Heart failure in diabetics: Risk stratification and new treatments

Ignatios Ikonomidis MD, PhD, FESC
Director of Echocardiography and Laboratory of Preventive Cardiology
Associate Professor in Cardiology, NKUA, Medical School, Attikon Hospital, Athens Greece
### Table 5  Burden of DM in Europe in 2011 and predictions for 2030

<table>
<thead>
<tr>
<th>Variable</th>
<th>2011</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (millions)</td>
<td>896</td>
<td>927</td>
</tr>
<tr>
<td>Adults (20–79 years; millions)</td>
<td>651</td>
<td>670</td>
</tr>
<tr>
<td><strong>DM (20–79 years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European prevalence (%)</td>
<td>8.1</td>
<td>9.5</td>
</tr>
<tr>
<td>Number with DM (millions)</td>
<td>52.6</td>
<td>64.0</td>
</tr>
<tr>
<td><strong>IGT (20–79 years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional prevalence (%)</td>
<td>9.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Number with IGT (millions)</td>
<td>62.8</td>
<td>71.3</td>
</tr>
<tr>
<td><strong>Type 1 DM in children (0–14 years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number with type 1 DM (thousands)</td>
<td>115.7</td>
<td>–</td>
</tr>
<tr>
<td>Number newly diagnosed/year (thousands)</td>
<td>17.8</td>
<td>–</td>
</tr>
<tr>
<td><strong>DM mortality (20–79 years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths: men (thousands)</td>
<td>281.3</td>
<td>–</td>
</tr>
<tr>
<td>Number of deaths: women (thousands)</td>
<td>316.5</td>
<td>–</td>
</tr>
<tr>
<td><strong>Healthcare expenditure due to DM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(20–79 years, Europe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total expenditure (billions of €)</td>
<td>75.1</td>
<td>90.2</td>
</tr>
</tbody>
</table>
Prevalence
DM and CVD
two
faces of the same coin
Diabetes mellitus

Hyperglycemia

Free fatty acids

Insulin resistance

Oxidative stress
Protein kinase C activation
RAGE activation

Endothelial layer

Vasoconstriction
Hypertension
VSMC growth

Inflammation
Chemokines (e.g., MCP-1)
Cytokines (e.g., IL-1)
CAMS (e.g., ICAM-1)

Thrombosis
Hypercoagulation
Platelet activation

Macrovascular complications of type 2 diabetes

- 80% of people with type 2 diabetes die from CVD
  - Peripheral vascular disease
    - e.g. intermittent claudication, gangrene, amputations
  - Cerebrovascular disease
    - e.g. stroke, transient ischaemic attacks
    - 2- to 4-fold increased mortality risk
  - Coronary heart disease
    - e.g. angina, heart attack, heart failure
    - 2- to 4-fold increased mortality risk

Framingham Heart Study

Risk of CVD events in patients with diabetes relative to non-diabetic subjects

- Any CVD event
- Stroke
- Intermittent claudication
- Cardiac failure
- Coronary heart disease
- Myocardial infarction
- Angina pectoris
- Sudden death
- Coronary mortality

*Risk of CVD events in patients with diabetes relative to non-diabetic subjects

*p<0.001; †p<0.05; ‡p<0.01; §p<0.1

Adapted from Kannel. *Am Heart J* 1990;120:672–6
Congestive heart failure is more common in patients with type 2 diabetes

*Prevalent CHF defined as any inpatient/outpatient diagnosis of CHF (identified from the electronic medical records of those diagnosed with T2D prior to January 1, 1997)
†Incident CHF cases identified as those presenting without a baseline diagnosis of CHF (search carried forward from January 1, 1997 for 30 months)
CHF, congestive heart failure; NGT, normal glucose tolerance; T2D, type 2 diabetes

Adapted from Nichols et al. Diabetes Care 2001;24:1614–9
Glycaemic control and risk of developing heart failure in diabetes

Adapted from Iribarren et al. Circulation 2001;103:2668–73
DM in patients with HF

Clinical Trial                        Diabetic Patients

SOLVD                        25.8%
MERIT-HF                    24.5%
ELITE II                   24.0%
Val-HeFT                 25.4%
COPERNICUS          25.7%
OPTIME-CHF (hospitalized)  44.2%
VMAC (hospitalized)       47.0%

Thrainsdottir et al. 2005;28:642
Acute heart failure in patients with diabetes mellitus: Clinical characteristics and predictors of in-hospital mortality

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diabetics</th>
<th>Non diabetics</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>11.7%</td>
<td>9.8%</td>
<td>0.01</td>
</tr>
<tr>
<td>Discharge home</td>
<td>63.8%</td>
<td>61.7%</td>
<td></td>
</tr>
<tr>
<td>Discharge to rehabilitation facility</td>
<td>5.2%</td>
<td>5.5%</td>
<td></td>
</tr>
<tr>
<td>Discharge to care facility</td>
<td>6.0%</td>
<td>6.5%</td>
<td></td>
</tr>
<tr>
<td>Internal ICU transfer</td>
<td>9.6%</td>
<td>11.2%</td>
<td></td>
</tr>
<tr>
<td>Transfer to other hospital</td>
<td>3.8%</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td>Functional status on discharge</td>
<td></td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>NYHA I–II</td>
<td>64%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>NYHA III–IV</td>
<td>36%</td>
<td>33%</td>
<td></td>
</tr>
</tbody>
</table>


ALARM Registry, Parissis J, Ikonomidis I et al. Int J Cardiol 2012
DM and heart failure (1)

- DIABHYCAR trial: heart failure (HF) was a major cause of hospitalization in patients with T2DM.
- BEST trial: T2DM increased the risk of hospitalization in patients with HF.
- MERIT-HF: patients with HF and T2DM had one-year hospitalization of 31%, compared with 24% for those free from DM.
Incidence of fatal or non-fatal MI by diabetes and CV status during a 7-year follow-up in Finland

*No previous MI at baseline
MI, myocardial infarction

Tests for CAD

Asymptomatic Diabetic Patients With Other Risk Factors

Symptomatic - Pre-Test Probability

Low (<15%)
Intermediate (15%-50%)
Intermediate-High (>50%)

EBCT/CIMT

CCS <400 or IMT <1mm
CCS ≥400 or IMT ≥1mm

Stress SPECT or Stress Echo

No Ischemia
Mild-Single Vessel Ischemia
Severe-Two or Three Vessel Ischemia

Consider

Medical Therapy

Catheterization +/- Revascularization

Diabetes +1 risk factor of target organ damage

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>It should be considered to classify patients with DM as at very high or high risk for CVD depending on the presence of concomitant risk factor and target organ damage.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>It is not recommended to assess the risk for CVD in patients with DM based on risk scores developed for the general population.</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>It is indicated to estimate the urinary albumin excretion rate when performing risk stratification in patients with DM.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Screening for silent myocardial ischaemia may be considered in selected high risk patients with DM.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)

www.escardio.org/guidelines
Θήλη, 57 ετών, προσέρχεται στις 31/10/2012, ΑΠ=140/90 mmHg, GLUC=130 mg/dl Κάπνισμα (+), Δυσλιπ. (+),

EF=60%  

προσέρχεται στις 21/01/2016 Δύσπνοια στην ελάχιστη προσπάθεια, HbA1c= 11

EF=35%
Στεφαναια νόσος 3- αγγείων
ΣΤΕΦΑΝΑΙΑ ΝΟΣΟΣ 3-ΑΓΓΕΙΩΝ

**Central Pressure Analysis**

<table>
<thead>
<tr>
<th>BP (mmHg)</th>
<th>Aix (%)</th>
<th>PP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>133</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SP Amp</th>
<th>PP ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.11</td>
</tr>
</tbody>
</table>

