TARGETING THE AUTONOMIC NERVOUS SYSTEM TO REDUCE CARDIOVASCULAR RISK IN T2DM THERAPY.

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Prevalence of Autonomic Neuropathy Rises with the Prevalence of Diabetes

ARE WE HURTIMG PEOPLE WITH INTENSIFICATION OF GLYCEMIC CONTROL????
AUTONOMIC IMBALANCE AN EMERGING RISK

Diabetes Prevalence Categories

1. DCCT Study Group, Diabetologia, 1998, 41:416
CLASSES OF GLUCOSE LOWERING AGENTS FOR TREATING TYPE 2 DIABETES

- Sulfonylureas
- Metformin
- Human Insulin
- Alpha-glucosidase Inhibitors
- Thiazolidinediones
- Insulin Analogues
- GLP-1 Receptor Agonists
- Glinides
- DPP-4 Inhibitors
- Inhaled Insulin
- Pramlintide
- SGLT2 Inhibitors
- Bromocriptine
- Colesevelam

“All who drink of this treatment recover in a short time. Except for those who died. Thus, it appears to be effective in all but the incurable cases.”

Galen

Too Many Notes: Up and Down the Scales of Diabetic Therapy

Aaron Vinik MD Guest Editor; Clinical Therapeutics
Autonomic Nerve Dysfunction: The Crystal Ball of Cardiovascular Risk and Brittle Diabetes.
# Effect of Intensive Glucose Lowering on Macrovascular Complications of Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>VADT&lt;sup&gt;1&lt;/sup&gt; (n=1700)</th>
<th>ACCORD&lt;sup&gt;2&lt;/sup&gt; (n=10250)</th>
<th>ADVANCE&lt;sup&gt;3&lt;/sup&gt; (n=11140)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c – Std vs. Intensive</strong></td>
<td>8.4 vs. 6.9</td>
<td>7.5 vs. 6.5</td>
<td>7.3 vs. 6.5</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td></td>
<td></td>
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<tr>
<td>CVD death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hazard Ratio for primary outcome (95% CI)</strong></td>
<td>0.87 (0.730 – 1.04)</td>
<td>0.90 (0.78 – 1.04)</td>
<td>0.94 (0.84 – 1.06)</td>
</tr>
<tr>
<td><strong>Hazard Ratio for mortality (95% CI)</strong></td>
<td>1.065 (0.801 – 1.416)</td>
<td>1.22 (1.01 – 1.46)</td>
<td>0.93 (0.83 – 1.06)</td>
</tr>
</tbody>
</table>


*P=0.04
### Evidence for CAN as a Contributor to All-Cause Mortality in the ACCORD Participants

<table>
<thead>
<tr>
<th>HRV Measure</th>
<th>Adjusted for Treatment Allocation, CVD History and other Covariates *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (CAN + / CAN -)</td>
</tr>
<tr>
<td>CAN 1</td>
<td>1.55</td>
</tr>
<tr>
<td>CAN 2</td>
<td>2.14</td>
</tr>
<tr>
<td>CAN 3</td>
<td>2.07</td>
</tr>
</tbody>
</table>

- Proportional Hazards Models used to assess CAN effects on mortality

* Other covariates: baseline values of age, gender, ethnicity, diabetes duration, HbA1c, BMI, SBP, DBP, LDLc, triglycerides, HDLc, UA/CR ratio, retinopathy, amputation, and use of TZD, insulin, beta-blockers, ACEi, ARBs, statins, alcohol and cigarettes

Pop-Busui et al, Diabetes Care, 2010, 33:1578-84
DIAD Study: Polyneuropathy and Cardiac Autonomic Neuropathy (CAN) Predict Cardiac Death/MI over 5 years

Routine Screening for CAD in asymptomatic type 2 diabetic patients
Primary endpoint: cardiac death or non-fatal myocardial infarction

