**DECLARE-TIMI 58: Participants’ Baseline Characteristics**

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**Abstract:**

**Background:** Cardiovascular (CV) outcome trials with new glucose lowering agents (GLA) are designed to prove CV safety in high CV risk populations. However, the level of CV risk differs greatly among trials, which may influence comparability and generalizability of results.

**Aim:** We describe baseline characteristics of participants randomized in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58) trial, the pivotal study to assess CV outcomes with dapagliflozin.

 **Results:** The DECLARE-TIMI 58 trial randomized and will analyze 17,160 patients with type 2 diabetes (T2D) to treatment with dapagliflozin (10 mg/day) or matching placebo. The participants' mean age (SD): 63.8±6.8, 62.6%: male, mean diabetes duration: 11.8±7.8 years, HbA1c: 8.3%±1.2% and BMI: 32.1±6.0 kg/m2. Randomization included 6,971 (40.6%) patients with atherosclerotic cardiovascular disease (CVD), and 10,189 (59.4%) patients with multiple risk factors (MRF) for CV disease (defined as men: age ≥55 or women: ≥60; with at least one of: dyslipidemia, hypertension, or smoking). Patients with CVD compared with patients with MRF were younger (62.5±8.1 vs. 64.7±5.6 years), more frequently male (72.1% vs. 56.1%), less often used metformin (74.6% vs. 81.2%), more often used insulin (44.2% vs. 36.4%), and more frequently used statins, aspirin, clopidogrel and beta blockers (82.2% 71.1%, 24.7% and 66.6% vs. 63.7%, 39.1%, 1.5% and 32.3%), respectively.

**Conclusion:** The DECLARE-TIMI 58 trial is expected to provide conclusive data on the effect of treatment with dapagliflozin versus placebo, each in addition to standard of care, on CV outcomes in a broad patient population with T2D and CVD or MRF for CVD.

**Introduction:**

Sodium glucose co-transporters 2 (SGLT2) inhibitors are glucose lowering agents (GLA) developed for the treatment of hyperglycaemia in patients with type 2 (1) and type 1 (SGLT-2 inhibitors, including dapagliflozin, are currently under development for use in type 1 diabetes) (2) diabetes. Their mechanism of action is selective inhibition of the SGLT2 cotransporters which are located in the first segment of the kidney proximal tubules (3). SGLT2 reabsorbs 80-90% of the glucose filtered by the glomeruli, by coupling the electrochemical energy produced by active sodium transport to the co-transport of glucose (3). Inhibition of SGLT2 leads to glycosuria and lowers blood glucose levels. Dapagliflozin, a member of the SGLT2 inhibitor drug class, was previously shown to be effective in lowering glucose and HbA1c in diverse clinical settings including drug naïve patients (4-6), as an add-on and/or compared with a variety of other GLAs (7-11), and insulin (12,13) for up to 4 years (14,15). In addition to the glucose lowering effect, treatment with SGLT2 inhibitors results in an average of 2-3 kg weight loss (mainly fat mass), attributed predominantly to glycosuria and resultant calorie loss (16). Additionally, a small but significant reduction of 2-3 mmHg in systolic blood pressure has been observed. The underlying mechanisms of the blood pressure effects may involve: reduced renin angiotensin system activity due to tubular glomerular feedback (17,18), improved vascular function, and alterations in hormonal signalling as extra-renal protective effects (19-21).

The main adverse events identified to date with this drug class include increased risk for genital mycotic and urinary tract infections (22). From post-marketing data, safety communications have been issued for a potential increased risk of (euglycemic) diabetic ketoacidosis (DKA) (23,24) and an FDA warning regarding a risk for acute renal failure (25). A numerical imbalance was observed in the incidence of transitional cell carcinoma of the bladder in the phase 2-3 of dapagliflozin development program (22). Dapagliflozin has been approved for use in type 2 diabetes (T2D) by world-wide regulators, including in the US, having met pre-marketing safety requirements.

