDz & ASCVDz: 'When There Is Smoke, There Is Fire'





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Medical Director, Borgess Diabetes & Endocrine Center

MOA Autumn Scientific Convention 10/28/23



Objectives

- 1. Discuss The Need To Address Cardio-Renal-Metabolic Risk In Patients With T2DM Beyond Standard of Care.
- 2. Establish ASCVDz As The Most Common CVDz in Patients With T2DM.
- 3. Explore How ASCVDz Impacts Patients With T2DM.
- 4. Review Recommendations From Major Medical Societies For Patients With T2DM & ASCVDz, Or ASCVDz Risk Factors.
- 5. Realize The Importance Of A Team-Based Approach To Reduce Cardio-Renal-Metabolic Risk In Patients With T2DM.



Disclosures

- Speaker Bureau Lilly, Novo, Corsept Therapeutics, Astra-Zeneca, Boehringer Ingelheim, Abbvie, Horizon Therapeutics.
- ▼I Will Not Discuss Off Label Use And / Or Investigational Use In My Presentation.
- All MOA Planners, Reviewers, And Course Directors Have No Relevant Financial Relationships With ACCME-Defined Commercial Interests.
- My Presentation Today Will Be Fair, Balanced, Free of Commercial Bias & Fully Supported By Scientific Evidence



New Patient To The Office

- 64 y/o Male. T2DM Since 2015.
- ACS August 2020, Stent x 2 (LAD, RCA)
- ✓ Metformin 1,000 mg BlDay. HbA_{1c} 6.9%

Treat The Patient
Not Their Sugar
Reduce CV Risk
Not Only The HbA_{1c}

Should We Modify The Glucose Lowering Medication?

No HbA_{1c} = Good

Yes
No Evidence
Based Medication

Pre-2008

HbA_{1c}

Lower
The

Better

HbA_{1c}

2008-2015

Lower Better Avoid Hypo & Weight Gain CV Events

Since 2015

BP, LDL
Glucose
Agents Proven
Safety Efficacy

The Connection Between A1c & CVDz Is A Key Consideration



A 1% Increase In Mean A1c Is Associated With A 22% Greater Risk Of CV Events In T2DM Patients

Retrospective Observational Case-Control Study Using EMR 2,456 Pts With T2DM Nichols GA et al. *Diabetes Care.* 2014;37(1):167-172



Does Better Control Improve Outcomes? Meta-Analysis 14 Randomized Controlled Trials

14 Trials
Comprising
95,502
Patients

	Number Trials	RR (95% CI)	P Interaction
MACE	14	0.95	0.23
Expanded MACE	14	0.96	0.17
All-Cause Death	12	0.99	0.67
CV Death	12	0.98	0.92
MI	14	0.92	0.15
Stroke	14	0.99	0.27
HF	14	1.14	0.002
USA	7	0.97	0.05
Coronary Revascularization	6	0.92	0.07

Udell JA et al., Lancet Diabetes Endocrinol. 2015;3:356-366

Effects Of Glucose Lowering Medications On CV Outcomes With RCT

	Met	SU	Acarb	TZD	DPP4	SGLT2	GLP1	Basal Insulin	Meal Time Insulin	Intensive Insulin Therapy
Any CVOT	X	X	X	Yes	Yes	Yes	Yes	Yes	X	X
Effects On MACE	X	X	X	++ Pio	= ? CHF	+++	+++	= Glar	X	X



When To Treat T2DM As A Vascular Disease?

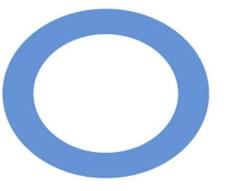
- CVD Leading Cause of Morbidity and Mortality Among Patients with T2DM.
- **▼** Two Out of Every Three T2DM Patients Die From CVDz.
- ADA / EASD / ACC Announced An Update To The Standard of Care Guidelines for Medical Co-Management T2DM & Established ASCVDz / CKDz / CHF.
- ▼ Two 'Newer Classes' of Medications, GLP-1 Analogues & SGLT-2i Recommended as a 'Second-Line' Medical Therapy.

Time To Disrupt The Glycemic Centered Approach

- Think Of DM As A Vascular Dz. & Preferentially Select <u>Proven</u> Second-Line Classes Of Diabetes Rx. Targeting <u>Preservation</u> Of Heart, Brain, & Kidney Function In Pts With Comorbid T2DM, CVD, HF and / or CKD.
- ▼While the Recommendation GLP-1 RA & SGLT-2i By the ADA / EASD / ACC Was Based Upon a Thorough Review Of The Literature & Landmark Studies, Clinicians May Not Widely Adopt These Lifesaving Guidelines & Rx. For Their Pts For Years To Come.
- Unfortunately, Even In The Information Age, Lifesaving Knowledge Travels Slowly - The Legacy Healthcare System.

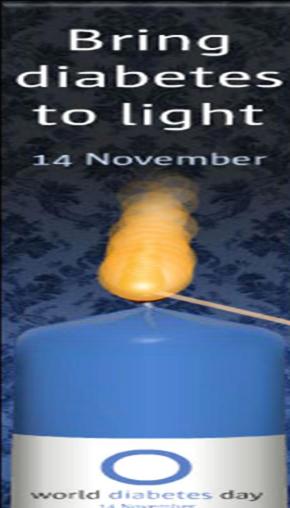


"Nourishing Development: Halting the Diabetes
Epidemic Through Healthy Eating;
Diabetes Education and Prevention"