<table>
<thead>
<tr>
<th>Event / No event</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 (53%) / 228 (21%)</td>
<td>4.33</td>
</tr>
<tr>
<td>9 (28%) / 127 (12%)</td>
<td>2.83</td>
</tr>
<tr>
<td>7 (22%) / 122 (11%)</td>
<td>2.36</td>
</tr>
</tbody>
</table>

Adjusted HR (95% CI)

Young et al., JAMA 2009; 301: 1547-55
The Role of Somatic and Autonomic Neuropathy in Accord and DIAD Studies

- **Baseline CAN**
  - 1.55-2.14 times as likely to die compared to individuals without CAN

- **CAN in the presence of DPN**
  - HR for sudden death 2.95 \( p=0.008 \)

- **DIAD study**
  - Loss of change from lying to standing a measure of parasympathetic function \( HR=4.33 \)

Vinik, Maser, Ziegler Diabetes Care 33, July 2010
Relative Risk of Mortality from CAN

Prevalence Rate Ratios and 95% CI from 15 Studies; p<0.0001; n=2900

2.14 (1.83-2.51) Pooled data
3.45 if > 2 abnormalities CAN

Vinik et al., Diabetes Care 26: 1553-79, 2003
Sudden death isn’t so bad. Anyone who has spent an evening with an insurance salesman knows this.

Woody Allen
Metabolic Memory and Glycemic Legacy. Megatrials in Diabetes: from Excitement to Frustration

Start of intensive therapy in UKPDS

Ideal course = early and sustained glycemic control

Start of intensive therapy in VADT

Drives risk of Complications

Risk of complications continues despite glycemic control

Persons More or Less likely to Have Bad Legacy and Events with Intensification of Treatment

- **Albumin:creatinine >300:** HR 1.74 (95% CI: 1.37-2.21)
- **African American:** HR 1.43 (95% CI: 1.20-1.71)
- **BMI > 30:** HR 0.65 (95% CI: 0.50-0.85)
- **Long Duration >12-15 y of Diabetes:** HR 1.03 (95% CI: 1.02, 1.05)
- **Every 1 yr increase in age:** HR 1.03 (95% CI: 1.02-1.43)
- **Autonomic Nerve Dysfunction:** HR 4.43
- **Numb feet:** HR 2.8
- **Coronary Artery Disease or calcification:** HR Risk =2-4 X
- **Previous Hypoglycemic Event:** HR 3.3
- **Women:** HR 1.21 (95% CI: 1.02-1.43)
# Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↓</td>
<td>←</td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td>↓</td>
<td>↓</td>
<td>←</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
</tbody>
</table>

Kendall DM, Bergenstal RM. © International Diabetes Center 2009

Recent trials of newer glucose-lowering agents have been neutral on the primary CV outcome.

- **SAVOR-TIMI 53**: HR: 1.0 (95% CI: 0.89, 1.12)
- **EXAMINE**: HR: 0.96 (95% CI: UL ≤ 1.16)
- **TECOS**: HR: 0.98 (95% CI: 0.88, 1.09)
- **ELIXA**: HR: 1.02 (95% CI: 0.89, 1.17)
- **EMPA-REG OUTCOME**: HR: 1.02 (95% CI: 0.89, 1.17)

**CV**, cardiovascular; **HR**, hazard ratio; **DPP-4**, dipeptidyl peptidase-4
*Saxagliptin, alogliptin, sitagliptin*

Adapted from Johansen OE. World J Diabetes 2015;6:1092-96
Hospitalisation for heart failure

Cumulative incidence function. HR, hazard ratio
Empagliflozin Modulates Several Factors Related to CV Risk

- Reduced BP
- Reduced arterial stiffness
- Reduced albuminuria
- Reduced uric acid
- Reduced glucose
- Reduced insulin
- Reduced sympathetic nervous system activity
- Reduced weight
- Reduced visceral adiposity
- Reduced oxidative stress
- Increased HDL-C
- Increased LDL-C
- Increased triglycerides