**PWV (Pulse Wave Velocity)**

<table>
<thead>
<tr>
<th>PWV CF (m/s)</th>
<th>C-F Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.8</td>
<td>600</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TT (ms)</th>
<th>Tol. (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46.7</td>
<td>2.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PWV CR (m/s)</th>
<th>C-R Distance</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>TT (ms)</th>
<th>Tol. (ms)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>PWV CD (m/s)</th>
<th>C-D Distance</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>TT (ms)</th>
<th>Tol. (ms)</th>
</tr>
</thead>
</table>
Principles for diagnosis and management

Cardiovascular disease (CVD) and Diabetes mellitus (DM)

Main diagnosis: DM±CVD
- CVD unknown: ECG, Echocardiography, Exercise test, Holter ECG
- CVD known: ECG, Echocardiography, Holter ECG, If positive cardiology consultation

Abnormal: Cardiology consultation, Ischaemia treatment, Non-invasive or invasive
- Normal: Follow up

Main diagnosis: CVD±DM
- DM unknown: HbA1c, FPG, If needed OGGT, Blood lipids, If MI/ACS aim for reasonable glycaemic control
- DM known: Screen for microangiopathy, If poor glycaemic control, diabetology consultation

Newly detected: DM or IGT, Diabetology consultation
- Normal: Follow up

Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)
Diabetic cardiomyopathy

Definition: “a distinct entity characterized by the presence of abnormal myocardial performance or structure in the absence of epicardial coronary artery disease, hypertension and significant valvular disease”

Risk factors for DCM

- High HbA1c
- Increased BMI
- Advancing age
- Associated CAD
- Retinopathy
- End-stage renal disease
- Proteinuria-albuminuria
- Duration of T2DM
- Use of insulin

DIABHYCAR study. Diabetes care 2003;26:855-860
Diabetes Mellitus
Different Aspect of the Same Disease

## Stage of diabetic cardiomyopathy

<table>
<thead>
<tr>
<th>Stages</th>
<th>Characteristics</th>
<th>Functional features</th>
<th>Structural features</th>
<th>Study methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stage</td>
<td>Depletion of GLUT4</td>
<td>No overt functional abnormalities or possible overt diastolic dysfunction but normal ejection fraction</td>
<td>Normal LV size, wall thickness, and mass</td>
<td>Sensitive methods such as strain, strain rate, and myocardial tissue velocity</td>
</tr>
<tr>
<td></td>
<td>Increased FFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carnitine deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ca(^{2+}) homeostasis changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle stage</td>
<td>Apoptosis and necrosis</td>
<td>Abnormal diastolic dysfunction and normal or slightly decreased ejection fraction</td>
<td>Slightly increased LV mass, wall thickness, or size</td>
<td>Conventional echocardiography or sensitive methods such as strain, strain rate, and myocardial tissue velocity</td>
</tr>
<tr>
<td></td>
<td>Increased AT II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced IGF-I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased TGF-β1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild CAN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late stage</td>
<td>Microvascular changes</td>
<td>Abnormal diastolic dysfunction and ejection fraction</td>
<td>Significantly increased LV size, wall thickness, and mass</td>
<td>Conventional echocardiography</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe CAN</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| AT II, Angiotensin II; CAD, coronary artery disease. |

Επιμήκης (Longitudinal)

Κυκλοτερής (Circumferential)

Ακτινική (Radial)
Η Ελικοειδής παραμόρφωση

Στροφική κίνηση κορυφής
(αντιωρολογιακή φορά)

Στροφική κίνηση βάσης
(ωρολογιακή φορά)
LV LONGITUDINAL STRAIN

Diabetic

Relative

Ikonomidis I, Pavlidis G et al. ESC 2014
Normal

Diabetic

MVO  EEF

T=988 msec

70 msec

33%  75%

26%  64%

85 msec

109x185 to 233x247

557x252 to 720x360
Subclinical LV dysfunction in asymptomatic diabetic patients assessed by 2D ST: correlation with diabetes duration

In addition to diastolic dysfunction,
- Longitudinal strain was significantly lower in diabetic patients compared with control subjects
- The decrease in LS correlated with duration of diabetes.
- Subclinical LV longitudinal dysfunction is frequently observed in asymptomatic diabetes patients with normal LVEF

Early detection of left ventricular dysfunction in first-degree relatives of diabetic patients by myocardial deformation imaging: The role of endothelial glycocalyx damage

Ignatios Ikonomidis a,*, George Pavlidis a, Vaia Lambadiari b, Fotini Kousathana b, Maria Varoudi a, Filio Spanoudi b, Eirini Maratou c, John Parissis a, Helen Triantafylldi a, George Dimitriadis b, John Lekakis a

a 2nd Cardiology Department, Attikon Hospital, National and Kapodistrian University of Athens, Medical School, Greece
b 2nd Department of Internal medicine, Research Unit and Diabetes Centre, Attikon Hospital, National and Kapodistrian University of Athens, Medical School, Greece
c Hellenic National Centre for the prevention of Diabetes and its complications HNDC, Greece
## Myocardial deformation and endothelial glycocalyx post OGTT

### Time, min

<table>
<thead>
<tr>
<th></th>
<th>Normoglycaemic subjects (n=20)</th>
<th>First degree relatives (n=40)</th>
<th>Dysglycaemic subjects (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>120 OGT</td>
<td>0</td>
</tr>
</tbody>
</table>

### pTw, deg

<table>
<thead>
<tr>
<th></th>
<th>Normoglycaemic subjects (n=20)</th>
<th>First degree relatives (n=40)</th>
<th>Dysglycaemic subjects (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16.9±6.5</td>
<td>14.2±4.7#</td>
<td>14.4±4.4</td>
</tr>
</tbody>
</table>

### pTwVel, deg/sec

<table>
<thead>
<tr>
<th></th>
<th>Normoglycaemic subjects (n=20)</th>
<th>First degree relatives (n=40)</th>
<th>Dysglycaemic subjects (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>105.7±35.5</td>
<td>102.1±36.5</td>
<td>92.6±34.4</td>
</tr>
</tbody>
</table>

### pUtwVel, deg/sec

<table>
<thead>
<tr>
<th></th>
<th>Normoglycaemic subjects (n=20)</th>
<th>First degree relatives (n=40)</th>
<th>Dysglycaemic subjects (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-112.4±36.4</td>
<td>-85.9±33.0†</td>
<td>-86.5±34.3</td>
</tr>
</tbody>
</table>

### GLS, %

<table>
<thead>
<tr>
<th></th>
<th>Normoglycaemic subjects (n=20)</th>
<th>First degree relatives (n=40)</th>
<th>Dysglycaemic subjects (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-19.2±2.1</td>
<td>-19.2±2.4</td>
<td>-18.4±2.6</td>
</tr>
</tbody>
</table>

### ENDO LS, %

<table>
<thead>
<tr>
<th></th>
<th>Normoglycaemic subjects (n=20)</th>
<th>First degree relatives (n=40)</th>
<th>Dysglycaemic subjects (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-20.1±3.4</td>
<td>-20.4±4.5</td>
<td>-19.0±4.2</td>
</tr>
</tbody>
</table>