world diabetes day



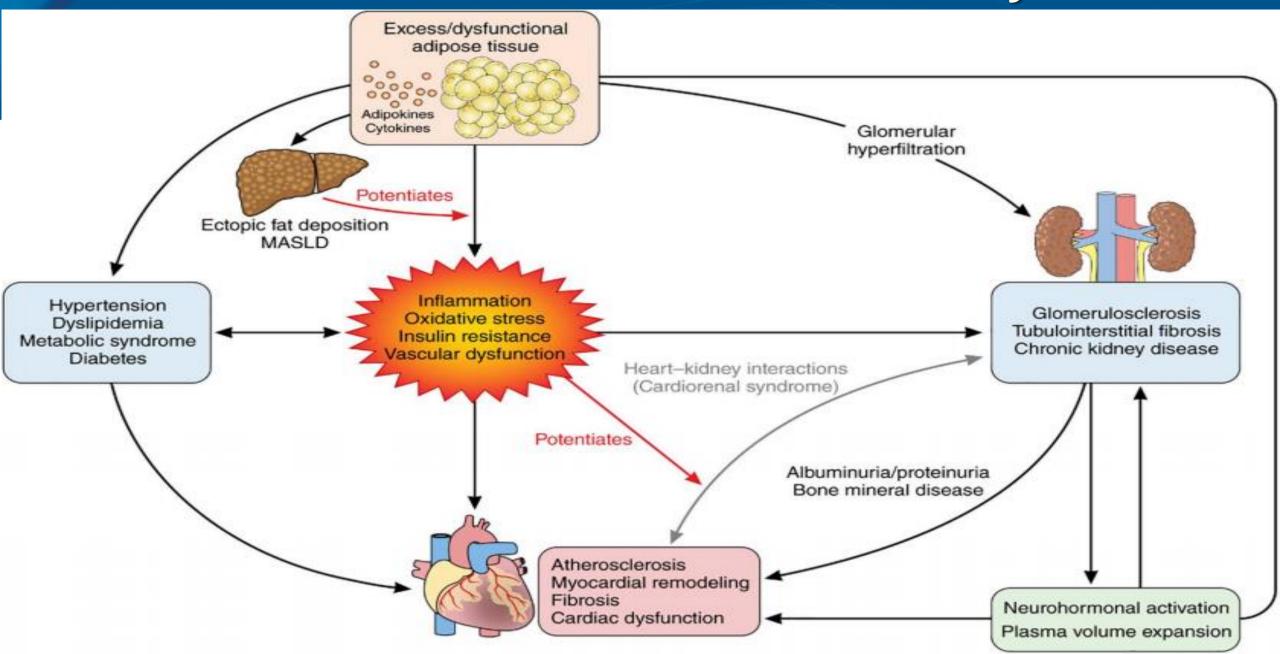


Global Symbol / Unite for Diabetes Awareness Campaign. Symbolizes Life and Health. Blue Reflects the Sky That Unites All Nations. Circle Signifies

Unity of the Global Community.



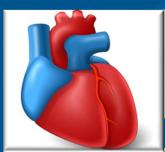
The Puzzles Of Cardio-Renal-Metabolic Syndrome



T2DM Affects: Pump, Plumbing & The Filter

- Treatments That Are <u>Dz Modifying</u> & That Address The Core Pathophysiolgic Defects
- Treatments That Are <u>Effective</u> Independent of Beta Cell Status & Thus Indifferent to Dz Stage
- ▼ Treatments That Are Weight Neutral or That Promote Weight Loss
- Treatments That <u>Avoid Hypoglycemia</u>
- Treatments That Are <u>Beneficial</u> In Their Impact On CVDz, CVDz Risk Factors, & Renal Dz
- Treatments Easily & Reliably Used By Patients In <u>Sustainable</u>
 Fashion (Improved Adherence)

T2DM: Central Role In CV & Renal Disease



Diabetes Affects the PUMP





Diabetes Affects the PLUMBING

ASCVD



Diabetes Affects the FILTER

Renal Disease



Can We Do More? Will Our Next Move Do Enough?

<u>Residual Risk</u> Remains For Patients With T2DM & Established CV Disease Treated With:

ACE / ARB's

Statins



ASA / Anti-Platelet Therapy Incidence of CV Death
Remains Higher in
Patients With Diabetes
Despite Advances In Care

Diabetes Meds

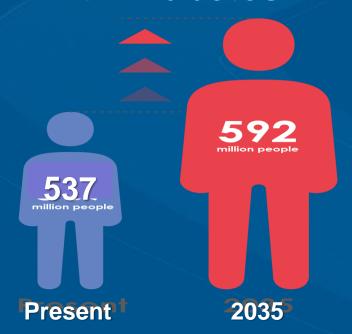
'Despite Our Best Efforts, 2 in 3
Adults with T2DM Will Die From a
CVDz - Related Event'...NIDDK





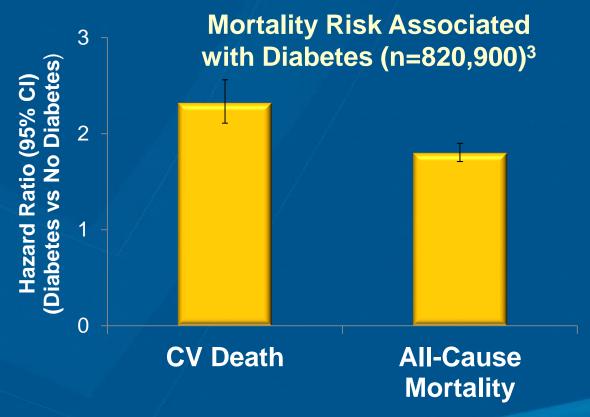
T2DM Increasingly Prevalent

Globally, 537 Million Living with Diabetes¹



This Will Rise to 700 Million by 2045¹

 At Least 68% of People >65 Years with Diabetes Die of Heart Disease²



- 1. IDF Diabetes Atlas 6th Edition 2018 http://www.idf.org/diabetesatlas;
- 2. Centers for Disease Control and Prevention 2019;
- 3. Seshasai et al. N Engl J Med 2011;364:829-41



Growing Problem of T2DM and CKD

~537
MILLION

Adults Are Living with Diabetes

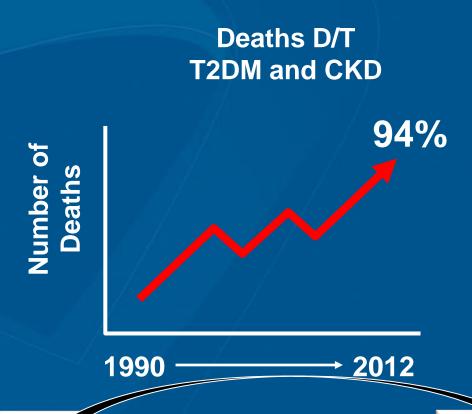
30 to 40%

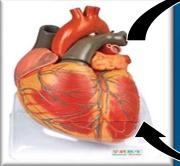
Of These Patients Will Develop CKD



Renal & Cardiac Systems Are Linked Acute Or Chronic Disorder of One Can Induce Dysfunction in the Other

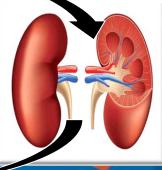
- 1. World Health Organization. Global Report on Diabetes. 2020.
- 2. Yee J. Diabetes Spectr. 2008;21(1):8-10.
- 3. Alicic RZ, et al. Clin J Am Soc Nephrol. 2017;12(12):2032-2045.