In 2008 the United States Food and Drug Administration (FDA) published guidance to the pharmaceutical industry regarding the establishment of CV safety of new GLA (26). The first CV safety trial completed with SGLT2 inhibitors was the EMPA-REG OUTCOME trial that assessed the CV safety of empagliflozin in 7,020 patients with T2D and prevalent atherosclerotic CVD (27). The trial was the first cardiovascular outcome trial (CVOT) with a GLA that demonstrated not only CV safety, but also CV superiority of empagliflozin. Empagliflozin was shown to reduce the primary composite endpoint of CV death, MI, or stroke as well as CV mortality, total mortality, hospitalization for heart failure (HF) and several renal outcomes (27,28). The subsequently published results of the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program also demonstrated a reduction in the composite primary cardiovascular endpoint with canagliflozin (29). There has not yet been a completed CVOT with dapagliflozin but its CV safety in populations with varying CV risk profiles was assessed in a dedicated meta-analysis (30) and as part of a larger meta-analysis that examined the CV safety of all SGLT2 inhibitors (31).

DECLARE-TIMI 58 trial is a randomized trial designed to establish the CV safety and potential CV benefit of dapagliflozin in a large and diverse population of patients with T2D and either CVD or MRF for CVD.

**Study design and population:**

The DECLARE-TIMI 58 trial [NCT01730534] is a multicenter, multinational, double-blind, placebo controlled, phase 3b study, with primary safety and co-primary efficacy end points. The primary safety objective of the trial is to establish that dapagliflozin is non-inferior to placebo by demonstrating that the upper boundary of the 2-sided 95% CI for the estimated risk ratio comparing the time to first event of the composite endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke (MACE) observed with dapagliflozin vs. placebo is less than 1.3, as mandated by the FDA guidance (26).

Other safety measurements that are collected throughout the trial include: serious adverse events and events of special interest (EOSI). EOSI includes: liver events, renal events, fractures, malignancies (particularly bladder cancer), hypersensitivity, genital and urinary infections, volume depletion and major hypoglycemic events. Amputations and diabetic ketoacidosis (DKA) are asked for at every visit and data is collected in specific forms. Liver events, malignancies and DKA are adjudicated.

The efficacy objectives of the trial are to determine whether treatment with dapagliflozin vs. placebo, when added to current background therapy will result in a reduction of the co-primary efficacy outcomes of MACE and the composite endpoint of CV death or hospitalization for HF. The secondary endpoints include a renal composite endpoint ]confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m2 and/or ESRD (dialysis ≥90 days or kidney transplantation, or confirmed sustained eGFR <15ml/min/1.73m2) and/or renal or CV death[ and all-cause mortality. Further details regarding the design of the DECLARE-TIMI 58 trial are discussed in a separate manuscript (32).

The study recruited patients with type 2 diabetes at increased CV risk according to 2 categories: 1) ≥40 years old with established atherosclerotic CV disease: ischemic heart disease, peripheral artery disease or cerebrovascular disease (CVD group), and 2) ≥55-year-old males and ≥60 year old females, with at least one of the following risk factors: dyslipidemia, hypertension or current smoking (MRF group). Patients in both groups might have other, non-ischemic cardiovascular disease, including heart failure and/or rhythm disorders. The main exclusion criteria were: HbA1c ≥12% or HbA1c<6.5% (6.5% to <7% capped at approximately 5%), AST or ALT >3 x ULN or total bilirubin >2.5 x ULN, creatinine clearance (CrCl) < 60 ml/min (based on the Cockcroft-Gault equation), unexplained hematuria, acute cardiovascular or cerebrovascular event within 8 weeks of randomization, lifetime history of bladder cancer or recurrent urinary tract infections, history of any malignancy (other than non-melanoma skin cancer) within the recent 5 years, use of an SGLT2 inhibitor, pioglitazone or rosiglitazone. Patients were randomized in a 1:1 ratio to dapagliflozin 10 mg/day or matching placebo.

A total of 1,390 subjects with MACE events will be required to have 85% power to demonstrate superiority of dapagliflozin to placebo if the true HR is 0.85, i.e., a 15% relative risk reduction, with a one-sided alpha of 0.0231. Approximately 17,150 randomized patients will be required for the study, with an assumed annual event rate of 2.1% on placebo.

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**Results:**

The DECLARE-TIMI 58 trial is presently being conducted in 33 countries at 882 sites led by cardiologists, endocrinologists, primary care physicians and nephrologists. A total of 25,836 patients were screened and after 1-2 months of single blind placebo run-in period with adequate compliance, 17,190 were randomized whereof 17,160 patients will be evaluated in the primary analysis, 30 patients were excluded from all analyses because of significant GCP violations at a single site in a different trial of dapagliflozin.