Adapted from Inzucchi SE, Zinman, B, Wanner, C et al. Diab Vasc Dis Res 2015;12:90-100
 CONTRASTING INFLUENCES OF RENAL FUNCTION ON BLOOD PRESSURE AND HBA1C REDUCTIONS WITH EMPAGLIFLOZIN IN PATIENTS WITH TYPE2 DIABETES AND HYPERTENSION (Decreased BP > than A1c)

 D. Cherney1, M. Cooper2, I. Tikkanen 3, S. Crowe4, O. E. Johansen 5, S. S. Lund4,

 THE SGLT2 INHIBITOR EMPAGLIFLOZIN REDUCES BLOOD PRESSURE AND MARKERS OF ARTERIAL STIFFNESS AND VASCULAR RESISTANCE IN TYPE2 DIABETES

 R. Chilton 1, I. Tikkanen 2, C. P. Cannon3, S. Crowe4, T. Hach4, H.

 EMPAGLIFLOZIN REDUCES SYSTOLIC BLOOD PRESSURE IN DIPPER AND NON-DIPPER PATIENTS WITH TYPE2 DIABETES AND HYPERTENSION

 R. Chilton 1, I. Tikkanen 2, S. Crowe3, O. E. Johansen 4, U. C. Broedl 3,

 These Effects may be a reflection of SGLT2 actions on the ANS. The EMPA-REGOUTCOME TM trial (NCT01131676) will evaluate whether these benefits will translate into cardiovascular risk reduction.
## Incidence of MI and HF in clinical trials in T2D:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Mean F/U (y)</th>
<th>HF Events/1000 person y</th>
<th>MI Events/1000 person y</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>Newly Diagnosed T2D</td>
<td>10</td>
<td>3.0</td>
<td>16.4</td>
</tr>
<tr>
<td>ACCORD</td>
<td>T2D + CVD or CV risk factors</td>
<td>3.5</td>
<td>7.7</td>
<td>11.7</td>
</tr>
<tr>
<td>BARI-2D</td>
<td>T2D + Stable CAD</td>
<td>5.3</td>
<td>40.1</td>
<td>17.6</td>
</tr>
<tr>
<td>TREAT</td>
<td>T2D + CKD + Anemia</td>
<td>2.4</td>
<td>44.3</td>
<td>16</td>
</tr>
<tr>
<td>SAVOR</td>
<td>T2D + CVD or CV risk factors</td>
<td>2.1</td>
<td>31.3</td>
<td>32.9</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>T2D + CVD</td>
<td>3.1 (median)</td>
<td>9.4</td>
<td>16.8</td>
</tr>
<tr>
<td>LEADER®</td>
<td>T2D + CVD or CV risk factors</td>
<td>3.8 (median)</td>
<td>12</td>
<td>16</td>
</tr>
</tbody>
</table>

“My mind sent a message to my hypothalamus, told it to release the hormone CRF into the short vessels connecting my hypothalamus and my pituitary gland. The CRF inspired my pituitary gland to dump the hormone ACTH into my bloodstream. My pituitary had been making and storing ACTH for just such an occasion, and nearer and nearer the zeppelin came. And some of the ACTH in my bloodstream reached the outer shell of my adrenal gland, which had been making and storing glucocorticoids for emergencies. My adrenal gland added the glucocorticoids to my bloodstream. They went all over my body, changing glycogen into glucose. Glucose was muscle food. It would help me fight like a wildcat or run like a deer.
The Autonomic Nervous System

Spectral Analysis of Heart Rate Variability

Very low-frequency (VLF) band [0.003-0.04 Hz]
Thermoregulatory activity: sympathetic

Low-frequency (LF) band [0.04-0.15 Hz]
Baroreceptor activity: parasympathetic & sympathetic

High-frequency (HF) band [0.15-0.4]
Respiratory activity: parasympathetic

Time: The SDNN of all normal R-R intervals (sdNN), =S and PS action on HRV,
The root-mean square of the difference of successive R-R intervals (RMSSD) : parasympathetic
QTc >440 ms

The Yin and Yang of the Autonomic Nervous System

Ventricular Function and Autonomic Imbalance

- **Ventricular function.** Abnormal left ventricular responses to exercise in patients with CAN.
- Depressed left ventricular systolic function in the absence of ischemic heart disease in approximately one-third of patients with autonomic neuropathy.
- Reduced mean ejection fractions at rest and with maximal exercise
- Abnormal diastolic function has been found in patients with more severe CAN.
- This finding was correlated with a reduction in catecholamine levels and postural hypotension, indicating sympathetic involvement with cardiac diastolic dysfunction.

