Incidence and Predictors of Cardiovascular Disease Among Type 1 and Type 2 Diabetes Mellitus in Tertiary Health Care Setting of Ethiopia: 8-Year Retrospective Follow Up Study.

Gebiso Debele (gebisa.roba123@gmail.com)  
Mettu University  

Bilisumamulifna Kefeni  
Mettu University  

Shuma Kanfe  
Mettu University  

Tadesse Ayele  
University of Gondar  

Haileab Wolde  
University of Gondar  

Melaku Yenit  
University of Gondar  

Mohammedjud Ahmed  
Mettu University  

Research Article

Keywords: Incidence, cardiovascular disease, predictors, type 1 and type 2 diabetes

DOI: https://doi.org/10.21203/rs.3.rs-107097/v1

License: ✌️ This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

Background: Cardiovascular disease (CVD) is a major cause of death and disability among people with diabetes in the world and it is being a major barrier to sustainable human development. Despite, CVDs have continued to devastate human survival, few studies in Ethiopia have focused on its prevalence which alone are insufficient to assess the risk of incident cardiovascular events. Therefore, we determined the incidence and predictors of cardiovascular disease among diabetic patients.

Methods: A retrospective cohort study was conducted on 399 randomly selected diabetes patients. Data were entered using Epi-Data and analyzed using Stata version 14. Multivariable Weibull proportional hazards regression analysis was used to identify the predictors of CVDs (namely, coronary heart disease (CHD), stroke, and peripheral arterial disease (PAD)) at 5% level of significance.

Results: After a median follow-up of 5.9 years, the overall incidence rate of CVD per 100 person–years was 2.71 (95% CI: 16.9–17.6). The Multivariable survival analysis showed a significant association of CKD; (Adjusted Hazard Ratio (AHR) (95%CI) 2.53 [1.36, 4.72]), Systolic blood pressure (SBP) >/= 140; (AHR (95%CI) (4.30 [2.12, 8.73]) and triglyceride >/= 200 mg/dl; (AHR (95%CI) (5.10 [2.02, 12.89]) with risk of incident CVD.

Conclusion: CVD is being a public health problem among diabetic patients in Ethiopia. SBP >/= 140, chronic kidney disease and high triglyceride were independent predictors of new CVD among diabetic patients. These findings emphasize the need of attention for CVD patients with CKD and HTN comorbidities and longer follow up period using prospective study design to determine the long-term effects of predictors of CVD among diabetic patients.

Introduction

Many Sub-Saharan African (SSA) countries including Ethiopia are facing a high burden of noncommunicable diseases (NCDs) (1). Diabetes mellitus (DM) is one of global epidemic NCD which was estimated to affect 463 million peoples globally and 4.3% of Ethiopian population according to 2019 International diabetic federation (IDF) (2). One of the severity of DM is explained by its association with risk of CVD and other clinical complications (3). Individual with DM had a two to eight-fold more risk of heart disease as well as an increased risk of mortality up to 3 times (4) and CVD is responsible for 80% of the mortality in diabetes (5).

CVDs are a group of diseases involving the heart or blood vessels and now it is the leading causes of diabetes-related morbidity and mortality (6). Globally, there were an estimated 422.7 million cases of CVD and Africa were one of the countries with the highest age-standardized prevalence in 2015 (7). The age-adjusted incidence rate of CVD was 6081.6 per 100,000 in 2017 (8). According to systematic literature review from 2007 to 2017 magnitude of CVD among DM was about 32.2% in the world (9).
CVD was the world's leading killers, responsible for a combined 15.2 million deaths in 2016, increased to 17.8 million in 2017 and remained the leading causes of death in the last 15 years (8, 10). According to 2015 global burden of disease there were 418, 285 and 349 per 100,000 death rates due to CVD in central, western and eastern SSA countries (7). CVD death had increased by more than 50% in SSA for the past three decades (11) and incline to happen at younger ages, leading to a high number of disability adjusted life years (12, 13).

Several epidemiological researchers around the world identified older age and longer duration of DM (14), high density lipoprotein cholesterol (HDL-C) level (15), smoking and heavy alcohol consumption (16), hypertension (HTN) (17, 18), poor glycemic control (high glycosylated hemoglobin (HbA1c) (18) and triglyceride (TG) (19) to be independent predictors for incident CVD. In response to the recent rise of CVDs in developing countries, World health organization (WHO) has identified very cost-effective interventions that are applicable even in low-resource settings for prevention and control of CVDs (20).

