HEART RESEARCH

Openventio PUBLISHERS

ISSN 2377-164X Open Journal http://dx.doi.org/10.17140/HROJ-4-141

Research

*Corresponding author
Sandro Gentile, MD, PhD
Department of Clinical and Experimental Medicine
University of Campania
"Luigi Vanviteli", Naples, Italy
E-mail: s.gentile1949@gmail.com

Volume 4 : Issue 3
Article Ref. #: 1000HROJ4141

Article History
Received: July 23rd, 2017
Accepted: July 27th, 2017
Published: July 28th, 2017

Citation
Fusco A, Colarusso S, Piscopo M, et al. Short-term cardio-vascular risk score changes in type 2 diabetic patients on empaglifozin: A real-life clinical experience. *Heart Res Open J*. 2017; 4(3): 46-56. doi: 10.17140/HROJ-4-141

Short-term Cardio-Vascular Risk Score Changes in Type 2 Diabetic Patients on Empaglifozin: A Real-Life Clinical Experience

Alessandra Fusco, MD[1]; Sara Colarusso, MD[2]; Marco Piscopo, MD[3]; Maria Rosaria Improta, MD[4]; Marco Corigliano, MD[1]; Emilia Martedi, MD[5]; Domenica Oliva, MD[6]; Antonietta Santorelli, MD[7]; Rosa Simonetti, MD[3]; Armando Giammarco, MD[2]; Caterina Colella, MD[5]; Luigia Miretto, MD[7]; Alessandra D'Alessandro, MD[8]; Viviana Russo, RND[1]; Giuseppina Guarino, MD, PhD[10]; Giampiero Marino, MD[10]; Gerardo Corigliano, MD[1]; Felice Strollo, MD, PhD[9]; Sandro Gentile, MD, PhD[10*]

[1]Italian Diabetes Association, Outpatients Diabetes Centers, Napoli (NA), Italy
[2]Italian Diabetes Association, Outpatients Diabetes Centers, Benevento, Italy
[3]Italian Diabetes Association, Outpatients Diabetes Centers, Napoli (NA), Italy
[4]Italian Diabetes Association, Outpatients Diabetes Centers, Castellammare di Stabia, Italy
[5]Italian Diabetes Association, Outpatients Diabetes Centers, Portici, Naples, Italy
[6]Italian Diabetes Association, Outpatients Diabetes Centers,Cava de' Tirreni, Italy
[7]Italian Diabetes Association, Outpatients Diabetes Centers, Gastroenterologia, Caserta, Italy
[8]Azienda Ospedaliera Universitaria Federico IInumero verde, Napoli (NA), Italy
[9]Endocrinology and Metabolism Unit, Elle-Di, Roma, Italy
[10]Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy

ABSTRACT

Objective: The aim of the study was to test both efficacy and safety of empaglifozin in type 2 diabetic out patients followed-up within a single institution.
Materials and Methods: One hundred seventy-eight consecutive patients treated with empaglifozin for 6 months were compared to 356 fully matched control patients on alternative drugs: side effects were monitored and changes from baseline were evaluated for body weight, body mass index (BMI), blood pressure, circulating glucose, HbA1c, uric acid, triglycerides, total, high density lipoprotein (HDL) and low density lipoprotein (LDL)-cholesterol levels, as well as creatinine clearance rate. The 10-year Cardiovascular Risk score (10-y CV-RS) was also assessed in all patients according to the cryogenic underground observatory for rare events (CUORE) calculation charts. Weight, BMI, systolic and diastolic blood pressure, as well as, HbA1c, glucose, cholesterol, triglyceride and uric acid levels, significantly decreased after treatment, along with the 10-y CV-RS which is in fact strongly related to the above.
Results: Virtually no changes were observed in creatinine clearance rate and HDL levels. 45% patients reported polyuria, 15% genital itching, 8% genital infections, 12% urinary tract infections, no volume depletion or keto-acidosis episodes were described.
Conclusion: In conclusion, in diabetic patients experiencing no previous major cardiovascular events, empaglifozin significantly improved all cardiovascular risk factors, including glucose control, and the 10-y CV-RS. Moreover it was well tolerated, so that no treatment discontinuation was needed even in case of urinary tract infections.

KEY WORDS: Type 2 diabetes mellitus (T2DM); Cardiovascular risk; Cardiovascular risk (CVR); SGLT2i; Empaglifozin; Adverse effects.

ABBREVIATIONS: CV: Cardiovascular; T2DM: Type 2 Diabetes Mellitus; SGLT2i: Sodium-glucose co-transporter-2 inhibitors; CVD: Cardiovascular disease; CHD: Coronary Heart Disease; CVE: Cerebrovascular events; PAD: Peripheral Arterial Disease; HF: Heart Failure.

HEART RESEARCH
Open Journal
Openventio PUBLISHERS
ISSN 2377-164X http://dx.doi.org/10.17140/HROJ-4-141

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease eventually leading to microvascular and cardiomacrovascular complications and to their consequent ever increasing economic burden.

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are new oral antidiabetic medications recently approved for the treatment of T2DM.[1-4] They enhance urinary glucose output and, through this mechanism, are known to significantly improve glycemic control,[5-7] and to cause both weight and fat mass loss.[8,9] Moreover, SGLT2 may add additional beneficial effects through decreasing systolic and diastolic blood pressure.[10] They are well-tolerated and mostly cause only mild adverse effects,[9] one of which, exacerbated by glycosuria, is represented by possible recurrent genitourinary infections.[11,12]

Empagliflozin is a highly selective SGLT2i improving glycemic control in patients with T2DM both *per se* and when added to metformin, sulfonylurea, or insulin.[13-15] In the Empa-Reg outcome study, when added to standard care in patients with T2DM and a high cardiovascular (CV) risk, empagliflozin reduced CV events, mortality and hospitalization as compared to placebo during a 48 month observation-period [Empa-Reg outcome].[14] Efficacy data reported so far for SGLT2 is derived from randomized clinical trials, while those from "clinical practice" are still missing.

Due to that, some of the most common questions posed by patients at the time of diagnosis, i.e. "*Will my disease be worse?"* or *"Will I get worse?*", in real life get highly variable answers by their doctors, who mostly talk about their own experience and, even when referring to large randomized controlled trials (RCTs), can only base their predictions on forecast risks derived from relatively short-duration (4 years at most) validated data.