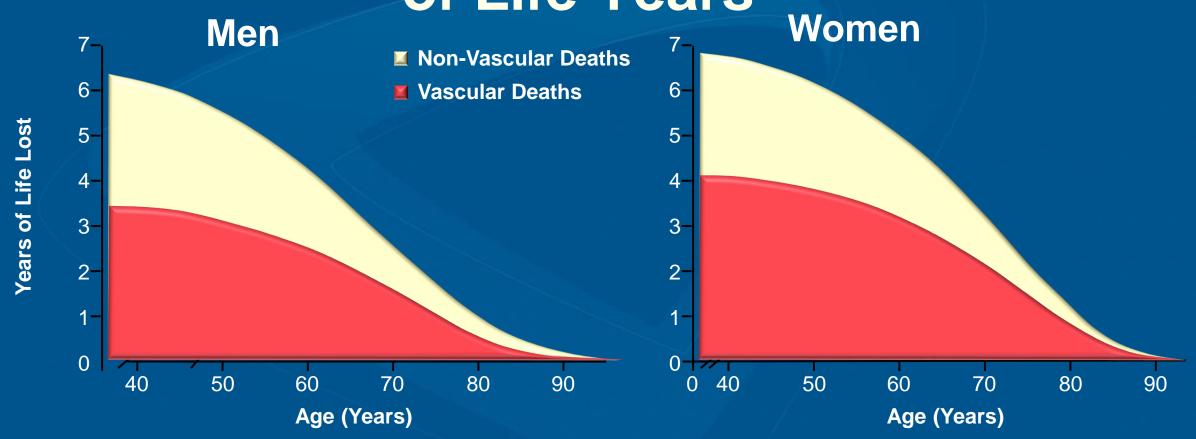


CKDz Patients
5 - 6 X

More Likely To Die CVDz
Than Advance To ESRD



Diabetes is Associated with Significant Loss of Life Years

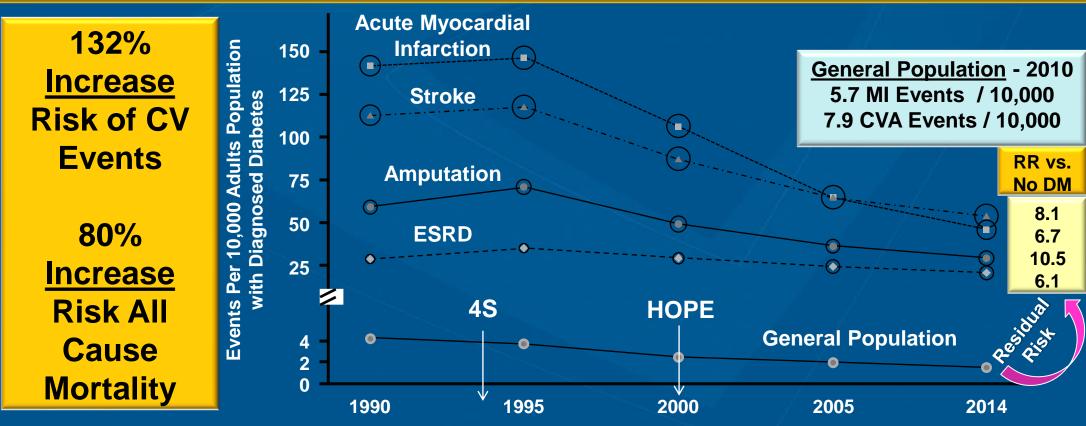


On Average, a 50-Year-Old Individual with Diabetes and No History of Vascular Disease Will Die ~ 7 Years Earlier Compared to Someone Without Diabetes



Substantial Reduction In The Rates of DM - Related Complications in the US in Recent Decades...

Various US Health Surveys and Data Systems were Used to Compare the Incidences of Diabetes-Related Complications from 1990–2014



...However, a Large Burden Persists... Growing Prevalence of Diabetes. Newer Therapies that Allow Us to Safely Intensify Rx Earlier Should Enable Further Reductions in These Complications...





Cholesterol
Assess ASCVD Risk,
personalize with
risk enhancers,
reclassify with
CAC as needed



High Blood Pressure

Maintain blood pressure below 130/80 mm Hg



Pharmacotherapy + behavior interventions recommended to maximize quit rates



Physical Activity

Perform ≥150 mins/week of moderate or ≥75mins/week of vigorous physical activity



Diet

Emphasis on intake of vegetables, fruits, nuts, legumes, fish and whole grains



Type II Diabetes

Control through diet and exercise.