### MID LS, %

<table>
<thead>
<tr>
<th></th>
<th>Normoglycaemic subjects (n=20)</th>
<th>First degree relatives (n=40)</th>
<th>Dysglycaemic subjects (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-16.8±2.8</td>
<td>-17.2±3.8</td>
<td>-16.9±3.4</td>
</tr>
</tbody>
</table>

### EPI LS, %

<table>
<thead>
<tr>
<th></th>
<th>Normoglycaemic subjects (n=20)</th>
<th>First degree relatives (n=40)</th>
<th>Dysglycaemic subjects (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-14.2±2.4</td>
<td>-14.7±3.4</td>
<td>-14.6±2.9</td>
</tr>
</tbody>
</table>

- GLS greater than -18%
- Subendocardial LS greater than -19.5%
- Peak Twisting less than 16 deg
differentiated FDR with LV dysfunction from normal controls with **sens 70% spec 75%**
Association of post-prandial glucose with impaired GLS at 2h OGTT
DIABETIC CARDIOMYOPATHY

5m after
DM – non obstructive CAD

CFR = 2.2
Treatment of heart failure in people with diabetes

- Builds on similar principles as in people without diabetes.
- ACE-I, ARBs, beta-blockers and MRAs essential.
- Diuretics for symptom relief.
- Ivabradine if heart rate >70 bpm.
- CRT and Heart Tx after careful consideration.
- Caution with TZDs.

Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)
Θεραπευτικές προεκτάσεις
Diabetes-related CV complications have declined with improved care, but substantial burden remains.

Adapted Gregg E et al. 

PAD, CHF, commonest 1st CVD events in DM 
Lancet D/E
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that glucose lowering is instituted in an individualized</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>manner taking duration of DM, co-morbidities and age into account.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>It is recommended to apply tight glucose control, targeting a near-normal HbA$_{1c}$ &lt;7.0% or &lt;53 mmol/mol to decrease microvascular complications in T1DM and T2DM.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A HbA$_{1c}$ target of $\leq$7.0% ($\leq$53 mmol/mol) should be considered for the prevention of CVD in T1 and T2 DM.</td>
<td>I1a</td>
<td>C</td>
</tr>
<tr>
<td>Basal bolus insulin regimen, combined with frequent glucose monitoring, is</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>recommended for optimizing glucose control in T1DM.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin should be considered as first-line therapy in subjects with T2DM</td>
<td>I1a</td>
<td>B</td>
</tr>
<tr>
<td>following evaluation of renal function.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Changes in global longitudinal strain (GLS) as determined by glycemic control.

A, The improvement in GLS by the final glycated hemoglobin (HbA1c) attained.

B, The improvement in GLS by the extent of reduction in HbA1c during the 12-month study period.
GLP-1 analogues

- Experimental and early clinical observations indicate favourable effects on myocardial performance.

- GLP-1:
  - improves cardiac function in heart failure
  - increases myocardial glucose intake
  - improves functional recovery following myocardial ischemia.

Ban K et al. Circulation 2008;117:2340-2350
## Glycemic control (n=104)

<table>
<thead>
<tr>
<th></th>
<th>Glucose, mg/dL</th>
<th>HbA1c, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 year</td>
</tr>
<tr>
<td>Drugs</td>
<td>155±40</td>
<td>122±22</td>
</tr>
<tr>
<td>GLP-1</td>
<td>165±44</td>
<td>131±20</td>
</tr>
<tr>
<td>GLP-1 + drugs</td>
<td>157±50</td>
<td>131±26</td>
</tr>
<tr>
<td>Insulin</td>
<td>180±56</td>
<td>131±36</td>
</tr>
<tr>
<td>Insulin + drugs</td>
<td>199±75</td>
<td>135±39</td>
</tr>
</tbody>
</table>

Ikonomidis et al ESC 2017
<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (n=30)</th>
<th>Metformin (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time, months</strong></td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td><strong>GLS, %</strong></td>
<td>-15.4±3</td>
<td>-16.6±2.7*</td>
</tr>
<tr>
<td><strong>GLSR, 1/sec</strong></td>
<td>0.77±0.2</td>
<td>0.89±0.2*</td>
</tr>
<tr>
<td><strong>pTw, deg</strong></td>
<td>15.5±4</td>
<td>13.2±6*</td>
</tr>
<tr>
<td><strong>Utw velocity, deg/sec</strong></td>
<td>-97±49</td>
<td>-112±52*</td>
</tr>
<tr>
<td><strong>%dpTw-Utw_{MVO}</strong></td>
<td>31±10</td>
<td>40±14*</td>
</tr>
<tr>
<td><strong>%dpTw-Utw_{PEF}</strong></td>
<td>43±19</td>
<td>53±22*</td>
</tr>
<tr>
<td><strong>cSBP, mmHg</strong></td>
<td>143±20</td>
<td>138±19*</td>
</tr>
<tr>
<td><strong>HR, bpm</strong></td>
<td>74±12</td>
<td>80±11*</td>
</tr>
<tr>
<td><strong>FMD %</strong></td>
<td>8.9±3</td>
<td>13.2±6†</td>
</tr>
<tr>
<td><strong>PWV, m/sec</strong></td>
<td>11.8±2.5</td>
<td>10.3±3.3*</td>
</tr>
<tr>
<td><strong>SBP, mmHg</strong></td>
<td>142±15</td>
<td>138±19*</td>
</tr>
</tbody>
</table>

Ikonomidis I., Lambadiari V, Lekakis J   Cardiovascular Diabetology 2017
Table 4. Univariate and multivariable association of PWV, GLS and FMD% post treatment with parameters of the study population.

<table>
<thead>
<tr>
<th></th>
<th>PWV &gt;10 m/sec</th>
<th>GLS &gt; -15%</th>
<th>FMD &lt;11%</th>
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<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariable</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>Odds ratio</td>
<td>p</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>HbA1c</td>
<td>1.499 (1.1-1.7)</td>
<td>0.035</td>
<td>1.709 (1.1-1.9)</td>
</tr>
<tr>
<td>Weight</td>
<td>1.037 (1-1.1)</td>
<td>0.096</td>
<td>1.200 (0.9-1.3)</td>
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<tr>
<td>BMI</td>
<td>1.142 (0.9-1.4)</td>
<td>0.071</td>
<td>1.241 (1-1.2)</td>
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<tr>
<td>Waist</td>
<td>1.252 (1-1.3)</td>
<td>0.045</td>
<td>1.077 (0.9-1.4)</td>
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<tr>
<td>HR</td>
<td>1.100 (1-1.2)</td>
<td>0.010</td>
<td>1.210 (1-1.4)</td>
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<tr>
<td>Liraglutide</td>
<td>0.333 (0.2-1.3)</td>
<td>0.018</td>
<td>0.367 (0.2-1.7)</td>
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</tbody>
</table>
Κύρια έκβαση
Θάνατος καρδιαγγειακής αιτιολογίας, μη θανατηφόρο έμφραγμα μυοκαρδίου, ή μη θανατηφόρο εγκεφαλικό

<table>
<thead>
<tr>
<th>Ασθενείς σε κίνδυνο</th>
<th>Χρόνος από την τυχαιοποίηση (μήνες)</th>
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<tbody>
<tr>
<td>Λιραγλουτίδη</td>
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<td>32</td>
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</tbody>
</table>

HR=0.87
95% CI (0.78, 0.97)
p<0.001 για τη μη κατωτέρωση
p=0.01 για την ανωτέρωση

Λιραγλουτίδη
Εικονικό φάρμακο

<table>
<thead>
<tr>
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<td>4.45</td>
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<tr>
<td></td>
<td>1.09</td>
</tr>
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<td></td>
<td>0.65</td>
</tr>
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</table>

HR=0.78
95% CI (0.66, 0.93)
p=0.007
Απαιτούμενος αριθμός προς θεραπεία ασθενών ώστε να προληφθεί...