Heart Rate as a Predictor of CVD


- patients with established stable heart, diabetes >55y, n=31531

- Compared heart disease patients with heart rate >78 bpm vs. <58 bpm

  - 39 percent increased risk of major vascular event,
  - 77 percent increased risk of cardiovascular disease death,
  - 65 percent increased risk of all-cause death
  - twice as likely to be hospitalized.
Increase in Heart Rate Associated with Risk of Death From Heart Disease

- Population based group of 13,499 men and 15,826 women in Norway without known CVD
- HR measured at entry and 10 y later
- After 12 year follow up:
  - 3,038 died: 975 CVD and 388 IHD
- Resting HR <70bpm increased to 85bpm
  - 90% increased risk of death from IHD
- Resting HR 70-85bpm increasing > 85 bpm,
  - 80% increased risk of death from IHD,

Autonomic Imbalance as a Predictor of Metabolic Risks, Cardiovascular Disease, Diabetes, and Mortality

- **Objectives:** to examine the contribution of autonomic imbalance, resting heart rate (RHR) and heart rate variability (HRV) on the development of five metabolic risk outcomes, and on cardiovascular disease, diabetes, and early mortality.

- **Design:** Secondary analysis of prospective data from Offspring Cohort participants (N 1882) in the Framingham Heart Study (FHS). Participants at FHS Exam 3 (1983–1987) with 1) age years 18 or older, and 2) data on RHR, HRV, and five measures of metabolic risk (blood pressure, fasting glucose, triglycerides, high-density lipoprotein [HDL] cholesterol, and body mass index [BMI]) at three follow-up visits over 12 years.

- **Result:** Autonomic Imbalance Predicts CVD, DM, MI and All Cause Mortality refutes the age old reliance on the Framingham Risk Calculator

Abnormal heart rate recovery at 1 minute after Treadmill Max <18 beats/minute (35%)
Hazard ratios for the Composite Event According to abnormal exercise treadmill testing parameters adjusted for age, sex.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest HR &gt;100/min</td>
<td>2.04 (1.24–3.37)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>HRR1 &lt; 18 beats</td>
<td>1.77 (1.12–2.81)</td>
<td>0.015</td>
</tr>
<tr>
<td>Chrono incomp</td>
<td>1.89 (1.18–3.01)</td>
<td>&lt;0.008</td>
</tr>
</tbody>
</table>

Zafrir et al European Journal of Preventive Cardiology 2015
Restoring Autonomic Balance

- Lifestyle Intervention
- Medications
Therapy for Diabetic Autonomic Imbalance

- Prevention DCCT
- Functional
  - Beta Blockers, Anti cholinergics, pyridostigmine
  - Exercise
  - Use of percent heart rate reserve/ rate of perceived exertion
- Prospects for reversal
  - ACE inhibitors
  - Beta Blockers
  - Calcium Channel Antagonists
  - Alpha-lipoic acid
  - Aldose reductase inhibitors
  - Neurotrophic Agents
  - Intensive staged treatment
**Specific Therapies for Autonomic Imbalance**

- **Physical Training**
  - Endurance training improves HRV in patients with minimal abnormalities
    - Havorka et al Cardiac Res 97, 34: 206-214
  - Use of perceived exertion to prescribe exercise intensity in diabetic autonomic neuropathy
  - Chronic Exercise is Associated with enhanced cutaneous blood flow in type 2 diabetes.
  - Exercise restores cutaneous innervation in prediabetic neuropathy Smith, Singleton
Effect of Dog Walking on Vagal Activity in Senior Citizens