Although, WHO predicts a rapid increase of CVDs in SSA by 2030, researchers perceive that CVDs are not a priority public health problem in the region (21). This perception is undermining the existing burden of the problem in this continent. Despite, CVDs have continued to devastate the human survival through the premature deaths of its workforce, few studies in Ethiopia have limited to crosssectional studies which alone are insufficient to assess the risk of incident cardiovascular events. Therefore, we determined the incidence and predictors of cardiovascular disease among diabetic patients, from 2012 to 2020.

**Methods And Materials**

**Study setting, design and period**

This is a retrospective follow up study done at Jimma University Medical center (JUMC) to assess the incidence and predictors of CVD among diabetic patients from September 5, 2012 to February 25, 2020. JUMC is one of the largest public hospitals that found in Jimma zone, Oromia regional state, Ethiopia. It is found at about 352 kilometers (KM) from Addis Ababa, the capital city of Ethiopia. Every year approximately 9,000 inpatient and 80,000 outpatients were served in hospital, coming from the catchment population of about 15 million people. In addition to other services, chronic disease follows-up service is being provided and diabetic clinic is found separated from other chronic disease.

**Study population**

Our reference population involves all type 1 DM (T1DM) and type 2 DM (T2DM) patients (age of 15 years and above) who had follow-up at JUMC and all newly diagnosed T1DM and T2DM patients during the study period were our study population. The study population was recruited from September 5, 2012 to September 8, 2015 and each case was followed until February 25 2020. Once diagnosed for T1DM or T2DM follow up immediately started for all patient. We followed our cohort of DM patients to measure the primary outcomes and new cases of CVD were recorded among diabetic patients during the follow up.
period. Diabetic patients with no history of CVD at baseline were included in the study. Patients with unknown date of diabetes and cardiovascular disease diagnosis were excluded from the study.

**Measurements and operational definition**

Our primary outcome was CVD and defined as the first non-fatal CHD, stroke, or PAD, diagnosed by specialized physicians based on the clinical assessment and confirmed using diagnostic tests. We excluded sudden death from the definition and only non-fatal CVD was included. A non-fatal CHD was confirmed using the WHO’s criteria in case of raised levels of cardiac biomarkers with either symptoms or electrocardiograms suggestive of ischemia (22). A non-fatal stroke was defined as typical dysfunction of neurology that last > 24 hour excluding other diagnoses and was taken from patients records. Peripheral arterial occlusion was defined as an sudden onset arterial event with a duration of greater than 2 weeks, and resulted in symptomatic limb ischemia (23). In case when a subject had experienced greater than one endpoint, the first event was used to define the onset of CVD. Once patients diagnosed with T1DM or T2DM they immediately started follow up making imbalance nature of data. Our independent variables include: socio-demographics, clinical parameters, laboratory and comorbidities characteristics. Socio-demographics includes: age, sex and residence. Clinical and laboratory characteristics includes: type of DM, type of treatment, family history of diabetes, body mass index (BMI) and classified as low (<18.5 kg/m²), normal (18.5-24.9 kg/m²) and high (≥ 25 kg/m²) according to WHO criteria (24)), HDL-C, low density lipoprotein cholesterol (LDL-C), TG, total cholesterol, diastolic blood pressure (DBP), SBP, baseline fasting blood sugar (FBS), creatinine and history of acute complication. The third characteristic assessed was the comorbidities and this includes HTN (based on physician-registered diagnosis on the medical record when SBP ≥ 140 mmHg and DBP ≥ 90 mmHg), diabetic retinopathy, CKD and diabetic retinopathy.

**Sample size and sampling procedure**

The final sample size of 424 was calculated using Schoenfeld formula for survival analysis (25) using 8.1% probability of events and 2.74 adjusted hazard ratio (AHR) of TG from previous studies (14, 19). We assumed 95% confidence level, 80% power and 10% of withdrawal probability and this sample was computed using Stata version 14. Then subjects were selected using simple random sampling technique by collecting the identification number of DM patients from the registration book.