The aim of our study was to verify the short-term efficacy and safety of empaglifozin under real life conditions in an attempt to provide appropriate answers to the above mentioned questions. To achieve that we evaluated our diabetic patients for 6-month changes in their metabolically relevant parameters and 10-year CV risk score (10-y CVrs). The latter was calculated according to the Italian CUORE risk-scoring equation,[16-19] considered to be more appropriate to the population under study than others based on populations with different eating habits and different CV mortality rates.

MATERIALS AND METHODS

Study Design

The present report is an observational study carried out in an outpatient setting. We analyzed a series of patients with T2DM followed-up by a network of 10 outpatient diabetes centers (DCs) from AID (Associazione Italiana Diabete) participating in the so called Associazione Medici Diabetologi (AMD) Annals Initiative, all having the same organization structure and previously documented to attain the same performance levels and therefore considered to be a single institution.[20] Participating DCs adopted the same software for everyday outpatient management. A dedicated software package allowed data extraction for further analysis (AMD Data File).

The latter, in fact, could import information exclusively from patients previously signing an informed consent to data anonymous utilization for better diabetes control and improved quality of life (QoL). All DCs received their local Ethics Committee approval for database utilization and the study conformed to the Helsinki Declaration.

The diagnosis of type 2 diabetes was made/confirmed within each participating DC according to criteria defined by the ADA Standards of Medical Care in Diabetes 2014.[21] The International Classification of Diseases, Clinical Modification (ICD-9-CM, V82.9 2014) was used to define T2DM diagnosis and comorbidities/complications.[22]

The DC network recorded blood pressure (BP), glucose, HbA1c, total, low-density lipoprotein and high-density lipoprotein cholesterol (TC, LDL-C and HDL-C, respectively), triglycerides (Tg) and serum uric acid (UA) as measured by high standard auto-analyzers in public laboratories successfully participating in nationwide quality control programs. All electro-medical devices used to evaluate patients were certified and periodically validated in accordance with the International Standards Organization (ISO) directive.[23]

Kidney function was assessed by both serum creatinine and urinary albumin excretion rate measurements. Estimated creatinine clearance rate (i.e., glomerular filtration rate, estimated glomerular filtration rate (eGFR) was equation.[24] calculated for each patient based on a standardized serum creatinine assay and the chronic kidney disease epidemiology collaboration (CKD-EPI). Only patients having at least one serum creatinine measurement and concordant eGFR values during the last 3 months were included in the study.

Inclusion criteria were: HbA1c higher than 7% despite metformin at maximal tolerated dosage and/or insulin therapy. BMI>25 kg/m^2, 35<age<69yrs, eGFR>60 ml/min/1.73m^2.

Exclusion criteria were: a history of recurrent urinary tract infections or previous urinary or pelvic surgery, poor adherence to therapy, severe liver disease, kidney failure, neoplasms, steroid therapy, previous cardiovascular events and clinical conditions favoring ketoacidosis.

The 7.0% (53 mmol/mol) HbA1c cut off was chosen according to both the algorithm by Ceriello et al[25] and ADA's "Standards of Medical Care in Diabetes", both meant at reducing the incidence of microvascular diseases without increasing the risk for hypoglycemia.[21] Less stringent HbA1c targets,[26-28]

ISSN 2377-164X http://dx.doi.org/10.17140/HROJ-4-141

which would have been appropriate for specific, mostly fragile, populations were not taken into account, because, as stated above, critically-ill people or those with recent cardiovascular events or with rapidly progressing clinical conditions were not included in the study.

One hundred seventy-eight T2DM patients consecutively referring to the DCs and receiving add-on treatment with empaglifozin 10 mg (Treatment Group: TG) were enrolled. Empaglifozin 10 mg was added to metformin and/or insulin therapy according to prescribing criteria defined by the Italian Drug Agency (AIFA). As reference group 356 subjects with similar general clinical characteristics who were not taking empaglifozin were also enrolled in a 1:2 ratio, treatment *versus* control, respectively (Control Group: CG). All patients were followed-up for 6 months.

They were assessed for the above mentioned blood chemistry parameters, body weight (BW), body mass index (BMI), blood pressure, and eGFR at baseline as well as after 3 and 6 months. Drug safety and tolerability was also monitored in terms of aspartate aminotransferase (AST) (U/l), alanine aminotransferase (ALT) (U/l), γ-glutamyltransferase (γ-GT) (U/l), total bilirubin (mg/dL), alkaline phosphatase (U/l), eGFR (ml/min/khm^2), urea mg/dL (mg/dL), micro-macro-hematuria, cylindruria, ketonuria, urinary tract infections, genital infections, polyuria, other infectious diseases for safety and of asthenia, headache, nausea/vomiting, other gastrointestinal disorders, allergic reactions, mild or severe hypoglycemia for tolerability.

The individual 10-y CVrs was assessed using the CUORE project calculator. The CUORE project was an epidemiological and ischemic heart disease prevention project launched in 1998.[16] This score enables us to estimate the probability of experiencing any CV events (mainly myocardial infarction or stroke) for the first time over the next 10 years based on eight CV risk factors including age, gender, systolic BP (SBP), TC, HDL-C, diabetes mellitus, smoking habit and use of antihypertensive medications.[17-19] It was validated in patients 35 to 69 years of age without previous major cardiovascular accidents. It cannot be used in case of extreme risk factor values, including systolic blood pressure (SBP) higher than 200 mmHg or less than 90 mmHg, TC higher than 320 mg/dL or less than 130 mg/dL, HDL less than 20 mg/dL or higher than 100 mg/dL.

Statistical Analysis

Data are presented as mean values±standard deviation (M±SD). Categorical variables are given as frequencies and percentages. Repeated measures ANOVA was applied for intergroup and intragroup comparisons at the three chosen time points. *p* values <0.05 were taken as statistically significant. All analyses were performed using the STATA software, version 14 (Stata-Corp LP, College Station, Tex).

RESULTS

Clinical features of the whole study cohort population are reported in Table 1.

Table 1: Descriptive Features of the Enrolled Population. Data are Expressed as Mean+SD or as n. and Percent Rate in Case of Categorical Variables: 78 Subjects had more than a Single Complication.