Motooka et al., MJA 2006; 184: 60-63
Restoration of Autonomic Balance

SE, β-blocker

SW, Vasopressor

PE, Anti-Cholinergic

N=57

N=185

N=50

Vinik, Maser, Ziegler Diabetic Medicine 2010 Prophet of Doom or Hope
Drug Effects on Mortality in CHF Patients

Realization of the importance of the brain in regulating metabolism

“The last and perhaps most important player to be implicated in the pathogenesis of type 2 diabetes is the brain…”

- Preclinical studies have shown that cerebral insulin resistance leads to increased HGP and reduced muscle glucose uptake.
- An MRI study in humans has shown that hypothalamic inhibition of appetite following glucose ingestion was reduced and delayed in obese, insulin-resistant subjects, despite an increased plasma insulin response.
- Whether the impairment in hypothalamic response in obese subjects contributes to or is a consequence of the insulin resistance and weight gain remains to be determined. The hypothalamus of diabetic humans have a reduction in GLP-1 Receptors.
Morning administration (within 2 hours of waking) of Bromocriptine Corrects Low dopaminergic tone in hypothalamus in early morning in diabetes

 Restoration of morning peak in dopaminergic activity (via D2 receptor-mediated activity)

Sympathetic tone
HPA axis tone
Hepatic gluconeogenesis
FFA and TG
Insulin resistance
Inflammation/hypercoagulation

Impaired glucose metabolism, hyperglycemia and insulin resistance
Adverse cardiovascular pathology

Decreased postprandial glucose levels
Reduction in insulin resistance
Day-long reduction in plasma glucose, TGs and FFAs

Fonseca. Use of Dopamine agonists in Type-2-Diabetes. Oxford American Pocket Cards. OUP, 2010
## Impact of Bromocriptine-QR on CV Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Bromocriptine-QR (N=2054), n (%)*</th>
<th>Placebo (N=1016), n(%)*</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death-inclusive composite cardiovascular end point</td>
<td>39 (1.9)</td>
<td>33 (3.2)</td>
<td>0.61 (0.38 to 0.97)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (0.3)</td>
<td>9 (0.9)</td>
<td>0.41 (0.15 to 1.11)</td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (0.2)</td>
<td>6 (0.6)</td>
<td>0.44 (0.13 to 1.43)</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>9 (0.4)</td>
<td>9 (0.9)</td>
<td>0.52 (0.21 to 1.30)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>9 (0.4)</td>
<td>6 (0.6)</td>
<td>0.77 (0.27 to 2.16)</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>11 (0.5)</td>
<td>8 (0.8)</td>
<td>0.72 (0.29 to 1.80)</td>
</tr>
<tr>
<td>CV death</td>
<td>4 (0.2)</td>
<td>2 (0.2)</td>
<td>0.48 (0.07 to 3.43)</td>
</tr>
<tr>
<td>Coronary revascularization following a primary end point (ie, CABG after MI)</td>
<td>9 (0.4)</td>
<td>11 (1.1)</td>
<td>0.43 (0.18 to 1.03)</td>
</tr>
<tr>
<td>MACE composite—myocardial infarction, stroke, CV death</td>
<td>14 (0.7)</td>
<td>15 (1.5)</td>
<td>0.48 (0.23 to 1.00)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CV, cardiovascular; CABG, coronary artery bypass graft; MACE, major cardiovascular adverse event; MI, myocardial infarction. *Percentage of events per total number per group: 2054 bromocriptine-QR, 1016 placebo.