ένας θάνατος από κάθε αιτία

ένα MACE

66

για 3 έτη

98

MACE: Μείζον καρδιαγγειακό ανεπιθύμητο συμβάν.
EMPAGLIFLOZIN

- Inhibitors of sodium–glucose cotransporter 2 reduce rates of hyperglycemia in patients with type 2 diabetes by decreasing renal glucose reabsorption, thereby increasing urinary glucose excretion

- is associated
  - with weight loss and reductions in BP without increases in heart rate
  - Reduction of arterial stiffness and vascular resistance
  - visceral adiposity, albuminuria, and plasma urate
SGLT2 inhibitors

Hospitalisation for heart failure

Cumulative incidence function. HR, hazard ratio

HR 0.65
(95% CI 0.50, 0.85)
p = 0.0017
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration</th>
<th>Group Characteristics</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>for 5.4 years</td>
<td>5% diabetes, 26% hypertension</td>
<td>30</td>
</tr>
<tr>
<td>Ramipril</td>
<td>for 5 years</td>
<td>38% diabetes, 46% hypertension</td>
<td>56</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>for 3 years</td>
<td>T2DM with high CV risk</td>
<td>39</td>
</tr>
</tbody>
</table>

1. 4S investigator. Lancet 1994; 344: 1383-89, [link](http://www.trialresultscenter.org/study2590-4S.htm);
Συμπεράσματα

- Διαβήτης και η καρδιαγγειακή νόσος είναι δυο όψεις του ίδιου νομίσματος
- Είναι απαραίτητη διάγνωση του διαβήτη σε ΚΔ αλλά και η διάγνωση ΚΔ νόσου σε ασθενείς με διαβήτη
- Η έγκαιρη θεραπεία του μειώνει τις επιπλοκές και βελτιώνει την πρόγνωση
- Νέες θεραπείες έχουν ευεργετικά αποτελέσματα στην καρδιακή λειτουργία
ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ
MicroRNAs or miRNAs are small noncoding RNA molecules (≈22 nucleotides) which downregulate gene expression by a post transcriptional mechanism controlling approximately 30% of all protein-coding genes of mammalian genome.

During the past 7 years, researchers have identified several miRNAs and their specific mRNA targets altered in diabetic cardiomyopathy using experimental models at preclinic level.

The early detection of diabetic cardiomyopathy using miRNAs biomarker could serve to intensify the antidiabetes treatment and cardioprophylactic therapies in patients with high risk of diabetes-derived diastolic dysfunction before it appears.
Experimental strategies for circulating microRNA identification as potential biomarkers

Θεραπευτικές προεκτάσεις
Diabetes-related CV complications have declined with improved care, but substantial burden remains.

PAD, CHF, commonest 1st CVD events in DM
Lancet D/E

Adapted Gregg E et al.
## Glycaemic control in patients with diabetes

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that glucose lowering is instituted in an individualized</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>manner taking duration of DM, co-morbidities and age into account.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>It is recommended to apply tight glucose control, targeting a near-normal</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>HbA$_{1c}$ ($&lt;$7.0% or $&lt;$53 mmol/mol) to decrease microvascular complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in T1DM and T2DM.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A HbA$_{1c}$ target of $\leq$7.0% ($\leq$53 mmol/mol) should be considered</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>for the prevention of CVD in T1 and T2 DM.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal bolus insulin regimen, combined with frequent glucose monitoring, is</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>recommended for optimizing glucose control in T1DM.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin should be considered as first-line therapy in subjects with T2DM</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>following evaluation of renal function.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)
Change HbA1c1 <1%

-5
-10
-15
-20
-25

Baseline 1-year

n=34

Change HbA1c1 >=1%

Baseline 1-year

n=71

GLS, %

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>6</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>8.7±3</td>
<td>6.2±0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Fasting Glucose, mg/dL</strong></td>
<td>172±44</td>
<td>108±19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>PWVc, m/sec</strong></td>
<td>12.3±2.9</td>
<td>11.3±3.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>PBR, μm</strong></td>
<td>2.17±0.2</td>
<td>2.05±0.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>pUntwVel, deg/sec</strong></td>
<td>-88±31</td>
<td>-98±33</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>%dpTw-Utw_{MVO}</strong></td>
<td>25±9</td>
<td>31±2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>%dpTw-Utw_{PEF}</strong></td>
<td>46±17</td>
<td>56±19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>FMD%</strong></td>
<td>8.6±5</td>
<td>12.2±6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Glucose-lowering treatment in patients with heart failure

- **Metformin**: lower mortality rates, lower rates of all-cause hospital admission and fewer adverse events.

- **Sulphonylureas**: no relationship was seen between sulphonylurea and heart failure mortality in UKPDS, but in the Saskatchewan Health database, mortality (52 vs. 33%) and hospitalization (85 vs. 77%) were higher among patients treated with sulphonylureas than with metformin during an average of 2.5 years of follow-up.

- **Thiazolidinediones**: induce sodium retention and plasma volume expansion *contraindicated in HF*. 
DPP-4 inhibitors

- **SAVOR-TIMI**: saxagliptin treatment was associated with an increased risk for hospitalization for heart failure. This increase in risk was highest among patients with elevated levels of natriuretic peptides, prior heart failure, or chronic kidney disease.

- **EXAMINE**: In patients with type 2 diabetes and recent acute coronary syndromes, alogliptin did not increase the risk of heart failure outcomes.

- **TECOS**: Among patients with type 2 diabetes and established cardiovascular disease, adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events.
Insulin

A retrospective cohort study of 16,417 patients with DM and a primary diagnosis of heart failure did not reveal any association between the use of insulin and mortality in comparison with several other classes of glucose-lowering drugs.

In the ORIGIN trial, people at high CAD risk plus IFG, IGT or T2DM received insulin glargine or standard care, which mainly included metformin and sulphonylurea treatment. During the 6.2-year-long follow-up period there was no difference in hospitalization for heart failure.

GLP-1 analogues

Experimental and early clinical observations indicate favourable effects on myocardial performance.

GLP-1:
- improves cardiac function in heart failure
- increases myocardial glucose intake
- improves functional recovery following myocardial ischemia.

Ban K et al. Circulation 2008;117:2340-2350
## Glycemic control (n=104)

<table>
<thead>
<tr>
<th></th>
<th>Glucose, mg/dL</th>
<th>HbA1c, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 year</td>
</tr>
<tr>
<td>Drugs</td>
<td>155±40</td>
<td>122±22</td>
</tr>
<tr>
<td>GLP-1</td>
<td>165±44</td>
<td>131±20</td>
</tr>
<tr>
<td>GLP-1 + drugs</td>
<td>157±50</td>
<td>131±26</td>
</tr>
<tr>
<td>Insulin</td>
<td>180±56</td>
<td>131±36</td>
</tr>
<tr>
<td>Insulin + drugs</td>
<td>199±75</td>
<td>135±39</td>
</tr>
</tbody>
</table>

Ikonomidis et al ESC 2017
Effects of 6-month treatment with the glucagon like peptide - 1 analogue liraglutide on arterial stiffness, left ventricular myocardial deformation and oxidative stress in subjects with newly diagnosed type 2 diabetes.