Metformin (primary therapy), SGLT-2 inhibitor or GLP-1 receptor agonist (secondary)



Low-dose aspirin for primary prevention now reserved for select high-risk patients

Treatment With Standard Of Care Does Not Completely Eliminate CV Risk

Residual CV Risk: The Risk For CV Events Still Remaining After Patients Are Treated With Optimal Standard CV Risk Reduction & T2DM Care, Despite Achievement LDL, BP & Glycemic Goals

CARDS

Atorvastatin vs Placebo

37% CV Relative Risk Reduction

5.8% VS 9% That Experienced A CV Event

TNT

High Dose vs Low Dose Statin

25% CV Relative
Risk Reduction
Compared to
Conventional
13.8% vs 17.9%
That Experienced A

CV Event

STENO-2

Intensive vs Conventional Therapy

45% CV Relative
Risk Reduction
Compared To
Conventional

65% VS 84% That Experienced A CV Event

HOPE

ACE Inhibitor vs Placebo

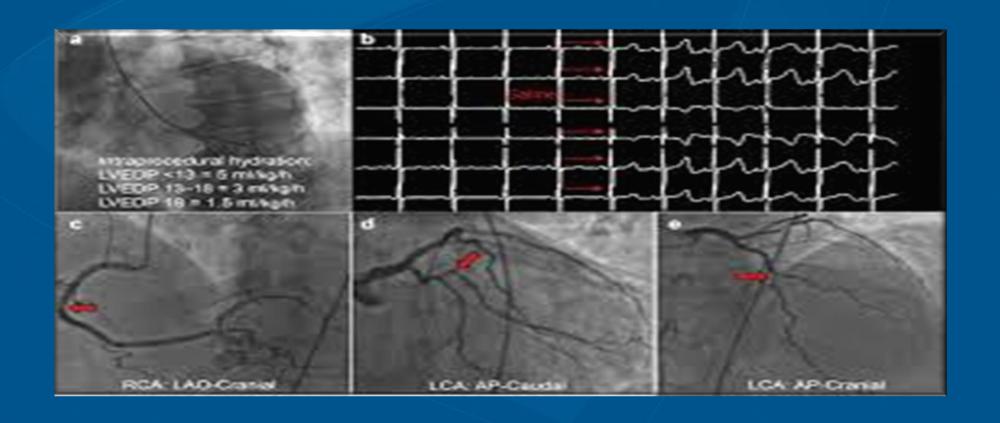
25% CV Relative Risk Reduction Compared To Placebo

15.3% vs 19.8% Experienced A CV Event

- 1. Fruchart J, et al. Cardiovasc Diabetol. 2014;13(26)2-17. 2. Colhoun HM et al. Lancet. 2004;364(9435):685-696.
- 3. Shepard J et al. Diabetes Care. 2006;29(6):1220-1226. 4. Gaede P et al. Diabetologia. 2016;59(11):2298-2307.
- 5. Gerstein H et al. *Lancet.* 2000;355:253-259

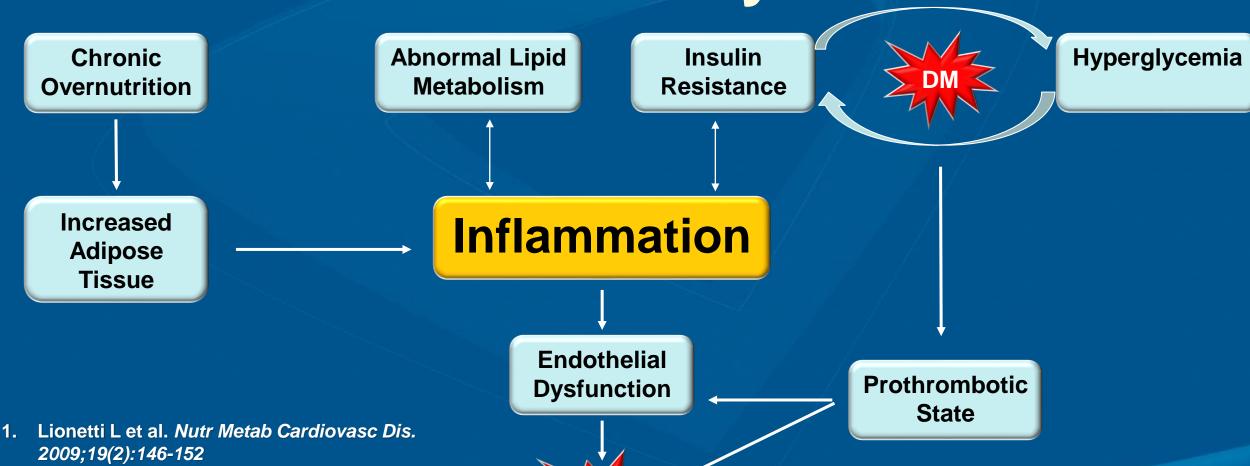


How Can T2DM Exacerbate ASCVDz?





These Events Can Be Further Exacerbated By T2DM



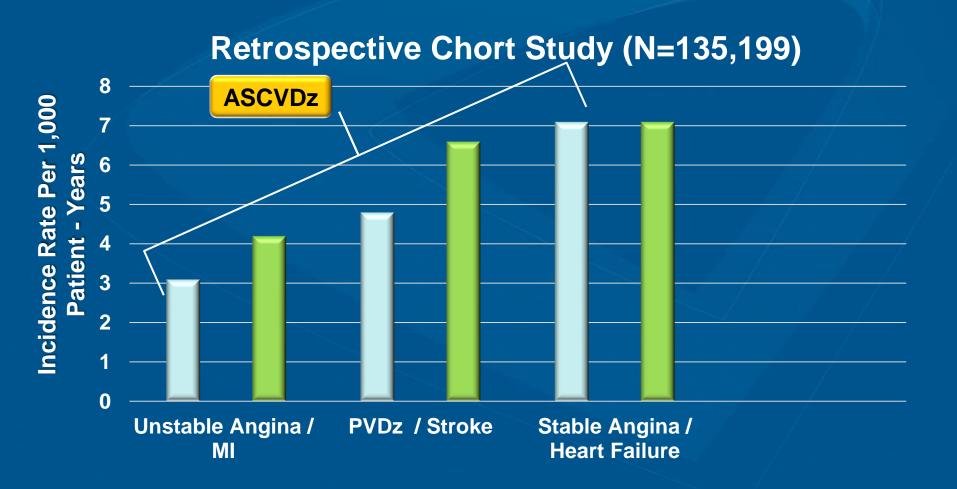
- 2. Chen L et al. *Int J Endocrinol*. 2015;2015:508409
- 3. Sears B et al. Lipids Health Dis. 2015;14:121
- 4. Ryden L et al. *Eur Heart J.* 2013;34(39):3035-87
- 5. Paneni F et al. Eur Heart J. 2013;34(31)2443-46

What Is The Most Common Type Of CVDz In Patients With T2DM?