Table 1 and Figure 1 present baseline demographic and clinical characteristics of the entire trial population as well as of the 6,971 (40.6%) patients classified at baseline in the CVD group and the 10,189 (59.4%) patients classified in the MRF group.

The overall trial population is predominately male (62.6%) with an average age of 63.8 years (SD 6.8). The average BMI is 32.1 kg/m2 (SD 6.0) and average HbA1c is 8.3% (SD 1.2) (Table 1). Distribution of recruitment is: Europe (44.5%), North America (31.9%), Latin America (10.9%) and Asia/Pacific (12.7%), leading to a predominately white (79.6%) population (Figure 1A). Diabetes duration at baseline was heterogeneous, spanning from <5 years to >20, with approximately half of the population having disease duration of ≥10 years (Figure 1B).

Patients with CVD compared with those with MRF were more likely to be male (72.1% vs. 56.1%), had similar diabetes duration (12.0 vs. 11.7 years) and mean HbA1c (8.33% vs. 8.26%). Both subgroups had a high prevalence of CV risk factors especially medically treated hypertension (87.7% and 90.6% in the CVD and MRF groups, respectively). Nearly 10% (n=1,698) of the overall trial population had heart failure at baseline and over 6% had atrial fibrillation at baseline, both collected by the investigators using specific questions (Table 1). Data regarding heart failure at baseline and during the trial that was retrospectively and prospectively collected included ejection fraction wherever available.

There was less use of metformin and sulfonylurea in the CVD group compared to the MRF group (74.6% vs. 81.2% and 38.0% vs. 43.2% respectively). There was greater use of insulin in the CVD group compared to the MRF group (44.2% vs. 36.4%) (Figure 1C). There was a high level of use of anti-hypertensive medication in the trial, with a markedly higher use of beta-blockers in the CVD group (66.6% vs. 32.3%) (Figure 1D). There was higher use of anti-platelets and anti-coagulant agents in the CVD group (aspirin: 71.1% vs. 39.1%, clopidogrel: 24.7% vs. 1.5%, warfarin: 6.1% vs 3.5% and NOACs: 2.1% vs 1.1%) (Figure 1E). Lastly, there was higher use of lipid lowering agents, most noticeably statins in the CVD group (82.2% vs. 63.7%) (Figure 1F).

Previous MI, PCI and CABG were reported in 20.9%, 21.3% and 9.8% of the entire trial population and in 51.4%, 52.4% and 24.1% of the CVD population, respectively (Table 2). Previous ischemic stroke was recorded in 6.5% and 15.9% of the entire study population and the CVD group (Table 2).

There were very small differences in baseline blood pressure (both systolic and diastolic), LDL and HDL cholesterol, triglycerides and eGFR between the MRF and CVD groups (Table 3).

While creatinine clearance (CrCl) < 60 ml/min (based on the Cockcroft-Gault equation) was an exclusion criteria, the mean eGFR, when calculating with the MDRD (modification of diet in renal disease) formula, was 86.1 (standard deviation (SD) 21.8) ml/min/1.73m2, including 1,565 patients (9.1%) with eGFR <60 ml/min/1.73m2 (Table 1). 1,393 patients (8.1%) were reported by the investigators as having nephropathy, however there were 5,192 (30.2%) patients with urinary albumin:creatinine ratio ≥30 mg/g.

**Discussion:**

It has been well established that improved glycemic control is associated with a reduced rate of microvascular complications; however, data regarding the effect of glycemic control on macrovascular outcomes are much weaker with significant discordance (33). The development of new classes of GLAs that reduce conventional CV risk factors (weight and blood pressure), such as glucagon like peptide-1 receptor agonists (GLP-1 RA) and SGLT2 inhibitors, raised the hope that these novel GLAs might decrease CV risk in patients with T2D.

These expectations were first met with the publication of the EMPA-REG OUTCOME trial results that demonstrated a 14% relative risk reduction (HR 0.86 95% CI 0.74-0.99) in the primary MACE outcome of CV death/MI/stroke, mostly due to a 38% relative risk reduction (HR 0.62 95%CI 0.49-0.77) in CV mortality with the SGLT2 inhibitor empagliflozin vs. placebo (27). The recently published CANVAS Program evaluating canagliflozin vs. placebo in 2 trials that were combined for primary analysis, also demonstrated a 14% reduction (HR 0.86 95%CI 0.75-0.97) in the primary 3-point MACE outcome of CV death/MI/stroke with a positive contribution of all three components (29). The DECLARE-TIMI 58 trial with its larger and broader population and the planned longer follow-up will distinguish this trial from previously published CVOTs with SGLT2 inhibitors.