*Vaia Lambadiari¹, MD, PhD, vlambad@otenet.gr, *George Pavlidis¹, MD, PhD, geo_pavlidis@yahoo.gr, Foteini Kousathana¹, MD, PhD, f.kousathana@hotmail.com, Maria Varoudi², MD, mvaroudi@gmail.com, Dimitrios Vlastos², MD, dimitrisbvr@hotmail.com, Eirini Maratou³, MD, maratou@hotmail.com, Dimitrios Georgiou⁴, MSc, digeorgiou@yahoo.gr, Ioanna Andreadou⁴, PhD, jandread@pharm.uoa.gr, John Parissis², MD, PhD, jparissis@yahoo.com, Helen Triantafyllidi², MD, PhD, seliani@hotmail.com, John Lekakis², MD, PhD, lekakisster@gmail.com, Efstathios Illidromitis², MD, PhD, illidromitis@yahoo.gr, George Dimitriadis¹, MD, PhD, gdimitr@uoa.med.gr, Ignatios Ikonomidis², MD, PhD, ignoik@otenet.gr
<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (n=30)</th>
<th>Metformin (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time, months</strong></td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td><strong>GLS, %</strong></td>
<td>-15.4±3</td>
<td>-16.6±2.7*</td>
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<td>0.79±0.3</td>
<td>0.82±0.3</td>
</tr>
<tr>
<td><strong>pTw, deg</strong></td>
<td>15.5±4</td>
<td>13.2±6*</td>
</tr>
<tr>
<td></td>
<td>16.2±5</td>
<td>15.0±6</td>
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<tr>
<td><strong>Utw velocity, deg/sec</strong></td>
<td>-97±49</td>
<td>-112±52*</td>
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<td>-100±41</td>
<td>-98±43</td>
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<td>29±18</td>
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<tr>
<td><strong>%dpTw-Utw_{PEF}</strong></td>
<td>43±19</td>
<td>53±22*</td>
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<td></td>
<td>45±19</td>
<td>50±16</td>
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<tr>
<td><strong>cSBP, mmHg</strong></td>
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<tr>
<td></td>
<td>142±18</td>
<td>140±18</td>
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<tr>
<td><strong>HR, bpm</strong></td>
<td>74±12</td>
<td>80±11*</td>
</tr>
<tr>
<td></td>
<td>71±12</td>
<td>68±10</td>
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<tr>
<td><strong>FMD %</strong></td>
<td>8.9±3</td>
<td>13.2±6†</td>
</tr>
<tr>
<td></td>
<td>8.8±5</td>
<td>11.8±6*</td>
</tr>
<tr>
<td><strong>PWV, m/sec</strong></td>
<td>11.8±2.5</td>
<td>10.3±3.3*</td>
</tr>
<tr>
<td></td>
<td>11.2±3</td>
<td>11±3</td>
</tr>
<tr>
<td><strong>SBP, mmHg</strong></td>
<td>142±15</td>
<td>138±19*</td>
</tr>
<tr>
<td></td>
<td>142±19</td>
<td>141±16</td>
</tr>
</tbody>
</table>

Ikonomidis I., Lambadiari V, Lekakis J  Cardiovascular Diabetology 2017 (in press)
<table>
<thead>
<tr>
<th></th>
<th>PWV &gt;10 m/sec</th>
<th>GLS &gt; -15%</th>
<th>FMD &lt;11%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariable</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>Odds ratio</td>
<td>p</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>HbA1c</td>
<td>1.499</td>
<td>0.035</td>
<td>1.104</td>
</tr>
<tr>
<td></td>
<td>(1.1-1.7)</td>
<td></td>
<td>(0.9-2)</td>
</tr>
<tr>
<td>Weight</td>
<td>1.037</td>
<td>0.096</td>
<td>1.099</td>
</tr>
<tr>
<td></td>
<td>(1-1.1)</td>
<td></td>
<td>(1-1.1)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.142</td>
<td>0.071</td>
<td>1.325</td>
</tr>
<tr>
<td></td>
<td>(0.9-1.4)</td>
<td></td>
<td>(1-1.5)</td>
</tr>
<tr>
<td>Waist</td>
<td>1.252</td>
<td>0.045</td>
<td>1.132</td>
</tr>
<tr>
<td></td>
<td>(1-1.3)</td>
<td></td>
<td>(1-1.5)</td>
</tr>
<tr>
<td>HR</td>
<td>1.100</td>
<td>0.010</td>
<td>1.070</td>
</tr>
<tr>
<td></td>
<td>(1-1.2)</td>
<td></td>
<td>(1-1.3)</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.333</td>
<td>0.018</td>
<td>0.815</td>
</tr>
<tr>
<td></td>
<td>(0.2-1.3)</td>
<td></td>
<td>(0.3-1.5)</td>
</tr>
</tbody>
</table>

Table 4. Univariate and multivariable association of PWV, GLS and FMD% post treatment with parameters of the study population.
Θεραπευτικες προεκτασεις
Diabetes-related CV complications have declined with improved care, but substantial burden remains.

PAD, CHF, commonest 1st CVD events in DM
Lancet D/E

Adapted Gregg E et al.
# Glycaemic control in patients with diabetes

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that glucose lowering is instituted in an individualized manner taking duration of DM, co-morbidities and age into account.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>It is recommended to apply tight glucose control, targeting a near-normal $\text{HbA}_{1c} &lt; 7.0%$ or $&lt; 53$ mmol/mol to decrease microvascular complications in T1DM and T2DM.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A $\text{HbA}_{1c}$ target of $\leq 7.0%$ ($\leq 53$ mmol/mol) should be considered for the prevention of CVD in T1 and T2 DM.</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>Basal bolus insulin regimen, combined with frequent glucose monitoring, is recommended for optimizing glucose control in T1DM.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Metformin should be considered as first-line therapy in subjects with T2DM following evaluation of renal function.</td>
<td>IIA</td>
<td>B</td>
</tr>
</tbody>
</table>

Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)
<table>
<thead>
<tr>
<th></th>
<th>Time, months</th>
<th></th>
<th></th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>0</td>
<td>8.7±3</td>
<td>6.2±0.9</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td><strong>Fasting Glucose, mg/dL</strong></td>
<td>6</td>
<td>108±19</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PWVc, m/sec</strong></td>
<td>0</td>
<td>12.3±2.9</td>
<td>11.3±3.2</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td><strong>PBR, μm</strong></td>
<td>0</td>
<td>2.17±0.2</td>
<td>2.05±0.2</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td><strong>pUntwVel, deg/sec</strong></td>
<td>0</td>
<td>-88±31</td>
<td>-98±33</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td><strong>%dpTw-Utw_{MVO}</strong></td>
<td>0</td>
<td>25±9</td>
<td>31±2</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td><strong>%dpTw-Utw_{PEF}</strong></td>
<td>0</td>
<td>46±17</td>
<td>56±19</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td><strong>FMD%</strong></td>
<td>0</td>
<td>8.6±5</td>
<td>12.2±6</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>
Glucose-lowering treatment in patients with heart failure

- **Metformin**: lower mortality rates, lower rates of all-cause hospital admission and fewer adverse events.

- **Sulphonylureas**: no relationship was seen between sulphonylurea and heart failure mortality in UKPDS, but in the Saskatchewan Health database, mortality (52 vs. 33%) and hospitalization (85 vs. 77%) were higher among patients treated with sulphonylureas than with metformin during an average of 2.5 years of follow-up.