ASCVDz Is The Most Common Form Of CVDz In Patients With T2DM



Combined
Incidence
ASCVDz 3 Fold
Higher Than
Heart Failure

Newly Dx T2DM Btw 2003 - 2014

- 1. An J et al. BMJ Open Diab Res Care. 2021;9e001847.
- 2. Das SR et al. *J AM Coll Cardiol*. 2020;76(9):1117-1145



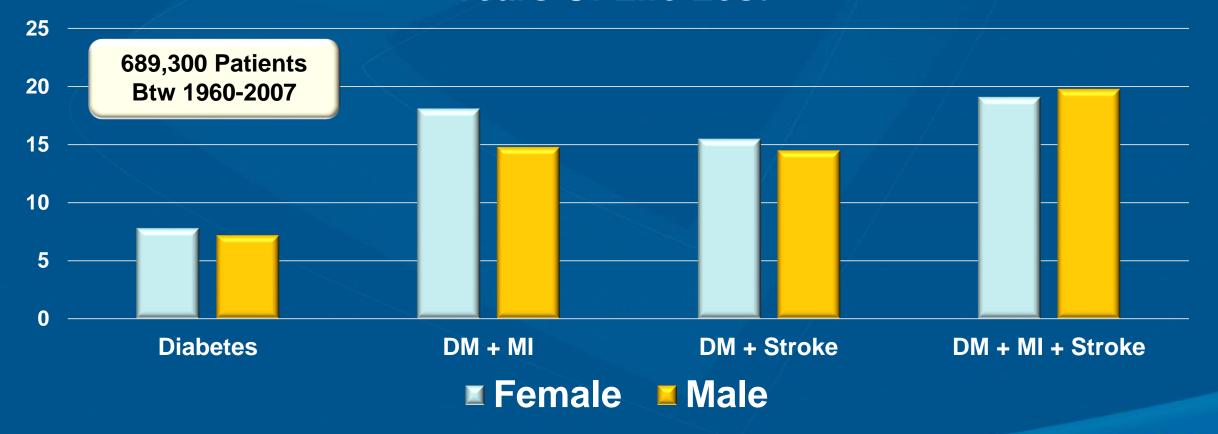
By How Many Years Was Life Expectancy Reduced In Patients Age 50 With T2DM And ASCVD (MI & Or CVA)?

- According To The Emerging Risk Factors Collaborations Study
 - A. Up To 6 Years
 - B. Up To 9 Years
 - C. Up To 12 Years
 - D. Up To 19 Years



ASCVDz Was Associated With Up To 19 Years Of Future Life Lost

Years Of Life Lost



Emerging Risk Factors Collaboration et al. *JAMA*. 2015;314(1):52-60. Association of Cardiometabolic Multi-Morbidity With Mortality



How Does ASCVDz Impact Patients With T2DM?





ASCVDz Is The Number One Cause Of Morbidity & Mortality In Patients With T2DM

ASCVDz Occurs

14.6 Years Earlier

And With <u>Greater Severity</u> In Patients With T2DM vs Patients Without T2DM



People With T2DM Have A

2-4 x Higher Risk

of Stroke Or MI vs Those

Without T2DM









Patients With T2DM Are At A Higher Risk of Stroke





1. Emerging Risk Factors Collaboration. *Lancet.* 2010;375(9733):2215-2222

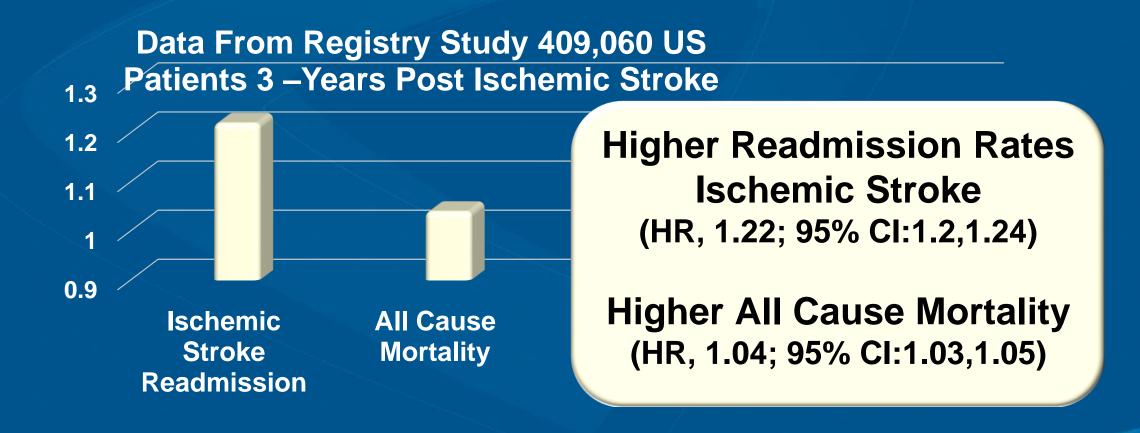


What Are The Differences In Outcomes For Patients With Stroke & T2DM vs Patients With Stroke Without T2DM?