Casuistry					
Variable	**Treatment Group**		**Control Group**		
	n=178		**n=356**		
	n.	**% (range)**	**n.**	**% (range)**	***p***
Female	102	57.4	199	55.9	ns
Age (years)	60.7±10.3	(41-68)	60.5±9.9	(40-67)	ns
BMI (kg/m^2)	30.6±4.5	(26.8-44.1)	30.4±4.6	(27.0±43.9)	ns
Normal weight	16	8.9	32	6.5	ns
Overweight	105	58.9	203	57.0	ns
Obese	57	32.2	130	36.5	ns
Diabetes duration (years)	9.2±7.1	(3-14)	9.4±7.7	(4-13)	ns
SBP (mmHg)	134,2±10,9	-	135.4±9.8	-	ns
DBP (mmHg)	81.7±7.3	-	80.9±6.9	-	ns
Subjects on Met alone	-	60.7	-	59.9	ns
Subjects on Insulin w/wo Met	-	39.3	-	41.1	ns
Biochemical parameters (M±SD)					
	n.	**%**	**n.**	**%**	***p***
Fasting blood glucose (mg/dl)	191.7±40.5	-	189.5±44.3	-	ns
HbA1c (%)	8.7±0.8	-	8.8±0.9	-	ns
Total Cholesterol (mg/dl)	179.3±36.4	-	175.7±33.9	-	ns
HDL Cholesterol (mg/dl)	43.9±8.9	-	44.8±9.6	-	ns
LDL Cholesterol (mg/dl)	103.2±29.5	-	107.5±25.9	-	ns

HEART RESEARCH
Open Journal
Openventio PUBLISHERS
ISSN 2377-164X http://dx.doi.org/10.17140/HROJ-4-141

Triglycerides (mg/dl)	165.9±61.4	-	171.4±59.6	-	ns
Creatinine (mg/dl)	0.9±0.6	-	0.8±0.5	-	ns
eGFR (ml/min/1.73m^2)	90.1±17.7	-	90.3±13.8	-	ns
Smokers (%)	-	47	-	50	ns
Lipid-lowering treatment (%)	-	60	-	62	ns
Antihypertensive treatment (%)	-	65	-	66	ns
Aspirin (%)	-	47	-	41	ns
Diabetes-related Complications					
	n.	**%**	**n.**	**%**	***p***
Overall	-	44	-	46.3	ns
Retinopathy BG	-	14.8	-	15.3	ns
Nephropathy*	-	13.1	-	12.5	ns
Autonomic Neuropathy	-	10.7	-	11.2	ns
Peripheral Neuropathy	-	14.7	-	15.1	

*Presence of microalbuminuria and/or eGFR>90 ml/min/1.73 m^2 or >60 <90 ml/min/1.73 m^2
SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; Met=metformin; w/wo=with or without.

Median age of investigated patients was 60 years in both the TG and the CG (interquartile (IQ) range: 41-68 and 40-47 years, respectively), 42.6% and 44.1% patients were male, respectively, and median diabetes duration was 9.2 and 9.4 years, respectively (IQ range: 3-14 and 4-13 years, respectively). Median BMI was 30.6 and 30.4 kg/m^2 (IQ range 26.8-44.1 and 27.0-43.9 kg/m^2, respectively). Glycemic control was poor, being median HbA1c>8.5% in both target group (TG) and control group (CG), with a fasting glucose level around 190 mg/dL, whereas lipid parameters and BP levels were moderately good, being LDL-C103 and 107 mg/dL, respectively, and mean BP close to 135/80 mmHg in both groups. Median eGFR was 90 ml/min/1.73 m^2 (IQ range 68-102 in both groups). In Table 1 also clinical characteristics are described including smoking habits, microvascular complications, use of aspirin, and lipid lowering or antihypertensive drugs.

Effect of Empaglifozin Treatment

No patients on empaglifozin added to metformin and/or insulin dropped off. Table 2 describes the effects of treatment.

Table 2: Parameter Changes within the Two Groups during the Follow-up Period.

	Treatment Group (n. 178)				**Control group (n. 356)**			
	Baseline T0	3 months T3	6 months T6	%Δ$^{\$}$	Baseline T0	3 months T3	6 months T6	%Δ$^{\$}$
Body weight (kg)	88.4±15.3	85.7±14.8*	84.8±14.8* °	-4.1	89.4±14.5	88.5±14.1^	88.06±13.2^	-1.5
BMI (kg/m^2)	31.7±3.8	30.7±3.6**	29.8±5.1* °	-5.4	30.4±4.6	30.4±4.4	30.2±3.9^	-0.5
Hb1Ac (%)	8.7±0.8	7.8±0.7**	7.5±0.7* °	-13.9	8.8±0.9	8.8±0.9^^	8.6±0.7^	-1.5
FPG (mg/dl)	191.7±40.5	143.1±2.3*	129.1±20.6* °	-32.7	189.5±44.3	182±31.5^	181.3±23.5^	-4.3
SBP (mm Hg)	134.2±10.9	126.7±6,9*	125.6±7.6* °	-6.4	135.4±9.8	135.2±9.6^	134.8±8.8^^	-0.4
DBP (mm Hg)	81.7±7.03	77.8±5.3*	77.5±5.2* °	-5.3	80.9±6.9	80.7±6.3	80.6±5.8^	-0.3
TChol (mg/dl)	179.3±36.4	175.6±24.8**	168.3±23.8** °°	-6.1	175.7±33.9	177.3±31.1	173.6±28.6^^	-1.2
HDL-C (mg/dl)	43.9±8.9	46.3±6.9**	45.8±10.6**	+4.4	44.8±9.6	44.3±7.2	43.8±7.5^^	-0.2
LDL-C (mg/dl)	103.2±29.5	100.4±27.1	89.9±25.6** °°	-12.9	107.5 ±25.9	106.4±24.6	105.1±22.6^	+2.3
Triglycerides (mg/dl)	165.9±61.4	144.3±49.2**	136.9±51.1* °	-17.5	171.4 ±59.6	169.4±44.2	167.9±46.6^	+2.2
Uric acid (mg/dl)	5.4±1.0	5.3 ±0.8	5.1±1.0$^{\$}$ °°	-5.6	5.5±1.1	5.4±1.0	5.4±0.9^^	-1.1
eGFR ml/min/1.73m^2)	90.1±17.7	90.5±16.7	92.9±14.7	+3.1	90.3±13.8	74.5±18.4^#	67.7±12.3^#	-25
10-y CV-RS	12.7±10.2	-	10.6±7.6*	-18.2	12.5±9.9	-	12.2±7.2	-2.2
*p<0.01 *vs.* T0; °p<0.01 *vs.* T3; **p<0.05 *vs.* T0; °°p<0.05 *vs.* T3; $^{\$}p$<0.05 *vs.* T3;					^p<0.01 *vs.* TG; ^^p<0.05 *vs.* TG; #p.0.01 *vs.* Baseline CG			
$^{\$}$ %Δ *vs.* baseline								

%Δ=percent difference observed between T6 and T0.
10-y CV-RS = 10 year individual cardiovascular risk score.