- **Thiazolidinediones**: induce sodium retention and plasma volume expansion *contraindicated in HF.*
DPP-4 inhibitors

- **SAVOR-TIMI**: saxagliptin treatment was associated with an increased risk for hospitalization for heart failure. This increase in risk was highest among patients with elevated levels of natriuretic peptides, prior heart failure, or chronic kidney disease.

- **EXAMINE**: In patients with type 2 diabetes and recent acute coronary syndromes, alogliptin did not increase the risk of heart failure outcomes.

- **TECOS**: Among patients with type 2 diabetes and established cardiovascular disease, adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events.
A retrospective cohort study of 16,417 patients with DM and a primary diagnosis of heart failure did not reveal any association between the use of insulin and mortality in comparison with several other classes of glucose-lowering drugs.

In the ORIGIN trial, people at high CAD risk plus IFG, IGT or T2DM received insulin glargine or standard care, which mainly included metformin and sulphonylurea treatment. During the 6.2-year-long follow-up period there was no difference in hospitalization for heart failure.

GLP-1 analogues

- Experimental and early clinical observations indicate favourable effects on myocardial performance.

- GLP-1:
  - improves cardiac function in heart failure
  - increases myocardial glucose intake
  - improves functional recovery following myocardial ischemia.

Ban K et al. Circulation 2008;117:2340-2350
# Glycemic control (n=104)

<table>
<thead>
<tr>
<th></th>
<th>Glucose, mg/dL</th>
<th>HbA1c, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 year</td>
</tr>
<tr>
<td>Drugs</td>
<td>155±40</td>
<td>122±22</td>
</tr>
<tr>
<td>GLP-1</td>
<td>165±44</td>
<td>131±20</td>
</tr>
<tr>
<td>GLP-1 + drugs</td>
<td>157±50</td>
<td>131±26</td>
</tr>
<tr>
<td>Insulin</td>
<td>180±56</td>
<td>131±36</td>
</tr>
<tr>
<td>Insulin + drugs</td>
<td>199±75</td>
<td>135±39</td>
</tr>
</tbody>
</table>

Ikonomidis et al ESC 2017
<table>
<thead>
<tr>
<th>Effect of treatment with GLP-1 RA liraglutide versus treatment with metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, months</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>GLS, %</td>
</tr>
<tr>
<td>GLSR, 1/sec</td>
</tr>
<tr>
<td>pTw, deg</td>
</tr>
<tr>
<td>Utw velocity, deg/sec</td>
</tr>
<tr>
<td>%dpTw-Utw&lt;sub&gt;MVO&lt;/sub&gt;</td>
</tr>
<tr>
<td>%dpTw-Utw&lt;sub&gt;PEF&lt;/sub&gt;</td>
</tr>
<tr>
<td>cSBP, mmHg</td>
</tr>
<tr>
<td>HR, bpm</td>
</tr>
<tr>
<td>FMD %</td>
</tr>
<tr>
<td>PWV, m/sec</td>
</tr>
<tr>
<td>SBP, mmHg</td>
</tr>
</tbody>
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Ikonomidis I, Lambadiari V, Lekakis J Cardiovascular Diabetology 2017 (in press)
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<td>Multivariable</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>Odds ratio</td>
<td>p</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>HbA1c</td>
<td>1.499 (1.1-1.7)</td>
<td>0.035</td>
<td>1.709 (1.1-1.9)</td>
</tr>
<tr>
<td>Weight</td>
<td>1.037 (1-1.1)</td>
<td>0.096</td>
<td>1.200 (0.9-1.3)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.142 (0.9-1.4)</td>
<td>0.071</td>
<td>1.241 (1-1.2)</td>
</tr>
<tr>
<td>Waist</td>
<td>1.252 (1-1.3)</td>
<td>0.045</td>
<td>1.077 (0.9-1.4)</td>
</tr>
<tr>
<td>HR</td>
<td>1.100 (1-1.2)</td>
<td>0.010</td>
<td>1.210 (1-1.4)</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.333 (0.2-1.3)</td>
<td>0.018</td>
<td>0.367 (0.2-1.7)</td>
</tr>
</tbody>
</table>
Ikonomidis I., Lambadiari V, Lekakis J et al. Cardiovascular Diabetology 207 (in press
LEADER: Σχεδιασμός μελέτης

9340 ασθενείς
• Διπλά τυφλή
• Εισαγωγή περίοδος 2 εβδομάδων με εικονικό φάρμακο

Λιραγλουτίδη 0,6–1,8 mg OD + καθιερωμένη θεραπεία
Εικονικό φάρμακο + καθιερωμένη φροντίδα

30 ημέρες

Παρακολούθηση ασφάλειας

Διάρκεια 3,5–5 ετών

Παρακολούθηση ασφάλειας

Κύρια κριτήρια ένταξης
• ΣΔΤ2, HbA1c ≥7,0%
• Πρωτοθεραπευόμενοι με αντιδιαβητικό φάρμακο, OAD και/ή βασική ινσουλίνη /μείγματα
• Ηλικία ≥50 ετών και εγκατεστημένη καρδιαγγειακή νόσος ή χρόνια νεφρική ανεπάρκεια
• Ηλικία ≥60 ετών και παράγοντες κινδύνου για καρδιαγγειακή νόσο

Κύρια κριτήρια αποκλεισμού
• ΣΔ τύπου 1
• Χρήση GLP-1RA, DPP-4i, πραμικτίδης, ή ινσουλίνης ταχείας δράσης
• Οικογενειακό ή ατομικό ιστορικό MEN-2 ή MTC


Κύρια έκβαση
Θάνατος καρδιαγγειακής αιτιολογίας, μη θανατηφόρο έμφραγμα μυοκαρδίου, ή μη θανατηφόρο εγκεφαλικό

![Graph 1]

<table>
<thead>
<tr>
<th>Ασθενείς σε κίνδυνο</th>
<th>Χρόνος από την τυχαιοποίηση (μήνες)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Λιραγλουτίδη</td>
<td>4668</td>
</tr>
<tr>
<td>Εικονικό φάρμακο</td>
<td>4672</td>
</tr>
<tr>
<td></td>
<td>4593</td>
</tr>
<tr>
<td></td>
<td>4496</td>
</tr>
<tr>
<td></td>
<td>4400</td>
</tr>
<tr>
<td></td>
<td>4280</td>
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<tr>
<td></td>
<td>4172</td>
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<td>4072</td>
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<td>3982</td>
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<td></td>
<td>3982</td>
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<tr>
<td></td>
<td>1543</td>
</tr>
<tr>
<td></td>
<td>407</td>
</tr>
</tbody>
</table>

HR=0.87  
95% CI (0.78, 0.97)  
p<0.001 για τη μη κατωτερότητα  
p=0.01 για την ανωτερότητα

Καρδιαγγειακός θάνατος

![Graph 2]

<table>
<thead>
<tr>
<th>Ασθενείς σε κίνδυνο</th>
<th>Χρόνος από την τυχαιοποίηση (μήνες)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Λιραγλουτίδη</td>
<td>4.668</td>
</tr>
<tr>
<td>Εικονικό φάρμακο</td>
<td>4.672</td>
</tr>
<tr>
<td></td>
<td>4.641</td>
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<tr>
<td></td>
<td>4.599</td>
</tr>
<tr>
<td></td>
<td>4.558</td>
</tr>
<tr>
<td></td>
<td>4.505</td>
</tr>
<tr>
<td></td>
<td>4.445</td>
</tr>
<tr>
<td></td>
<td>4.382</td>
</tr>
<tr>
<td></td>
<td>4.322</td>
</tr>
<tr>
<td></td>
<td>1.723</td>
</tr>
<tr>
<td></td>
<td>484</td>
</tr>
</tbody>
</table>

HR=0.78  
95% CI (0.66, 0.93)  
p=0.007
Απαιτούμενος αριθμός προς θεραπεία ασθενών ώστε να προληφθεί...