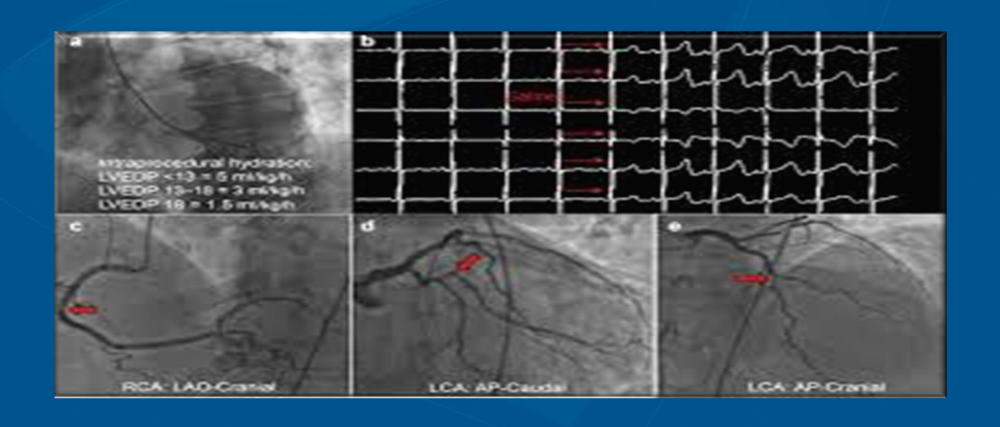


Patients With T2DM Have Higher Mortality, Readmission & Recurrence Post Stroke





What Do The Major Medical Societies Recommend For Patients With T2DM & CVDz?





Major Medical Societies Recommend GLP1-RA Or SGLT-2i With Proven CVDz Benefit For Patients With T2DM & CVDz

2020 ACC

Expert
Consensus
Decision Pathway

- Recommends

GLP1-RA Or SGLT2-i With

Demonstrated CVDz
Benefit (Label
Indication) As <u>First</u>
<u>Line Options</u> For
Patients With T2DM
& Established CVDz

2022 AHA

Scientific Statement

- Supports Use Of

GLP1-RA & An

SGLT2-i As

Antihyperglycemic Therapies Shown To Reduce CVDz Risk In Patients With T2DM **2023 ADA**

Standards Of Medical Care

-Rec: GLP1-RA

Therapy As The First Injectable Prior To Basal Insulin Use In A Majority Of Pts

- Supports <u>GLP1-RA</u>
For Patients With A
Compelling Need To
Minimize Hypoglycemia
&/Or Address Weight
Concerns

T2DM
Management
Algorithm

- Recommends A

GLP1-RA Or An

SGLT2-I For

Patients With T2DM

& Established

ASCVDz

Independent Of

Glycemic Control





Guidelines Are Evolving To Recommend Therapies That Prioritize CV Risk Reduction in T2DM

2020 ACC Expert
Consensus
Decision Pathway

2023 ADA Standards of Medical Care in T2DM

2023 AACE T2DM
Management
Algorithm

In Patients With T2DM & Established ASCVDz, The Use of <u>GLP-1 RA And/Or SGLT-2i</u> With Proven CVDz Benefit (Label Indication) Should Be Considered <u>Independently</u> Of Baseline A1c Or Individualized Targets

The 2023 ADA Standards Of Medical Care In Diabetes Recommends <u>GLP-1 RA</u>
<u>And/Or SGLT-2i</u> With Proven CVDz Benefits As Part Of The Glucose Lowering
Regimen & Comprehensive CV Risk Reduction In Patients With T2DM &
Established CVDz

For The First Time, T2DM Medications With Proven CVDz Benefit Are Recommended In Stroke Prevention Guidelines To Reduce The Risk For Future MACE

The AHA / ASA Guidelines For The Prevention Of Stroke Recommend That:

"In Patients With An Ischemic Stroke / TIA Who Also Have Diabetes, Treatment Of Diabetes Should Include Glucose-Lowering Agents With Proven CV Benefit To Reduce The Risk For Future Major Adverse Cardiovascular Events (ie. Stroke, MI, CV Death)"

A Call To Clinicans For The Use of GLP-1 RA / SGLT-2i With CV Benefit:

"Clinicians Should Now Engage Patients In A Discussion Of New Therapies. Through Shared Decision-Making, Clinicians Should Help Patients Decide If GLP-1 RA / SGLT-2i

Are Right For Them"



Diversity of Physiologic Effects SGLT-2i & GLP-1RA

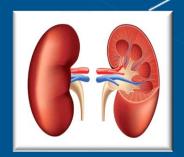
Vasodilation

SGLT-2 Inhibitors

GLP-1R Agonists

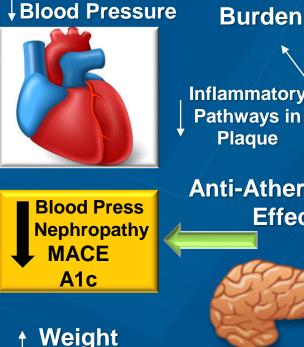
Sodium Retention / Hypervolemia RAAS Activation / Neurohormonal Activation / Inflammation / Ischemia / Altered Energetics

Nauck MA et al. Molecular Metab. 2021; 46:101102 Chad EC. Clin Diabetes. 2014;32(1):4-11



Glucosuria Natriuresis Uricosuria Hemodynamic Effect

Preload
Afterload
Epicardial Fat



Weight Loss Inflammatory
Pathways in
Plaque

Anti-Atherogenic
Effect

Insu
PostPrandial

Glucose

Plaque

Lesion

Permeability
TG
Inflammation
Lipid
Deposition

Gastric Motility

Insulin Glucagon

NO ↓ICAM-1 / VCAM 1

Improved Endothelial Function



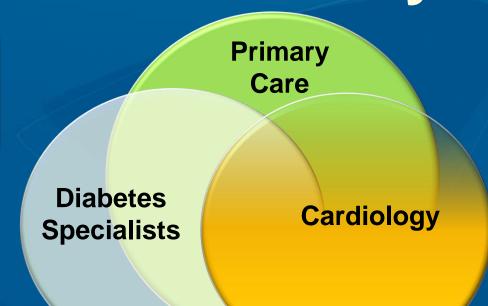
Call For Action To The Cardiology Community

Cardiologists 3 x More
Likely Than
Endocrinologists To See
Patients With T2DM &
CVDz



Physical Activity

Smoking Cessation Lipid & BP Lowering



Glucose Lowering SGLT-2i / GLP-1 RA With Proven CV Benefit Thrombo-Prevention
Advanced Invasive Therapies
PCI, AICD, CRT