 In EMPA-REG OUTCOME and the CANVAS Program, the relative risk for hospitalization for HF was reduced by 35% (HR 0.65 95%CI 0.50-0.85) and 33% (HR 0.67 95%CI 0.52-0.87) respectively (27,29). The DECLARE-TIMI 58 with combined co-primary efficacy outcomes of MACE and the composite endpoint of CV death or hospitalization for HF will provide an important view on common and important cardiac outcomes in patients with type 2 diabetes.

The safety analysis of the DECLARE-TIMI 58 trial will provide data on dapagliflozin in relation to some of the questions raised after the publication of the EMPA-REG trial and the CANVAS program (27,29). Both amputation related and DKA events are actively looked after and collected in specifically designed forms; thereby providing event rates for dapagliflozin and placebo and also ensuring a thorough collection of all the data related to these events.

The underlying hypothesis of the DECLARE-TIMI 58 trial is that the improvement of multiple metabolic and hemodynamic parameters including but not limited to glucose, blood pressure, weight, intra glomerular pressure, ketone metabolism and others (34-37), might improve CV outcomes not only in populations with established CV disease but also in populations with multiple CV risk factors. Therefore, this trial included 10,189 patients without previous CVD that comprise 59.4% of the trial population. In comparison, the EMPA-REG OUTCOME included only patients with prevalent atherosclerotic CVD and the CANVAS Program included 3,486 (34.4% of the program population) with MRF (27,29). The inclusion of the larger MRF population in DECLARE TIMI 58 increases the potential applicability of the trial results to a larger population of patients in a real-world setting. However, the trial was designed and powered to confirm the primary outcome in the entire study population.

The length of median follow-up in the EMPA-REG OUTCOME and CANVAS Program was 3.1 and 2.4 years, respectively. The longer follow-up of patients, in the DECLARE-TIMI 58 trial, [expected to be more than 4 years], will enable us to better detect not only the immediate effects of the drug, but also its' longer term effects that may be due to favourable effects on mediators of atherosclerotic CVD risk (e.g. blood pressure, weight, lipid profile, progression of kidney disease, etc.).

In addition, the large sample size, as well as the follow up time will enable evaluation of bladder cancer as follow up to the numerical imbalance of bladder cancer observed in the dapagliflozin phase 2 and 3 development program.

The rapid recruitment into the trial was made possible by the large number of countries and sites participating. This enrolment pattern minimizes the risk of a time dependent cohort effect caused by changes in background therapy as may be seen in trials in which the recruitment phase took several years (38) or in the combination of different trials, as was done in the CANVAS Program (29).

The DECLARE-TIMI 58 trial has a high proportion of patients taking statins, anti-platelets and/or anti-coagulant, beta-blockers and ACEI/ARB (39). This is in accordance with the FDA guidance that requires demonstrating CV safety and possible benefit of new GLAs in addition to best available guideline-directed therapy (26). Not surprisingly, there are differences in the frequency of use of CV drugs between the CVD and the MRF subgroups, most noticeably, in the CVD group there is a higher rate of use of: ACEI/ARB, beta blockers, diuretics, mineralocorticoid receptor antagonists, aspirin, clopidogrel, statins and ezetimibe, where these agents are more clearly indicated in treatment guidelines (39). Given the large sample size of the study, it will be possible to examine subgroups based on concomitant medication usage, but one would not expect an interaction by treatment affecting the overall analyses.

There are also differences between CVD and MRF populations regarding the distribution of GLAs, mainly higher use of insulin and lower use of metformin, sulfonylureas and DPP4 inhibitors in the CVD group. These differences might be attributed to differences in diabetes duration or renal function between the two subgroups. The difference in GLA use between the two groups may also lead to differences in the rate of hypoglycaemia and its consequences.