ένας θάνατος από κάθε αιτία

ένα MACE

66

98

για 3 έτη

MACE: Μείζον καρδιαγγειακό ανεπιθύμητο συμβάν.
What Explains the Macro- and Microvascular Improvements Observed in LEADER?

- 0.4% reduction in HBA1C\textsuperscript{[a]}
- -2.3 kg reduction in body weight\textsuperscript{[a]}
- -1.2 mm Hg reduction in systolic blood pressure\textsuperscript{[a]}
  
  Possible improvement in arterial stiffness

- Benefits observed preclinically on endothelial function, cardiac contractility, HF, etc\textsuperscript{[b-d]}

\textsuperscript{c} Cariou B. \textit{Diabetes Metab.} 2012;38:298-308.
EMPAGLIFLOZIN

Inhibitors of sodium–glucose cotransporter 2 reduce rates of hyperglycemia in patients with type 2 diabetes by decreasing renal glucose reabsorption, thereby increasing urinary glucose excretion.

- is associated
  - with weight loss and reductions in BP without increases in heart rate
  - Reduction of arterial stiffness and vascular resistance
  - visceral adiposity, albuminuria, and plasma urate
Study medication was given in addition to standard of care
- Glucose-lowering therapy was to remain unchanged for first 12 weeks

Treatment assignment double masked

The trial was to continue until at least 691 patients experienced an adjudicated primary outcome even

CV death

Hospitalization for heart failure
## CV death, MI and stroke

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with event/analysed</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>0.86</td>
<td>(0.74, 0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>0.87</td>
<td>(0.70, 1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>1.24</td>
<td>(0.92, 1.67)</td>
<td>0.1638</td>
</tr>
</tbody>
</table>

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction

*95.02% CI
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

<table>
<thead>
<tr>
<th>Medication</th>
<th>Years</th>
<th>High CV Risk</th>
<th>Pre-ACEi/ARB era</th>
<th>Pre-statin era</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>5.4 years</td>
<td>5% diabetes, 26% hypertension</td>
<td>&gt;80% ACEi/ARB</td>
<td>&lt;29% statin</td>
</tr>
<tr>
<td>Ramipril</td>
<td>5 years</td>
<td>38% diabetes, 46% hypertension</td>
<td>&gt;75% statin</td>
<td>1994</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>3 years</td>
<td>T2DM with high CV risk</td>
<td>2000</td>
<td>2015</td>
</tr>
</tbody>
</table>

1. 4S investigator. Lancet 1994; 344: 1383-89, [http://www.trialresultscenter.org/study2590-4S.htm](http://www.trialresultscenter.org/study2590-4S.htm);
Conclusions

- Liraglutide in the LEADER trial was associated with 13% benefit on the 3-point MACE and a significant reduction in CV death, as well as total mortality.

- Microvascular endpoints were significantly reduced, driven largely by renal benefit.

- The liraglutide AEs profile was quite favorable.

- LEADER and EMPA-REG should change the dynamic of T2DM management:
  - Not just about glucose anymore, but about managing CVD and preventing CV endpoints.
Συμπεράσματα

Διαβήτης και η καρδιαγγειακή νόσος είναι δυο όψεις του ίδιου νομίσματος

Είναι απαραίτητη διάγνωση του διαβήτη σε ΚΔ αλλά και η διάγνωση ΚΔ νόσου σε ασθενείς με διαβήτη

Η έγκαιρη θεραπεία του μειώνει τις επιπλοκές και βελτιώνει την πρόgnωση

Νέες θεραπείες έχουν ευεργετικά αποτελέσματα στην καρδιακή λειτουργία
ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ
HbA1c

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat).

weight

Systolic blood pressure

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat).
Γλυκοζυλισμένη αιμοσφαιρίνη (HbA1c)

ΕΤΟ στο μέγεθος 36: -0,40%
95% ΔΕ (-0,45, -0,34)

Χρόνος από την τροφοδοσία (μήνες)

Άρθρο σταθμών σε κάθε διανύσμα

Λογισμική: 4.195, 4.462, 4.350, 4.299, 4.126, 4.024, 3.902, 3.102, 2.509, 1.029, 1.001, 1.001

Σωματικό βάρος

ΕΤΟ στο μέγεθος 36: -2.3 kg
95% ΔΕ (-2.5, -2.0)

Χρόνος από την τροφοδοσία (μήνες)

Άρθρο σταθμών σε κάθε διανύσμα

Λογισμική: 4.667, 4.454, 4.324, 4.126, 3.809, 3.500, 3.103, 2.509, 1.001, 1.001, 1.001, 1.001
Έκθεση: 4.671, 4.401, 3.861, 3.703, 2.903, 2.509, 1.501, 1.501

Αρτηριακή πίεση

SBP
ΕΤΟ στο μέγεθος 36: 1.2 mmHg
95% ΔΕ (1.9, 0.5)

DBP
ΕΤΟ στο μέγεθος 36: 0.6 mmHg
95% ΔΕ (0.2, 1.0)

Χρόνος από την τροφοδοσία (μήνες)

Άρθρο σταθμών σε κάθε διανύσμα

Έκθεση: 4.672, 4.415, 4.295, 3.075, 3.699, 3.703, 3.500

Καρδιακή συχνότητα

ΕΤΟ στο μέγεθος 36: 3.0 bpm
95% ΔΕ (2.5, 3.4)

Χρόνος από την τροφοδοσία (μήνες)

Άρθρο σταθμών σε κάθε διανύσμα

Λογισμική: 4.666, 4.442, 4.333, 4.099, 3.000, 3.000, 3.703, 3.500
Έκθεση: 4.672, 4.454, 3.809, 3.699, 3.699, 3.703, 3.500

Κύρια έκβαση
Θάνατος καρδιαγγειακής αιτιολογίας, μη θανατηφόρο έμφραγμα μυοκαρδίου, ή μη θανατηφόρο εγκεφαλικό

Η κύρια σύνθετη έκβαση στην ανάλυση του χρόνου έως το συμβάν ήταν η πρώτη εμφάνιση θανάτου από καρδιαγγειακά αίτια, το μη θανατηφόρο έμφραγμα του μυοκαρδίου ή το μη θανατηφόρο εγκεφαλικό επεισόδιο. Η αθροιστική επίπτωση εκτιμήθηκε χρησιμοποιώντας τη μέθοδο Kaplan–Meier, και οι λόγοι κινδύνου εκτιμήθηκαν με τη χρήση μοντέλου παλινδρόμησης αναλογικού κινδύνου Cox. Οι αναλύσεις των δεδομένων περικόπηκαν στους 54 μήνες, επειδή λιγότερο από το 10% των ασθενών είχε χρόνο παρατήρησης άνω των 54 μηνών.

ΔΕ: διάστημα εμπιστοσύνης, CV: καρδιαγγειακός, HR: λόγος κινδύνου.
Changes in global longitudinal strain (GLS) as determined by glycemic control.

A, The improvement in GLS by the final glycated hemoglobin (HbA1c) attained.