HEART RESEARCH
Open Journal
Openventio PUBLISHERS
ISSN 2377-164X http://dx.doi.org/10.17140/HROJ-4-141

Significant differences were observed in all biochemical and clinical parameters between control and empaglifozin groups. The latter displayed a significant and progressive improvement in all parameters with a rapid decrease in fasting blood glucose and HbA1c as shown in Figures 1 and 2, respectively.

BW changes are reported in greater detail in Figure 3, describing TG patients after splitting into metformin-only-treated and insulin-treated (with or without metformin) subgroups: both of them showed a significant BW decrease despite higher levels being consistently attained in the latter.

Figure 4 clearly shows significant differences (p<0.01) between TG and CG as compared to baseline in percent improvement of almost all investigated parameters, with the biggest differences involving fasting blood glucose (-32,4% *vs*. -4.3% in CG, respectively), HbA1c (-13.9% *vs*. -1.5%, respectively), Tg (-17.5% *vs*. +2.2%, respectively), LDL-C (-12.9% *vs*. +2.3%, respectively).

10-year CV Risk Score

At baseline the 10-y CV-RS score was 12.6±10.2 in the TG (Table 2 and Figure 5) and 12.5±9.9 in the CG (n.s.). After the 6-month follow-up a significant decrease was observed (-18.2%, p<0.01) in the TG *versus* an only slight decrease in the CG (-2.2%, n.s.) (Figure 4).

Table 3 describes the results of the multivariate Cox regression analysis: systolic BP and antihypertensive treatment

Figure 1: Comparison of Fasting Plasma Glucose (mg/dL) in the Treatment Group (TG) *versus* the Control Group (CG).*=p<0.01.

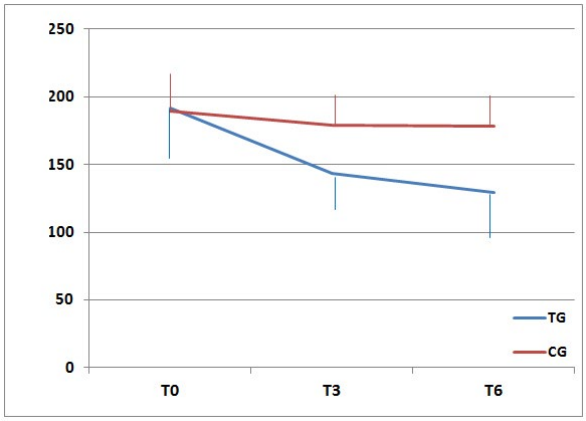


Figure 2: Comparison of HbA1c (%) in the Treatment Group (TG) *versus* the Control Group (CG).*=p<0.01.

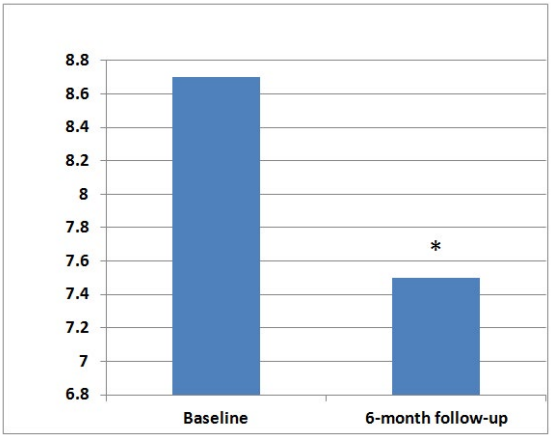
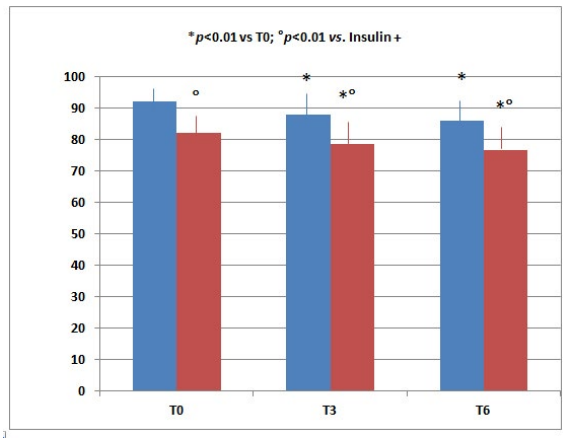
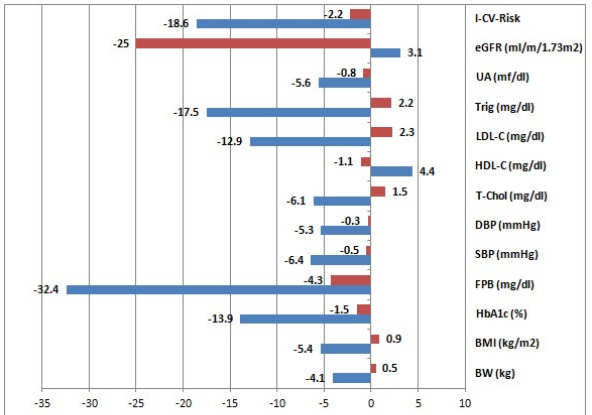


Figure 3: Body Weight Changes in Insulin Treated Patients (with or without metformin; Insulin +) as Compared to Those on Metformin only (Insulin -) within the Treatment Group (empaglifozin 10 mg/day).



Insulin+	*92*	*88*	*86*
Insulin-	*82*	*78,5*	*76,5*

Figure 4: Changes in Clinical Parameters from Baseline in Treatment Group (TG) Compared with Control Group (CG). All the differences were Statistically Significant (p<0.01).