Circadian Timed Bromocriptine-QR Reduces Elevated Heart Rate in T2DM Subjects

Chamarthi B, Vinik AI, Ezrokhi M, Cincotta AH. Dopamine agonist therapy reduces elevated heart rate and dysglycemia in Type 2 diabetes subjects. Diabetes. 2016;65(Suppl1):A317

Heart rate data derived from a subset of Cycloset Safety Trial subjects with baseline HbA1c ≥ 7.5

- Baseline RHR is a significant positive predictor of BQR-induced RHR reduction (β = -0.30, P=0.02) in subjects with baseline RHR ≥ 70
- The magnitude RHR reduction is an independent predictor of the magnitude of HbA1c reduction in subjects with baseline RHR ≥ 70 treated with B-QR.

Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>B-QR (n=55)</th>
<th>Placebo (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.1±1.4</td>
<td>60.0±1.2</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>73%</td>
<td>60%</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>60%</td>
<td>57%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.2±0.7</td>
<td>32.4±0.8</td>
</tr>
<tr>
<td>Duration of Diabetes (yrs)</td>
<td>7.5±0.6</td>
<td>8.8±1.2</td>
</tr>
<tr>
<td>Fasting Glucose (mg/dL)</td>
<td>157±5</td>
<td>168±6</td>
</tr>
<tr>
<td>Resting Heart Rate (bpm)</td>
<td>60±0.8</td>
<td>61±0.9</td>
</tr>
<tr>
<td>Systolic BP (mm/Hg)</td>
<td>132±2</td>
<td>135±2</td>
</tr>
<tr>
<td>Diastolic BP (mm/Hg)</td>
<td>79±1</td>
<td>77±2</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>69±1.8</td>
<td>69±2.1</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.14±0.02</td>
<td>1.14±0.03</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SEM for continuous variables and % for categorical variables.
Dopamine Agonist Therapy with Bromocryptine (BQR) Reduces Elevated Heart Rate and Dysglycemia in Type 2 Diabetes

- bRHR > 70 bpm (n=61 BQR) vs Placebo N=61)
  - BQR - 4 bpm vs placebo + 1.5 bpm p=0.003
  - RHR > 80 bpm (n=32) BQR - 9 bpm vs placebo + 2 bpm) p=0.004

- bRHR
  - <70 bpm A1c - 0.61 (p<0.009)
  - >70 bpm A1c - 0.71 (p<0.007)
  - >80 bpm A1c -1.13 p=0.01

- These findings support a sympatholytic mechanism for both reduction of RHR and A1c supporting the CVD event reduction.

Chamarthi, Vinik, Ezrohki and Cincotta ADA 2016, A 4306 Diabetes
CVD Risk Reduction With T2DM Therapies
Comparison of LEADER (Liraglutide), SUSTAIN-6 (Semaglutide), EMPA-REG (Empagliflozin) and Cycloset Safety Trial (Bromocriptine-QR)

Percent Reduction of Composite CVD Endpoint
(non fatal MI, non-fatal stroke, CV death, coronary revascularization, or hospitalization for unstable angina or heart failure*)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>% Risk Reduction</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>-10.5</td>
<td>0.88 (0.81-0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>-12</td>
<td>0.74 (0.62-0.89)</td>
<td>0.002</td>
</tr>
<tr>
<td>Empagliflozin*</td>
<td>-10</td>
<td>0.89 (0.78-1.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Bromocriptine-QR</td>
<td>-25</td>
<td>0.61 (0.38-0.97)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* EMPA-REG (empagliflozin trial) did not include hospitalization for heart failure in the composite
Effects of Liraglutide on Diurnal variation in hourly mean HR.

Kumarathurai P et al., Diabetes Care, Accepted 20 September 2016, DOI: 10.2337/dc16-1580.
SDNN changes during treatment periods in placebo and liraglutide treated patients.

Kumarathurai P et al., Diabetes Care, Accepted 20 September 2016, DOI: 10.2337/dc16-1580.
Effects of Bromocryptine on A1c based upon Resting Heart Rate

- Analysis of HbA1c reduction as a function of bRHR demonstrated HbA1c reductions with BQR vs P as follows:
  - < 70 BPM: -0.62 (P=0.009);
  - > 70 BPM: -0.71 (P=0.007),
  - > 80 BPM: -1.13 (P=0.01).