**Data collection and quality control**

This secondary data was collected by trained nurses from the medical records of the study participants using a preliminary reviewed uniform checklist. Checklist was checked for consistency and completeness. Data was cross-checked and clarified for any missing data. We followed subjects from the date of enrolment (September 5, 2012) until they were diagnosed to have CVD or February 25, 2020 (study exit date). Patients with diagnosed CVD before the date of enrolment were excluded. Those who died or lost to follow up before the study exit date and event free at exit date were considered as censored during analysis.
Data management and statistical analysis

Data were entered using Epi-Data version 4.6 and then exported to Stata version 14 for further data cleaning and analysis. Descriptive statistics like mean (standard deviation) or median (inter-quartile range) for continuous variables and frequencies (%) for categorical variables was used to describe the population. Cumulative incidence was computed by number of new cases (CVD) per total initial population and incidence rate was calculated as the number of new cases per by patient-years at risk. Bivariable analysis with a p values less than 0.2 were included in the multivariable regression. The Kaplan-Meier procedure was used to estimate the survival curves and Log-rank test to compare survival time between groups of categorical variables. schoenfeld residuals method was used to assess proportional hazard assumptions (PHA). The parsimonious survival model was selected based on Akakie Information Criterion (AIC) and goodness of fitness of the model was checked using Cox Snell residual plot. To deal with missing data, we compared model for multiple imputed data with complete case analysis and model with the lowest AIC was used for analysis. Finally, Weibull regression analysis was used to calculate the hazard ratios and variables with significance level of < 0.05 was used to identify the predictors of CVD.

Results

Out of 424 total sample, 25 (5.9%) subjects with incomplete records (unknown date of DM and CVD diagnosis and diagnosed CVD before the diabetes) were excluded making 94.1% of response rate. Then 399 type 1 and type 2 diabetic patients were retrospectively followed from September 5, 2012, to February 25, 2020.

Socio-demographic and clinical characteristics

The mean age at baseline was 43.93+/−15.87 years, with minimum and maximum ages of 15 and 90 years, respectively. Male patients accounted for 61.4% and urban residents reported in 59.15% of study participants and high proportion of CVD were from urban (65.6%). Majority (70.4%) of subjects had T2DM and SBP >/=140 constituted 36.8% of study participants. High percentage of CVDs were happened in T2DM (82.0%) and SBP >/=140 (77.1%). Further details on the socio-demographic and baseline clinical characteristics of the study sample are shown in Table 1.

Table 1: Socio-demographic and clinical characteristics of study participants, 2020.
| Variables                        | Status of Cardiovascular disease | Total (n=399) |
|---------------------------------|---------------------------------|---------------|
|                                 | CVD (n=61)                      | No CVD (n=338) |
| Age (mean +/- SD)               | 50.19 +/- 14.59                 | 42.79 +/- 15.78 | 43.93 +/- 15.87 |
| Sex                             |                                 |               |
| Male                            | 38 (62.3)                       | 207 (61.2)     | 245 (61.4)      |
| Female                          | 23 (37.7)                       | 131 (38.8)     | 154 (38.6)      |
| Residence                       |                                 |               |
| Urban                           | 40 (65.6)                       | 196 (58.0)     | 236 (59.2)      |
| Rural                           | 21 (34.4)                       | 142 (42.0)     | 163 (40.8)      |
| Family history of DM            |                                 |               |
| No                              | 50 (82.0)                       | 238 (70.4)     | 288 (72.2)      |
| Yes                             | 11 (18.0)                       | 100 (29.6)     | 111 (27.8)      |
| Type of DM                      |                                 |               |
| T1DM                            | 11 (18.0)                       | 107 (31.7)     | 118 (29.6)      |
| T2DM                            | 50 (82.0)                       | 231 (68.3)     | 281 (70.4)      |
| Type of treatment               |                                 |               |
| OHA                             | 37 (60.6)                       | 176 (52.1)     | 213 (53.4)      |
| Insulin                         | 12 (19.7)                       | 108 (31.9)     | 120 (30.1)      |
| Both                            | 12 (19.7)                       | 54 (16.0)      | 66 (16.5)       |
| Acute Complication              |                                 |               |
| No                              | 31 (50.8)                       | 198 (58.6)     | 229 (57.5)      |
| Yes                             | 30 (49.2)                       | 139 (41.1)     | 169 (42.5)      |
| BMI (kg/m^2)                    |                                 |               |
| <18.5                           | 2 (3.3)                         | 24 (7.1)       | 26 (6.5)        |
| 18.5-24.9                       | 12 (19.7)                       | 238 (70.4)     | 250 (62.7)      |
| >=25                            | 47 (77.0)                       | 76 (22.5)      | 123 (30.8)      |
| DBP                             |                                 |               |
| <90                             | 31 (50.8)                       | 240 (71.0)     | 271 (67.9)      |
| >=90                            | 30 (49.2)                       | 98 (29.0)      | 128 (32.1)      |
Comorbidities and laboratory characteristics