	BW (kg)	BMI (kg/m2)	HbA1c (%)	FPB (mg/dl)	SBP (mmHg)	DBP (mmHg)	T-Chol (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	Trig (mg/dl)	UA (mf/dl)	eGFR (ml/m/1.73m2)	I-CV-Risk
CG	0.5	0.9	-1.5	-4.3	-0.5	-0.3	1.5	-1.1	2.3	2.2	-0.8	-25	-2.2
TG	-4.1	-5.4	-13.9	-32.4	-6.4	-5.3	-6.1	4.4	-12.9	-17.5	-5.6	3.1	-18.6

I-CV-Risk=Individual CV Risk Score; UA= Uric Acid; Trig= Triglycerides; LDL-C=LDL-Cholesterol: HDL-C=HDL-Cholesterol; T-Chol=Total Cholesterol; DBP=Diastolic Blood Pressure; SBP=Systolic Blood Pressure; FPG=Fasting Plasma Glucose; BMI=Body Mass Index; BW=Body Weight.

ISSN 2377-164X http://dx.doi.org/10.17140/HROJ-4-141

Figure 5: Changes in the 10-year CV Risk Score after 6-Month Treatment with Empaglifozin 10 mg, Compared with Baseline.

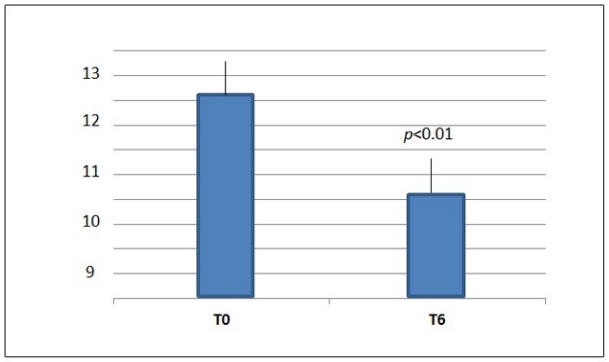


Table 3: Multivariate Cox Regression Analysis of all Parameters Contributing to the Final 10-y CV-RS (Individual 10-y Cardiovascular risk score in our Population.

	Hazard Ratio	*p*
Sex	1.085	<0.01
Age	1.090	<0.01
Diabetes	1.363	<0.001
Smoking	0.981	<0.05
Total Cholesterol	1.247	<0.001
LDL-C	1.121	<0.001
Systolic BP	1.395	<0.001
Antihypertensive Treatment	1.424	<0.001

were identified as major contributors to the individual 10-y CV-RS.

In greater detail, Figure 6 describes 10-y CV-RS changes in non-hypertensive and hypertensive TG patients. A significant difference (p<0.01) was deteted between them at baseline and at the end of follow-up, but, unlike the others, non-hypertensive subjects displayed only slight, non-significant intragroup changes.

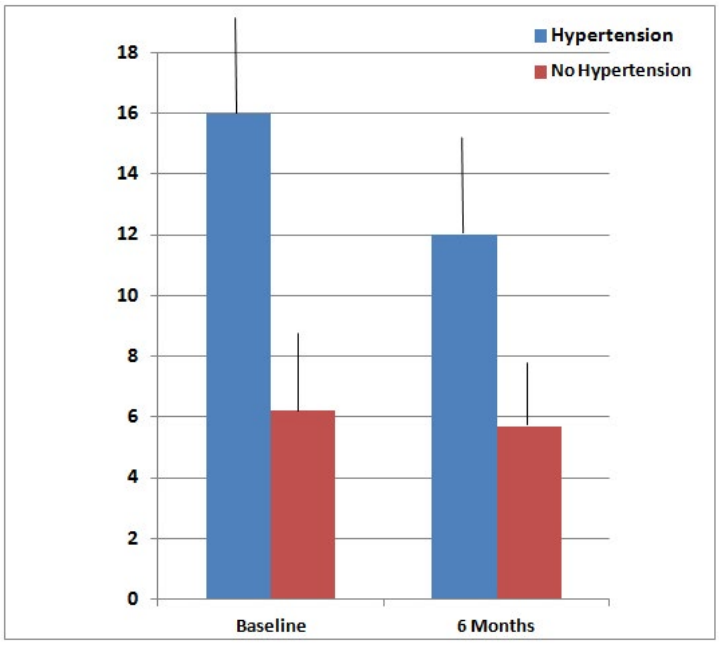
A similar result was observed when comparing insulin-treated to metformin-treated subjects (Table 4), who in fact displayed a significantly lower 10-y CV-RS than the others (p<0.01), being anyway a significant improvement observed (p<0.01) in both groups at the end of follow-up.

Safety Parameters and Side Effects

The upper part of Table 5 summarizes the results concerning safety parameters in the TG group: no significant differences were observed *versus* baseline in AST, ALS, γ-GT, total bilirubin, and blood urea; a similar behavior was observed for CG (not shown).

Unexpectedly, however, as seen in Figure 4 eGFR si-

Figure 6: Changes on 10 y CV Risk Score in T2DM People Treated with Empagnifozin when Splitted into Subjects with or without Hypertension, Respectively.



	Baseline		6 Months
Hypertension	16.0+9.0	*p*<0.01	10.0+7.8
No Hypertension	6.2+5.7	n.s.	5.7+4.6
	p<0.01		*p*<0.01

HEART RESEARCH
Open Journal
Openventio PUBLISHERS
ISSN 2377-164X http://dx.doi.org/10.17140/HROJ-4-141

Table 4: Comparison between the 10-y CV-RS (10 Year individual Cardiovascular Risk Score) in Empaglifozin Treated T2DM Subjects on Insulin with or without Metformin (Insulin +) or on Metformin alone (Insulin -) at Baseline (T0) and 6 Months (T6).

	10-y CV-RS		*p*
	T0	T6	
Insulin +	14.1±2.4	11.4±11.4	<0.001
Insulin -	9,7±1.9	7,8±1.8	<0.001
p	<0.01	<0.01	

Table 5: Safety Parameters and/or Adverse Effects in the Treatment Group. Data are Presented as Mean±DS or Number/Percent of Subject (%).