- The magnitude of RHR reduction is an independent predictor of the magnitude of HbA1c reduction with BQR but not P therapy ($\beta = 0.47$, P=0.001).

BINDU CHAMARTHI, AARON I. VINIK, MICHAEL EZROKHI, ANTHONY H. CINCOTTA ADA 2016
Effects of Bariatric Surgery on Heart Rate

Non-DM
Pre-DM
T2DM

Baseline Week 4 Week 12 Week 24 p value
Non-DM 77.92 ± 2.71 74.61 ± 2.27 68.38 ± 2.17 68.05 ± 2.48 <0.01
Pre-DM 75.39 ± 1.92 76.48 ± 2.00 72.89 ± 2.04 69.04 ± 2.16 <0.01
T2DM 77.35 ± 3.05 73.06 ± 2.48 67.31 ± 2.53 65.76 ± 2.05 <0.001

Casellini et al PLOS 1 2016
Pathogenesis Oriented Treatment
### Intensive Multifactorial Intervention in Type 2 Diabetes at 7.8y

<table>
<thead>
<tr>
<th>Complication</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephropathy</td>
<td>0.27</td>
</tr>
<tr>
<td>Autonomic Neuropathy</td>
<td>0.32</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments

“The antioxidant α-lipoic acid is the only pathogenetic treatment that has efficacy confirmed from several randomized controlled trials and confirmation in a meta-analysis (level A evidence).”

Tufaye et al., Diabetes Care 2010; 33: 2285–2293
**Diakan and NATHAN’s Studies**

α-Lipoic Acid (800 mg/day) for 4 months Improves Heart Rate Variability
and 600 mg/day for 4 y improves somatic neuropathy (NISLL +7)

Root Mean Squared Successive Difference (RMSSD)

- **Month 2**
  - α-Lipoic acid (n=27)
  - Placebo (n=26)

- **Month 4**
  - Nathan 600 mg/day, (n=233 vs placebo n=227)
  - 4 years

* p<0.05 vs Placebo

Fulfilling NATHAN’s Prophecy
Papanas and Maltezos
Angiology, 63, 81, 2012

Ziegler et al., Diabetes Care, 1997
Ziegler, Low, Litchy, Boulton, Vinik, Freeman et al, Diabetes Care 34: 1-7, 2011
The Paradigm Shift in the Management of Type 2 Diabetes

**Psychosocioeconomic Considerations**
- Highly Motivated, Adherent, Knowledgeable, Excellent Self-Care Capacities, Comprehensive Support Systems
- Less Motivated, Nonadherent, Limited Insight, Poor Self-Care Capacities, Weak Support Systems

**Hypoglycemia Risk**
- Low
- Moderate
- High

**Patient Age**
- 40
- 45
- 50
- 55
- 60
- 65
- 70
- 75

**Disease Duration**
- 5
- 10
- 15
- 20

**Other Comorbidities**
- None
- Few/Mild
- Multiple/Severe

**Established Neuro Vascular Complications**
- None

The major cause of CV complication and mortality remains heart disease. Cardiovascular events and heart failure is predicated upon by autonomic neuropathy and autonomic imbalance. The Framingham risk predictor can be put to rest. Efferent signals mediated by sympathetic/parasympathetic imbalance with sympathetic dominance or parasympathetic deficiency appear to be central to the pathogenesis of cardiac events. Rebalancing the ANS with exercise and autonomic agents is feasible. A central dopamine deficiency unbridles sympathetic function unleashing glycolysis, lipolysis, neoglucogenesis and ketogenesis. Insulin increases anorexigenic tone, hedonic behavior, and overall feeding homeostasis. Timed release of dopamine agonism with Bromocryptine can overcome this effect. These findings support a sympatholytic mechanism for 1) BQR induced reduction of both RHR and HbA1c in subjects with elevated RHR and 2) BQR's demonstrated impact to lower CVD events.