The baseline mean eGFR in the EMPA-REG OUTCOME and CANVAS Program were 74.1 ml/min/1.73m2 and 76.5 ml/min/1.73m2, respectively, while in the DECLARE-TIMI 58 trial it was 86.1 ml/min/1.73m2. It is possible that the different exclusion criteria in DECLARE TIMI 58 (CrCl<60 ml/min) could impact its potential to show similar clinical renal outcomes to those shown in the EMPA-REG OUTCOME trial that had more permissive renal inclusion criteria (28). Despite the fact that the DECLARE-TIMI 58 population has comparatively less severe renal dysfunction than the other 2 reported CVOTs of SGLT2i’s, the larger number of patients, the prolonged follow-up and the pre-specification of renal outcomes in the analysis of the DECLARE-TIMI 58 trial ensure that the trial is powered to assess renal outcomes with dapagliflozin (31).

**Summary:**

The DECLARE-TIMI 58 population is broad and includes large groups of patients with established CVD as well as with MRF for CVD. This diverse population will strengthen the external applicability of the trial results. The trial will also help to delineate the impact of prolonged treatment with dapagliflozin, an SGLT2 inhibitor, on patients with type 2 diabetes at high risk for CVD. The trial will broaden our knowledge regarding the CV and renal safety, as well as the potential benefit of dapagliflozin. The results will guide future therapeutic decision making in patients with T2D and increased CV risk.

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**Author Contributions:**

IR and OM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Raz and Mosenzon served as co-first authors and contributed equally to the work.

*Study concept and design: IR, OM, DLB, LAL, DKM, JW,IAMG-N, AML, PAJ, MSS, SDW*

*Conduct/data collection:IR, OM, MPB, AC, ETK, MGS, DLB, LAL, DKM, JW, IAMG-N, AML, PAJ, MSS, SDW*

*Statistical analysis: IR, OM, PAJ*

*Drafting of the manuscript: IR, OM*

*Critical revision of the manuscript for important intellectual content: All* *authors*

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**Table 1-** Patient baseline characteristics for the total population, cardiovascular disease and multiple risk factor population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **TOTAL****(N=17,160)** | **CVD(N=6,971)** | **MRF(N=10,189)** |
| **Sex- n, (%)** | Men | 10,738 (62.6) | 5023 (72.1) | 5715 (56.1) |
| **Age (years)** | mean (SD) | 63.8 (6.8) | 62.5 (8.1) | 64.7 (5.6) |
| **BMI (kg/m²)** | mean (SD) | 32.1 (6.0) | 32.1 (6.0) | 32.0 (6.0) |
| **HbA1c (%)** | mean (SD) | 8.29 (1.2) | 8.33 (1.2) | 8.26 (1.2) |
| **Cardiovascular Risk Factors –n, (%)** | LDL-C > 130 mg/dL  | 3174 (18.5) | 1110 (15.9) | 2064 (20.3) |
| On therapy for hypertension | 15343 (89.4) | 6116 (87.7) | 9227 (90.6) |
| Tobacco Use | 2488 (14.5) | 1031 (14.8) | 1457 14.3) |
| **Cardiac History n, (%)** | Angina pectoris | 2802 (16.3) | 2121 (30.4) | 681 (6.7) |
| Heart failure | 1698 (9.9) | 1133 (16.3) | 565 (5.5) |
| Atrial fibrillation/flutter | 1110 (6.5) | 599 (8.6) | 511 (5.0) |
| **Investigator-reported history of microvascular complications n, (%)** | Retinopathy | 2131 (12.4) | 922 (13.2) | 1209 (11.9) |
| Retinal laser treatment | 587 (3.4) | 279 (4.0) | 308 (3.0) |
| Nephropathy | 1393 (8.1) | 620 (8.9) | 773 (7.6) |

Based on data as of the 2nd of April 2017

CVD- Cardiovascular Disease

MRF- Multiple risk Factor

LDL - Low-density Lipoprotein

**Table 2-** Cardiovascular disease in the subset of patients with baseline cardiovascular disease

|  |  |  |  |
| --- | --- | --- | --- |
|  | **n** | **% of TOTAL(N=17,160)** | **% of CVD(N=6,971)** |
| Myocardial Infarction | 3580 | 20.9 | 51.4 |
| Percutaneous Coronary Intervention | 3655 | 21.3 | 52.4 |
| CABG | 1678 | 9.8 | 24.1 |
| Coronary Stenosis≥50% in at least 2 coronary arteries, by PCI | 2119 | 12.3 | 30.4 |
| Ischemic Stroke | 1107 | 6.5 | 15.9 |
| Carotid Stenting | 120 | 0.7 | 1.7 |
| Carotid Endarterectomy | 136 | 0.8 | 2.0 |
| Obstructive Peripheral Arterial Disease | 1025 | 6.0 | 14.7 |
| Peripheral Arterial Stenting | 271 | 1.6 | 3.9 |
| Peripheral Surgical Revascularization | 215 | 1.3 | 3.1 |
| Non-Traumatic Lower Extremity Amputation | 105 | 0.6 | 1.5 |
| Current symptoms of intermittent claudication | 933 | 5.4 | 13.4 |