	Baseline	**T3**	**T6**
AST *(U/l)*	26±3	26±4	22±4
ALT *(U/l)*	24±4	25±3	24± 4
γ-GT *(U/l)*	22±8	22±9	21±6
Total Bilirubin*(mg/dl)*	0.9±0.3	0.6±0.4	0.8±0.2
Alkaline phosphatase*(U/l)*	41±6	38±8	40±5
eGFR*(ml/min/khm²)*	90.1±17.7	90.5±16.7	92.9±14.7
Urea mg/dl *(mg/dl)*	22±5	21±4	22±6
micro-macro-hematuria	0	0	0
Cylindruria	0	0	0
Ketonuria	0	0	0
Urinary tract infections	2 (1.1)	5 (2.8)	6 (3.4)
Genital infections	0	7 (3.9)	9 (5.6)
Polyuria	0	76 (42.7)	58 (32.5)
Other infectious diseases	0	0	0
Asthenia	0	0	0
Headache	0	0	0
Nausea/vomiting	0	0	0
Other gastrointestinal disorders	1 (0.6)	2 (1.1)	2 (1.1)
Allergic reactions	0	0	0
Mild hypoglycemia	1 (0.6)	2 (1.1)	2 (1.1)
Severe hypoglycemia	0	0	0

gnificantly worsened in the CG after 6 months *versus* both baseline and TG (-25% as compared to +3.1%, respectively; $p<0.01$).

In the TG no changes were observed in urine analysis except, as expected, for glycosuria. A slight non-significant increase was observed in urinary infection rate *versus* baseline (3.4 *vs.* 1.1 %), whereas genital infection rate significantly increased (+5.6% *vs.* baseline; $p<0.05$). Other possible side effects were either absent or superimposable to baseline. In greater detail, also the rate of recorded mild/moderate hypoglycemic episodes was quite low and, in any case, did not significantly change with respect to baseline at the end of follow-up. As also expected, no side effects were reported in the CG, either at baseline or at the end of follow-up.

DISCUSSION

In patients with T2DM, the main cause of morbidity and mortality is cardiovascular (CV) disease. Diabetic kidney disease, which develops in approximately 40% of patients with T2DM, further increases the risk of CV-related morbidity and mortality. The sodium SGLT2i empagliflozin, which is known to provide effective metabolic control both *per se*[29] or as an add-on to other glucose-lowering agents[29-34] in patients with T2DM, was also shown to improve CV and renal outcomes in the large, randomized, placebo-controlled EMPA-REG OUTCOME trial in patients at high risk of CV events.[13-14] The underlying mechanisms for the CV and renal protective effects of empagliflozin are not fully understood, but are likely to involve a combination of several mechanisms, including empagliflozin-associated body weight and blood pressure reduction, enhanced diuresis, modified substrate utilization and tubulo-glomerular feedback activation. The results of ongoing CV outcomes trials with other SGLT2 inhibitors will potentially confirm whether the beneficial CV and renal effects observed in EMPA-REG OUTCOME are unique to empagliflozin or reflect a drug class effect.[35]

ISSN 2377-164X http://dx.doi.org/10.17140/HROJ-4-141

Guidelines for cardio-vascular disease (CVD) prevention recommend the use of risk scores to identify adults at high CVD risk expected to benefit the most from preventive therapy. Several scoring systems exist to help clinicians assess the 10-year CHD risk, being the Framingham risk score the most widely used among them.[36,37]

The Framingham-Study researchers[37] also proposed a new model for use in the primary care setting, patently differentiated by gender. This "reclassification" of CVR was based on three basically sound ideas: first, it was easier to just use four parameters which had been recognized as the major risk factors (RF) in cardiovascular epidemiology, i.e. cholesterol, blood pressure (BP), diabetes mellitus and smoking; second, the model could predict all CVD events [coronary heart disease (CHD), cerebrovascular events (CVE), peripheral arterial disease (PAD) and heart failure (HF)] and provided calibration factors for each entity that may be of interest to the physician; and third, the concept of vascular or heart age was included, which could be calculated from the model.

Moreover, according to the 2009 Canadian Cholesterol Guidelines[38] all cardiovascular risk assessment calculators are defective *per se*, nevertheless the Framingham Risk Score (FRS) is recommended for total CVD anticipation. It was validated in Canada with the Cardiovascular Life Expectancy Model, and has been shown to increase adherence to therapeutic measures. Anyway, the FRS has been shown to underestimate the risk in specific categories of patients, especially the young, women, and eventually those with the metabolic syndrome.

By adding just 2 measurements (a family history of premature CAD and high hsCRP) to the Framingham model, the Reynolds Risk Score (RRS) seemed to further improve physician's CVD risk prediction ability, particularly for those people who in the past were perceived as being at moderate risk and was validated in men and women in an American population.[39-40]

There is reason to believe; however, that the FRS or the RRS, although practical, may not be applicable to southern Europe or Mediterranean populations, whose CVD prevalence is lower than observed in northern, central and eastern Europe.[41]

Within the CUORE project a risk score algorithm for assessing individual risk for cardio-vascular events was developed and validated in the Italian population.[16-19] It is a simple tool to estimate the probability of undergoing a major cardiovascular event (myocardial infarction or stroke) over the next 10 years, provided the levels of eight risk factors are known, including sex, age, diabetes, smoking habit, systolic blood pressure, total cholesterol, HDL-cholesterol and antihypertensive treatment. The score provides a more accurate assessment than risk cards elaborated in collaboration with the Italian Institute of Health (ISS) under the same CUORE Project.[42]

Our data, obtained in an outpatient setting in real-life conditions during a relatively short follow-up period is in agreement with those coming from major trials in terms off ast improvement in glycemic control and of beneficial effects on blood pressure, lipids and body weight, counter balanced by only slight genitourinary troubles. Accordingly, in a recent large multinational intervention study based on de-identified health records across six countries (US, Norway, Denmark, Sweden, Germany and the UK) all available SGLT-2 is [canagliflozin (53%), dapagliflozin (42%), and empagliflozin (5%)] were associated with lower heart failure and mortality rates than other Glucose-Lowering Drugs. The homogeneity of the results obtained across countries, despite geographic variations in the use of a specific SGLT-2i, suggests that in real-world practice the benefits previously reported with empagliflozin in the context of a randomized clinical trial may be applicable to all SGLT is in a broad population of patients with T2DM and reflect a class effect.[43]

Our goal was in fact to convincingly answer above mentioned patient questions on possible treatment-related cardiovascular complications.

Using the Cox regression analysis we weighed single factors used by the individual CV risk calculator and we could realize arterial hypertension and antihypertensive treatment to be the leading ones. In fact, as seen in Table 4, age, sex and diabetes were highly significant *per se* but, as non-modifiable factors, could not be expected to contribute to risk reduction over time. Among modifiable risk factors, smoking habits were also significant, as expected, but less than the others in our hands and total cholesterol e LDL-C, which proved to be highly significant, had a much lower HR than systolic-BP and antihypertensive treatment. We cannot provide an explanation for such observation as our investigation was not powered enough for a meaningful statistical analysis of this finding which, being unexpected, had not been included among the goals of the study. However, we may hypothesize a possible mechanism behind it to be insulin resistance, which is known to be a strong factor contributing to arterial hypertension in people with T2DM. Further *ad hoc* designed studies are warranted to validate such hypothesis.