B, The improvement in GLS by the extent of reduction in HbA1c during the 12-month study period.
Hospitalisation for heart failure

Cumulative incidence function. HR, hazard ratio

HR 0.65
(95% CI 0.50, 0.85)
*p=0.0017

No. of patients
Empagliflozin 4687 4614 4523 4427 3988 2950 2487 1634 395
Placebo 2333 2271 2226 2173 1932 1424 1202 775 168
LEADER: Σχεδιασμός μελέτης

9340 ασθενείς

• Διπλά τυφλή

• Εισαγωγική περίοδος 2 εβδομάδων με εικονικό φάρμακο

Διάρκεια 3,5–5 ετών

Διαλογή

Τυχαίοποίηση (1:1)

Λιραγλουτίδη 0,6–1,8 mg OD + καθιερωμένη θεραπεία

Εικονικό φάρμακο + καθιερωμένη φροντίδα

Παρακολούθηση ασφάλειας

Παρακολούθηση ασφάλειας

30 ημέρες

Κύρια κριτήρια ένταξης

• ΣΔΤ2, HbA1c ≥7,0%

• Πρωτοθεραπευόμενοι με αντιδιαβητικό φάρμακο, OAD και/ή βασική υσυουλίνη /μειγματα

• Ηλικία ≥50 ετών και εγκατεστημένη καρδιαγγειακή νόσος ή χρόνια νεφρική ανεπάρκεια

• Ηλικία ≥60 ετών και παράγοντες κινδύνου για καρδιαγγειακή νόσο

Κύρια κριτήρια αποκλεισμού

• ΣΔ τύπου 1

• Χρήση GLP-1RA, DPP-4i, πραιμλυτιδής, ή υσουλίνης ταχείας δράσης

• Οικογενειακό ή ατομικό ιστορικό MEN-2 ή MTC


Κύρια έκβαση
Θάνατος καρδιαγγειακής αιτιολογίας, μη θανατηφόρο έμφραγμα μυοκαρδίου, ή μη θανατηφόρο εγκεφαλικό

![Graph](image1)

**HR=0.87**
95% CI (0.78, 0.97)  
*p*=0.001 για τη μη κατωτέροπτα  
*p*=0.01 για την ανωτέροπτα

<table>
<thead>
<tr>
<th>Ασθένειες σε κίνδυνο</th>
<th>Χρόνος από την τυχαιοποίηση (μήνες)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Λιραγλουτίδη</td>
<td>4668 4593 4496 4400 4280 4172 4072 3982 1562 424</td>
</tr>
<tr>
<td>Εικονικό φάρμακο</td>
<td>4672 4588 4473 4352 4237 4123 4010 3914 1543 407</td>
</tr>
</tbody>
</table>

Καρδιαγγειακός θάνατος

![Graph](image2)

**HR=0.78**
95% CI (0.66, 0.93)  
*p*=0.007

<table>
<thead>
<tr>
<th>Ασθένειες σε κίνδυνο</th>
<th>Χρόνος από την τυχαιοποίηση (μήνες)</th>
</tr>
</thead>
</table>
Απαιτούμενος αριθμός προς θεραπεία ασθενών ώστε να προληφθεί...

ένας θάνατος από κάθε αιτία

ένα MACE

για 3 έτη

MACE: Μείζον καρδιαγγειακό ανεπιθύμητο συμβάν.
What Explains the Macro- and Microvascular Improvements Observed in LEADER?

- 0.4% reduction in HBA1C
- -2.3 kg reduction in body weight
- -1.2 mm Hg reduction in systolic blood pressure
  - Possible improvement in arterial stiffness
- Benefits observed preclinically on endothelial function, cardiac contractility, HF, etc

---

EMPAGLIFLOZIN

- Inhibitors of sodium–glucose cotransporter 2 reduce rates of hyperglycemia in patients with type 2 diabetes by decreasing renal glucose reabsorption, thereby increasing urinary glucose excretion.

- is associated
  - with weight loss and reductions in BP without increases in heart rate
  - Reduction of arterial stiffness and vascular resistance
  - visceral adiposity, albuminuria, and plasma urate
Study medication was given in addition to standard of care
- Glucose-lowering therapy was to remain unchanged for first 12 weeks

Treatment assignment double masked

The trial was to continue until at least 691 patients experienced an adjudicated primary outcome even

CV death

Hospitalization for heart failure
## CV death, MI and stroke

<table>
<thead>
<tr>
<th>Event</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86</td>
<td>(0.74, 0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87</td>
<td>(0.70, 1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24</td>
<td>(0.92, 1.67)</td>
<td>0.1638</td>
</tr>
</tbody>
</table>

*95.02% CI

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

Simvastatin\(^1\) for 5.4 years

**30**

High CV risk
5% diabetes, 26% hypertension

Ramipril\(^2\) for 5 years

**56**

High CV risk
38% diabetes, 46% hypertension

Empagliflozin for 3 years

**39**

T2DM with high CV risk
92% hypertension

Pre-ACEi/ARB era

Pre-statin era

1994

2000

2015

1. 4S investigator. Lancet 1994; 344: 1383-89. [http://www.trialresultscenter.org/study2590-4S.htm](http://www.trialresultscenter.org/study2590-4S.htm)
Conclusions

- Liraglutide in the LEADER trial was associated with 13% benefit on the 3-point MACE and a significant reduction in CV death, as well as total mortality.

- Microvascular endpoints were significantly reduced, driven largely by renal benefit.

- The liraglutide AEs profile was quite favorable.

- LEADER and EMPA-REG should change the dynamic of T2DM management.
  - Not just about glucose anymore, but about managing CVD and preventing CV endpoints.
Συμπεράσματα

Διαβήτης και η καρδιαγγειακή νόσος είναι δυο όψεις του ίδιου νομίσματος

Είναι απαραίτητη διάγνωση του διαβήτη σε ΚΔ αλλά και η διάγνωση ΚΔ νόσου σε ασθενείς με διαβήτη

Η έγκαιρη θεραπεία του μειώνει τις επιπλοκές και βελτιώνει την πρόγνωση

Νέες θεραπείες έχουν ευεργετικά αποτελέσματα στην καρδιακή λειτουργία
ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ
Γλυκοζυμισμένη αιμοσφαιρίνη (HbA<sub>1c</sub>)

Σωματικό βάρος

Αριθμός ασθενών σε κάθε επίπεδο
Λαμβάνοντας μέγεθος 4467 4462 4335 4295 4192 4034 3817 3612 2549 1809 1012 766 87 1561

Χρόνος από την τυχαία πολιτική (μήνες)

ETD στο μέγεθος 36: 1.2 mmHg (95% ΔΕ (1.9, 0.5))

SBP

Καρδιακή συχνότητα

Φαίνεται εύκολο να αποκτήσει την μέγιστη τιμή από την τυχαία πολιτική (μήνες)

Βασικός μέγιστος τετάρτος: 10-14 και οπάτος: 14-18

Σωματικό βάρος (Σ)

Βασικός μέγιστος τετάρτος: 10-14 και οπάτος: 14-18

Πρόβλημα:

ΔΕ: Ακτινοβολία, ΕΤΔ: Προβλητική Τροποποίηση.

Αριθμός ασθενών σε κάθε επίπεδο
Λαμβάνοντας μέγεθος 4671 4421 4064 3670 3690 796 3506

Χρόνος από την τυχαία πολιτική (μήνες)

ETD στο μέγεθος 36: 3.0 bpm (95% ΔΕ (2.5, 3.4))
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