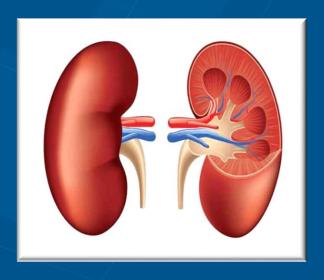


Step 1: Assess CVDz

Presence of ASCVDz, CKDz, HF Compelling Indication

ASCVDz Predominates HF Or CKDz Predominates









Glucose Lowering T2DM: Overall Approach

ASCVDz Predominates



GLP-1 RA With Proven CV Either Benefit Or

SGLT-2i With Proven CV Benefit If eGFR Adequate



Glucose Lowering T2DM: Overall Approach

HF Or CKDz Predominates



Preferably: SGLT-2i With Evidence Reducing HF and/or CKDz Progression in CVOTs if eGFR Adequate

Or

SGLT-2i Not Tolerated / Contraindicated, Add GLP-1 RA With Proven CV Benefit



Summary Of Indications For DM-Related Medications

	Type 2 Diabetes				Independent of Diabetes			
	CV Death	3P MACE	HF Hosp	CKD Progression	HFrEF Rx	All HF Rx	CKD Progression	Obesity
Empagliflozin	Yes		Yes	Yes	Yes	Yes	Yes	
Canagliflozin		Yes		Yes			Yes	
Dapagliflozin			Yes	Yes	Yes	Yes	Yes	
Liraglutide		Yes						Yes
Semaglutide		Yes	Under Review	Under Review				Yes
Dulaglutide		Yes						
Finerenone		Yes	Yes	Yes				

SGLT2i Meta-Analysis

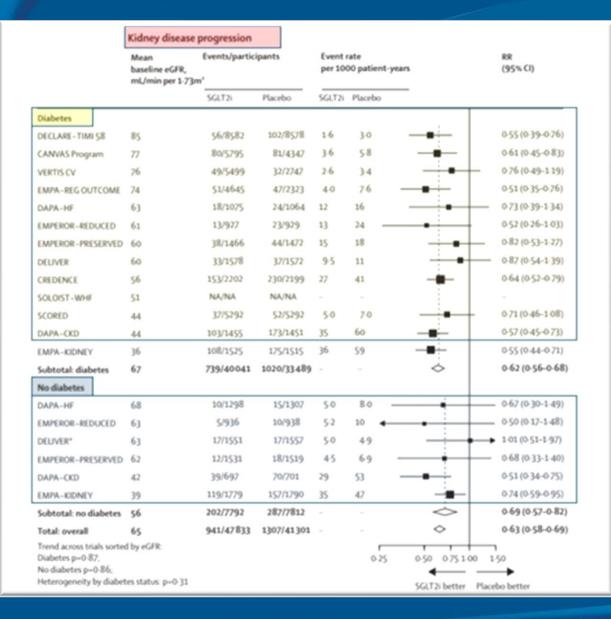


Table 1 Effect of SGLT2 inhibitors on clinical outcomes in adults with diabetic kidney disease

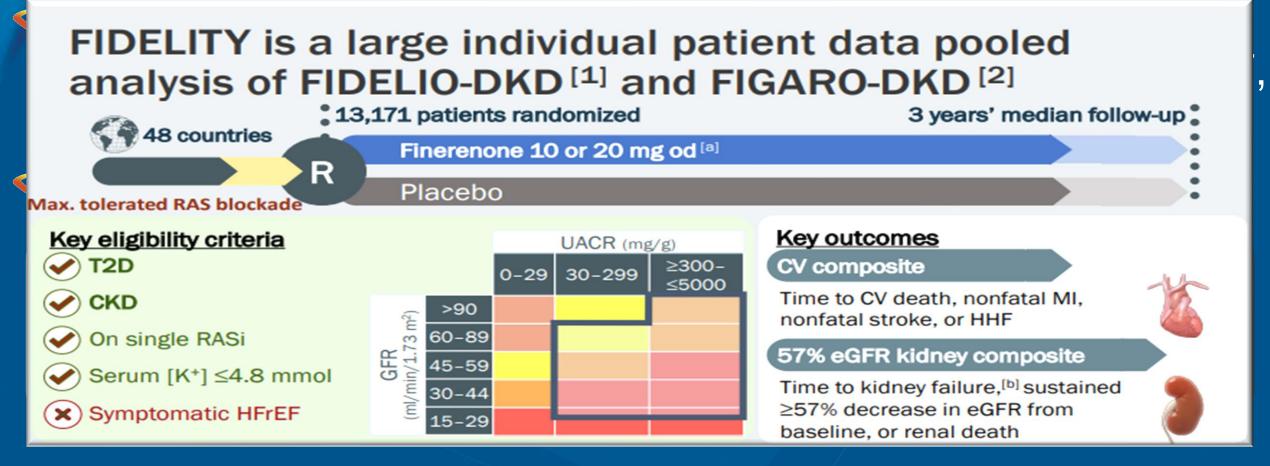
Outcome	No. studies	No. events	Sample size	HR (95% CI)
MACE	6	2271	21,913	0.83 (0.75-0.93)
Kidney composite	5	1197	21,195	0.66 (0.58-0.75)
HHF	6	1219	22,346	0.62 (0.55-0.71)
Cardiovascular death	5	953	20,539	0.84 (0.74-0.96)
Fatal and nonfatal MI	5	498*	20,108	0.78 (0.67-0.92)
Fatal and nonfatal stroke	5	332*	20,108	0.76 (0.59-0.97)
All-cause mortality	5	1451	21,406	0.86 (0.77-0.96)

Meta-Analysis of 13 SGLT2i Trials

Data Analysis of 13 SGLT2i Trials Involving 90,000
 Participants With & Without Type 2 Diabetes Or At Risk for CVD, HF, CKD.