CVD- Cardiovascular Disease

CABG - Coronary artery bypass grafting

PCI- Percutaneous Coronary Intervention

**Footnote:** Based on data as of the 2nd of April 2017

**Table 3-** Vital signs and laboratory measurements at screening for the total population, and the sub-populations with cardiovascular disease and multiple risk factors

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **TOTAL(N=17,160)** | **CVD(N=6,971)** | **MRF(N=10,189)** |
| **Systolic BP (mmHg)** | mean (SD)  | 135.0 (15.5) | 134.0 (15.9) | 135.6 (15.1) |
| **Diastolic BP (mmHg)** | mean (SD)  | 78.0 (9.1) | 77.4 (9.35) | 78.4 (8.9) |
| **Pulse (beats/min)** | mean (SD)  | 73.0 (10.6) | 71.5 (10.6) | 74.1 (10.5) |
| **Total cholesterol (mmol/l)** | mean (SD)  | 4.4 (1.2) | 4.2 (1.2) | 4.5 (1.1) |
| **LDL cholesterol (mmol/l)** | mean (SD)  | 2.3 (0.9) | 2.1 (0.9) | 2.4 (0.9) |
| **HDL cholesterol (mmol/l)** | mean (SD)  | 1.2 (0.3) | 1.2 (0.3) | 1.3 (0.3) |
| **Triglycerides (mmol/l)** | mean (SD)  | 2.0 (1.5) | 2.1 (1.7) | 2.0 (1.4) |
| **eGFR (mL/min/1.73 m²)** | mean (SD)  | 86.1 (21.8) | 86.1 (21.8) | 87.0 (21.4) |
| median (Q1, Q3) | 84.0 (71.0, 99.0) | 83.0 (69.0, 98.0) | 85.0 (72.0, 100.0) |
| **eGFR – n, (%)** | <60 mL/min/1.73m² | 1565 (9.1) | 761 (10.9) | 804 (7.9) |
| ≥60 - <90 mL/min/1.73m² | 8739 (50.9) | 3584 (51.4) | 5155 (50.6) |
| ≥90 mL/min/1.73m² | 6855 (39.9) | 2626 (37.7) | 4229 (41.5) |
| **Urinary ACR (mg/g)** | median (Q1, Q3) | 13.1 (6.0, 43.6) | 15.0 (6.3, 55.1) | 12.1 (5.9, 36.3) |
| **Urinary ACR– n, (%)** | <30 mg/g | 11652 (67.9) | 4452 (63.9) | 7200 (70.7) |
| 30 - ≤300 mg/g | 4023 (23.4) | 1784 (25.6) | 2239 (22.0) |
| >300 mg/g | 1169 (6.8) | 576 (8.3) | 593 (5.8) |

CVD- Cardiovascular Disease

MRF- Multiple risk Factor

BP –Blood Pressure

LDL - Low-density Lipoprotein

HDL - High-density Lipoprotein

ACR – Albumin-to-Creatinine Ratio

eGFR - Estimated Glomerular Filtration Rate

**Footnote:** Based on data as of the 2nd of April 2017

**Legend to Figures:**

**Figure 1-** Comparing patients' baseline characteristics between the cardiovascular disease (CVD) population and multiple risk factor (MRF) population.

Comparing different aspects of baseline characteristics between the CVD population and MRF population: race, region and ethnicity (Panel A), years since diagnosis of diabetes (Panel B) and different medication groups: glucose lowering therapy (Panel C), anti-hypertensive therapy (Panel D), anti-platelets/anti-coagulants (Panel E) and lipid lowering therapy (Panel F).

**Figure 1-** Comparing patients' baseline characteristics between the cardiovascular disease (CVD) population and multiple risk factor (MRF) population.

**Footnote:** Based on data as of the 2nd of April 2017