LIMITATIONS

The main limitations of our study are the small number of enrolled subjects compared to large RCTs and the relatively short follow-up period.

However, it should be considered that cardiovascular outcomes were already found to be positively affected in the EMPAREG OUTCOME study within less than 6 months and that, by using our population-based CV-Individual Risk Score within the apparently short observation period we chose, we could anyway confirm those favorable effects in terms of single CV risk factors contributing to the final score.

CONCLUSION

In conclusion, our results confirmed empaglifozin efficacy in terms of persistent control of both glucose and virtually all other

ISSN 2377-164X http://dx.doi.org/10.17140/HROJ-4-141

cardiovascular risk factors (weight, BMI, blood pressure, lipids, uric acid). As a consequence of that, the 10-year Cardiovascular Risk (CRA) score significantly decreased in diabetic patients without previous major cardiovascular events. Finally, the drug was well tolerated and, when present, genitourinary tract infections mostly resolved with specific medications without any need for treatment discontinuation.

AUTHORS' CONTRIBUTIONS

All authors contributed to study conception and design, data acquisition, analysis and interpretation, manuscript preparation and critical revision.

COMPLIANCE WITH ETHICAL STANDARDS

The study was organized and supported by the AID Study Group (non-profit organization for the study of endocrine and metabolic disorders), Naples, Italy in conformance with good clinical practice (GCP) standards. Written informed consent was obtained from all participants before enrollment; the study was conducted in accordance with the Declaration of Helsinki and was approved all the Ethics Committees of the Centers participating in the study.

HUMAN AND ANIMAL RIGHTS

All followed procedures were in accordance with the ethical standards of the institutional and national responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium-glucose transport: Role in diabetes mellitus and potential clinical implications. *Kidney Int*. 2009; 75(12): 1272-1277. doi: 10.1038/ki.2009.87

2. Oku A, Ueta K, Arakawa K, et al. T-1095, an inhibitor of renal Na+-glucose cotransporters, may provide a novel approach to treating diabetes. *Diabetes*. 1999; 48(9): 1794-1800. doi: 10.2337/diabetes.48.9.1794

3. Neumiller JJ, White JR Jr, Campbell RK. Sodium-glucose co-transport inhibitors: Progress and therapeutic potential in type 2 diabetes mellitus. *Drugs*. 2010; 70(4): 377-385. doi: 10.2165/11318680-000000000-00000

4. Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. *Endocr Rev*. 2011; 32(4): 515-531. doi: 10.1210/er.2010-0029

5. Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. *Trends Pharmacol Sci*. 2011; 32(2): 63-71. doi: 10.1016/j.tips.2010.11.011

6. Heise T, Seewaldt-Becker E, Macha S, Hantel S, Pinnetti S. Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with type 2 diabetes. *Diabetes Obes Metab*. 2013; 15(7): 613-621. doi: 10.1111/dom.12073

7. Whalen K, Miller S, Onge ES. The Role of Sodium-Glucose Co-Transporter 2 Inhibitors in the Treatment of Type 2 Diabetes. *Clin Ther*. 2015; 7(6): 1150-1166. doi: 10.1016/j.clinthera.2015.03.004

8. Defronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: A new path towards normalizing glycaemia. *Diabetes Obes Metab*. 2012; 14(1): 5-14. doi: 10.1111/j.1463-1326.2011.01511.x

9. Monami M, Dicembrini I, Mannucci E. Effects of SGLT-2 inhibitors on mortality and cardiovascular events: A comprehensive meta-analysis of randomized controlled trials. *Acta Diabetol*. 2017; 54(1): 19-36. doi: 10.1007/s00592-016-0892-7

10. Mazidi M, Rezaie P, Gao HK, Kengne AP. Effect of sodium-glucose cotransport-2 inhibitors on blood pressure in people with type 2 diabetes mellitus: A systematic review and meta-analysis of 43 randomized control trials with 22 528 patients. *J Am Heart Assoc*. 2017; 6(6)pii: e004007. doi: 10.1161/JAHA.116.004007

11. Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Urinary tract infections in patients with diabetes treated with dapagliflozin. *J Diabetes Complications*. 2013; 27(5): 473-478. doi: 10.1016/j.jdiacomp.2013.05.004

12. Nicolle LE, Capuano G, Fung A, Usiskin K. Urinary tract infection in randomized Phase III studies of canagliflozin, a sodium glucose cotransporter 2 inhibitor. *Postgrad Med*. 2014; 126(1): 7-17. doi: 10.3810/pgm.2014.01.2720

13. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015; 373(22): 2117-2128. doi: 10.1056/NEJMoa1504720

14. Scheen AJ. EMPA-REG OUTCOME: Empagliflozin reduces mortality in patients with type 2 diabetes at high cardiovascular risk. *Rev Med Liege*. 2015; 70(11): 583-589.

15. Wu JH, Foote C, Blomster J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: A systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2016; 4(5): 411-419. doi: 10.1016/S2213-8587(16)00052-8

16. Giampaoli S, Palmieri L, Donfrancesco C, Lo Noce C, Pi-

ISSN 2377-164X http://dx.doi.org/10.17140/HROJ-4-141

lotto L, Vanuzzo D, on behalf of The Osservatorio Epidemiologico Cardiovascolare/Health Examination Survey Research Group. Cardiovascular health in Italy. Ten-year surveillance of cardiovascular diseases and risk factors: Osservatorio Epidemiologico Cardiovascolare/Health Examination Survey 1998-2012. *Eur J Prev Cardiol*. 2015; 22(Suppl 2): 9-37. doi: 10.1177/2047487315589011

17. Giampaoli S, Palmieri L, Panico S, et al. Favorable cardiovascular risk profile (Low Risk) and 10-year stroke incidence in women and men: Findings on 12 Italian population samples. *Am J Epid*. 2006; 163(10): 893-902. doi: 10.1093/aje/kwj110