Main Safety: 2.12 RR Ketoacidosis T2DM on SGLT-2i, Amputation 1.06 RR (95% CI, 0.93 – 1.21)

Fidelity Summary & Conclusions



- Significant Reduction Incidence of hHF / New Onset AF
- Modest BP Effects (3.7 mmHg)
- Manageable Increase Hyperkalemia w Minimal Clinical Impact



Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice





Cardiovascular and kidney outcomes of combination therapy with sodium-glucose cotransporter-2 inhibitors and mineralocorticoid receptor antagonists in patients with type 2 diabetes and chronic kidney disease: A systematic review and network *meta*-analysis



36,186 Patients. Meta-Analysis. Combination of SGLT-2i's + MRA's Reduced Composite CV / Renal Events With Less Hyperkalemia Compared to SGLT-2i's or MRA's Alone



Cornerstone Treatments Diabetic Kidney Disease

Risk Factors
Management:

Plasma
Glucose
Blood Pressure
Weight Control
Smoking
Cessation
Lipid Control
Physical
Activity

ACEI/ARBs

Captopril IDNT RENAAL

ACE / ARB Max Tol Dose SGLT2i

CREDENCE DAPA-CKD SCORED EMPA -Kidney

Now

MRAs

FIDELIO-DKD FIGARO-DKD

New

GLP-1 RA

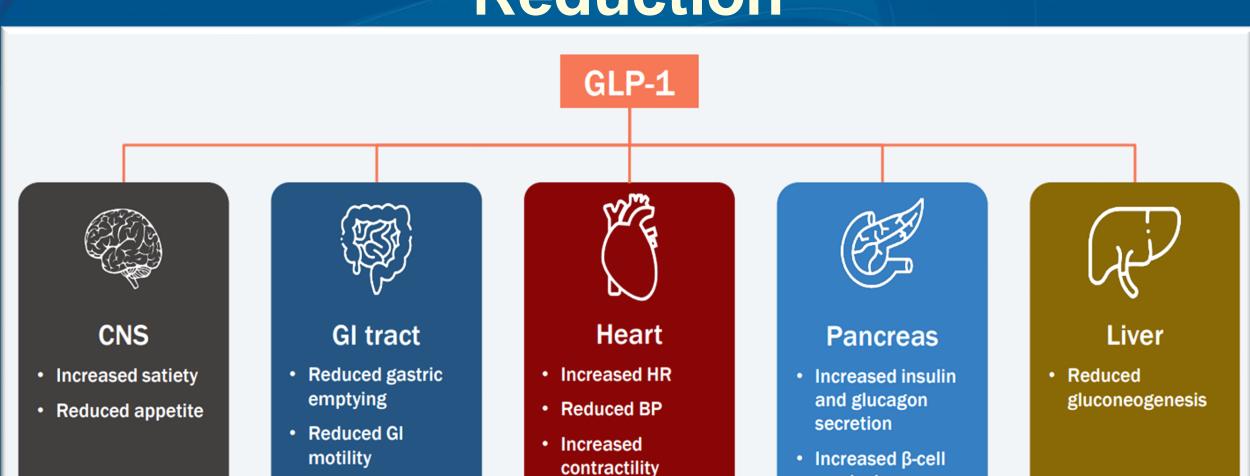
FLOW

Next?

Lewis et al., NEJM 1993, Lewis et al., NEJM 2001, Brenner et al., NEJM 2001, Perkovic et al., NEJM 2019, Bhatt et al., NEJM 2021, Bakris et al., NEJM 2020



GLP-1 RA Benefits Extend Beyond MACE Reduction





survival

The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease

Background

Evidence has emerged of potential kidney-protective effects of GLP-1RAs in people with T2D. FLOW is a dedicated kidney outcomes trial to assess semaglutide in a population with CKD and T2D at high risk of kidney disease progression.

Methods

Participants:



- Adults with T2D
- eGFR \geq 50 to \leq 75 ml/min/1.73 m² and UACR >300 to <5000 mg/g OR
- eGFR ≥ 25 to < 50 ml/min/1.73 m² and UACR > 100 to < 5000 mg/g

Composite primary endpoint:



Time to first occurrence of:

- Kidney failure (persistent eGFR <15 ml/ min/1.73 m² or initiation of CKRT);
- Persistent ≥50% reduction in eGFR; or
- Death from kidney or CV causes



Baseline characteristics



68.2% at very high risk for CKD progression according to KDIGO categorisation, eGFR of 47.0 (15) ml/min/1.73 m²; median UACR of 568 (range: 2-11 852) mg/g



Advanced type 2 diabetes:

Mean age 66.6 years Mean diabetes duration 17.4 years Mean HbA₁₆ 7.8%



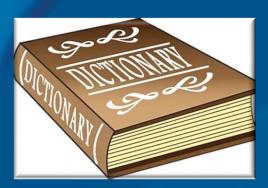
CKD, chronic kidney disease; CKRT, chronic kidney replacement therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA, ,, glycosylated haemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; OW, once weekly; s.c., subcutaneous; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; W, week.

Conclusion

FLOW will evaluate the effect of semaglutide on kidney outcomes in participants with CKD and T2D, and is expected to complete in late 2024.



What Is The Enemy? Winning The WAR



<u>Clinical Inertia</u>: (Noun) A Tendency To Do Nothing Or Remain Unchanged. Failure to Initiate / Intensify Rx Where A Patient's Health Would Likely Improve By Such. <u>Synonyms</u>: Inactivity,

More Work For Me

He / She Has 'Mild' Diabetes Why
Should I
Change
Anything?
...Doing
Fine

My Patient Is Stable On Current Therapy

Inconvenient For Him / Her

'Clinical Trials & Drug Discovery Are Only Part of the Overall Solution. The Knowledge Gained Needs to be Translated into Patient Care—Something We Have Done Poorly With ARNIs, a Class of Agents with a 20% Reduction in Mortality. If We Are to Win the War Against Cardio-Renal- Metabolic Syndrome, Science Will Need to be Coupled With Pragmatic & Deliberate Implementation Approaches With the Goal of Overcoming Inertia"

Think About Ways To
Overcome Clinical Inertia
As One Of Our Biggest
Impediments In
Knowledge Translation

Inaction, Inertness,

Passivity

Bhatt. Cell Metab. 2019;30:847.



"Traditional Wisdom is Short on Wisdom and Long on Tradition"

Mark Twain

"We Can't Solve Problems Using the Same Kind of Thinking We Used When We Created Them."

Albert Einstein