18. Palmieri L, Donfrancesco C, Giampaoli S, et al. Favorable cardiovascular risk profile and 10-year coronary heart disease incidence in women and men: Results from the Progetto CUORE. *Eur J Cardiovasc Prev Rehabil*. 2006; 13(4): 562-570. doi: 10.1097/01.hjr.0000221866.27039.4b

19. Ferrario M, Chiodini P, Chambless LE, et al. CUORE Project Research Group. Prediction of coronary events in a low incidence population. Assessing accuracy of the CUORE Cohort Study prediction equation. *Int J Epidemiol*. 2005; 34(2): 413-421. doi: 10.1093/ije/dyh405

20. Giorda CB, Nicolucci A, Pellegrini F, et al. Improving quality of care in people with type 2 diabetes through the Associazione Medici Diabetologi-annals initiative: A long-term cost-effectiveness analysis. *Diabet Med*. 2014; 31(5): 615-623. doi: 10.1111/dme.12366

21. American Diabetes Association. Standards of Medical Care in Diabetes. *Diabetes Care*. 2014; 37(suppl 1): S11-S63. doi: 10.2337/dc14-S014

22. National Center for Health Statistics. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Web site. http://www.cdc.gov/nchs/icd/icd9cm.htm. Accessed March 2017.

23. ISO - Ministero della Salute. ATTUAZIONE DELLA DIRETTIVA 93/42/CEE CONCERNENTE I DISPOSITIVI MEDICI. Decreto lgs. 24 febbraio 1997, n. 46 emendato col D. lgs. 25.01.2010,n.37 - Recepimento Direttiva 2007/47/CE. Web site. http://www.salute.gov.it/imgs/c_17_paginearee_1636_listafile_itemname_1_file.pdf. Accessed July 22, 2017.

24. Levey AS, Stevens LA, Schmid CH, et al; CKDEPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009; 150 (9): 604-612.

25. Ceriello A, Gallo M, Armentano V, Perriello G, Gentile S, De Micheli A; Associazione Medici Diabetologi. Personalizing treatment in type 2 diabetes: A self-monitoring of blood glucose inclusive innovative approach. *Diabetes Technol Ther*. 2012; 14(4): 373-378. doi: 10.1089/dia.2011.0233

26. American Diabetes Association. Standards of Medical Care in Diabetes 2016. *Diabetes Care*. 2016; 39(1): S13-S22. doi: 10.2337/dc16-S001

27. Nathan DM, Buse JB, Davidson MB, et al; American Diabetes Association.; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: Aconsensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009; 32(1): 193-203. doi: 10.2337/dc08-9025

28. Akalin S, Berntorp K, Ceriello A, et al; Global Task Force on Glycaemic Control. Intensive glucose therapy and clinical implications of recent data: A consensus statement from the Global Task Force on Glycaemic Control. *Int J Clin Pract*. 2009; 63(10): 1421-1425. doi: 10.1111/j.1742-1241.2009.02165.x

29. Roden M, Weng J, Eilbracht J, et al; EMPA-REG MONO trial investigators. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol*. 2013; 1(3): 208-219. doi: 10.1016/S2213-8587(13)70084-6

30. Häring HU, Merker L, Seewaldt-Becker E, et al; EMPA-REG MET Trial Investigators. Empagliflozin as add-on to metformin in patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2014; 37(6): 1650-1659. doi: 10.2337/dc13-2105

31. Häring HU, Merker L, Seewaldt-Becker E, et al; EMPA-REG METSU Trial Investigators. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: A 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2013; 36(11): 3396-3404. doi: 10.2337/dc12-2673

32. Kovacs CS, Seshiah V, Swallow R, et al; EMPA-REG PIO™ trial investigators. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: A 24-week, randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2014; 16(2): 147-158. doi: 10.1111/dom.12188

33. Naing S, Poliyedath A, Khandelwal A, Sigala T. Impact of EMPA-REG OUTCOME® on the management of type 2 diabetes mellitus: A review for primary care physicians. *Postgrad Med*. 2015; 128(8): 822-827. doi: 10.1080/00325481.2016.1245093

34. Søfteland E, Meier JJ, Vangen B, Toorawa R, Maldonado-Lutomirsky M, Broedl UC. Empagliflozin as add-on therapy in patients with type 2 diabetes inadequately controlled with linagliptin and metformin: A 24-week randomized, double-blind,

ISSN 2377-164X http://dx.doi.org/10.17140/HROJ-4-141

parallel-group trial. *Diabetes Care*. 2017; 40(2): 201-209. doi: 10.2337/dc16-1347

35. Barnett AH, Mithal A, Manassie J, et al EMPA-REG RENAL trial investigators. *Lancet Diabetes Endocrinol*. 2014; 2(5): 369-384.

36. Rodondi N, Locatelli I, Aujesky D, et al. Health ABC Study. Framingham risk score and alternatives for prediction of coronary heart disease in older adults. *PLoS One*. 2012; 7(3): e34287. doi: 10.1371/journal.pone.0034287

37. D'Agostino RB, Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. *Circulation*. 2008; 117(6): 743-753. doi: 10.1161/CIRCULATIONAHA.107.699579

38. Genest J, McPherson R, Frohlich J, et al. Canadian cardiovascular society/canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult. *Can J Cardiol*. 2009; 25(10): 567-579.

39. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: The reynolds risk score. *JAMA*. 2007; 297(6): 611-619. doi: 10.1001/jama.297.6.611

40. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: The Reynolds Risk Score for men. *Circulation*. 2008; 118(22); 2243-2251. doi: 10.1161/CIRCULATIONAHA.108.814251

41. Artigao-Rodenas LM, Carbayo-Herencia JA, Divisón-Garrote JA, et al; on behalf of the Grupo de EnfermedadesVasculares de Albacete (GEVA). Framingham risk score for prediction of cardiovascular diseases: A population-based study from southern Europe. *PLoS One*. 2013; 8(9): e73529. doi: 10.1371/journal.pone.0073529

42. Istituto Superiore di Sanità. Carta del rischio cardiovascolare. Progetto CUORE 2016. Web site. http://www.cuore.iss.it/valutazione/carte-pdf.pdf. Accessed July 22, 2017.

43. Kosiborod M, Cavender MA, Fu AZ, et al; CVD-REAL Investigators and Study Group. Lower risk of heart failure and death in patients initiated on sglt-2 inhibitors versus other glucose-lowering drugs: The CVD-REAL study. *Circulation*. 2017: 136(3): 249-259. doi: 10.1161/CIRCULATIONAHA.117.029190