Table 2 shows the study baseline laboratory and comorbidities characteristics of study participants. The median (IQR) of baseline FBS and creatinine was 186(99) and 0.86 (0.52), respectively. Regarding the lipid profile of the study participants: 30.8%, 38.8% and 23.6% of patients had triglyceride >/= 200md/dl, LDL-C >/= 100 md/dl and HDL-C <40 md/dl, respectively. Nearly one fifth (20.3%) and 15.8% of patients had diabetic retinopathy and chronic kidney disease comorbid, respectively.

Table 2: Laboratory and comorbidities characteristics of study participants, 2020.
| Variables                  | Status of Cardiovascular disease | Total (n=399) |
|---------------------------|---------------------------------|--------------|
|                           | CVD (n=61)                      | No CVD (n=338) |              |
| Baseline FBS, Median (IQR)| 178 (92)                        | 242 (115)    | 186 (99)     |
| Creatinine, Median (IQR)  | 1.1 (1.55)                      | 0.81 (0.39)  | 0.86 (0.52)  |
| Total cholesterol (mg/dL) |                                 |              |              |
| <200                      | 30 (49.2)                       | 224 (66.3)   | 254 (64.3)   |
| 200-239                   | 9 (14.7)                        | 65 (19.2)    | 74 (18.7)    |
| >/=240                    | 22 (30.1)                       | 45 (13.3)    | 67 (17.0)    |
| Triglyceride (md/dL)      |                                 |              |              |
| <150                      | 9 (14.8)                        | 183 (54.1)   | 192 (48.1)   |
| 150-199                   | 11 (18.0)                       | 73 (21.6)    | 84 (21.1)    |
| >/=200                    | 41 (67.2)                       | 82 (24.3)    | 123 (30.8)   |
| LDL-C (md/dL)             |                                 |              |              |
| <100                      | 24 (39.3)                       | 217 (64.2)   | 241 (61.2)   |
| >=100                     | 37 (60.7)                       | 116 (34.3)   | 153 (38.8)   |
| HDL-C (md/dL)             |                                 |              |              |
| >/=40                     | 33 (54.1)                       | 268 (79.3)   | 301 (76.4)   |
| <40                       | 28 (45.9)                       | 65 (19.2)    | 93 (23.6)    |
| Chronic kidney disease    |                                 |              |              |
| No                        | 27 (44.3)                       | 309 (91.4)   | 336 (84.2)   |
| Yes                       | 34 (55.7)                       | 29 (8.6)     | 63 (15.8)    |
| Diabetic retinopathy      |                                 |              |              |
| No                        | 39 (63.9)                       | 279 (82.5)   | 318 (79.7)   |
| Yes                       | 22 (36.1)                       | 59 (17.5)    | 81 (20.3)    |
Incidence of cardiovascular disease among diabetic patients

We followed study subjects for a median follow up period of 5.89 years (minimum of .66 and maximum of 7.50 years) after initiation of treatment for a total of 2250.4 PY. The entire cumulative incidence of CVD in this study was 15.29 % (61/399; 95% CI: [12.07, 19.18]). The total incidence density was 2.71; 95%CI: [2.11, 3.48] with 2.82; 95%CI: [2.05, 3.87] and 2.55; 95%CI: [1.69, 3.83] per 100 PY among males and females, respectively (no significant difference, p = 0.876). Among diabetic patients who were free from any type of CVD at the start of study, the cumulative proportion of developing CVD was 0.0452, 0.0862, 0.1394 and 0.2511 at year 2, 4, 6 and at the end of the study, respectively (Fig. 1).

Predictors of CVD among diabetic patients

To evaluate the effect of the number of factors on the risk of patients to develop new-onset CVD we fitted Weibull regression which has the lowest AIC compared to all other model. The tolerance of factors ranged from 0.48 to 0.89 and variance inflation ranged from 1.12 to 2.10, indicating an absence of multicollinearity. Schoenfeld residual to test the proportional hazards assumption was not significant (P-value for each variable ranged from 0.111 to 0.777 with global P-value of 0.535) indicates that PHA was satisfied. As well, the Cox Snell residual plot showed the goodness of fitness of the model was satisfied because the cumulative hazard plot follows 45 degree or a straight line through the origin with slope one (Fig. 2). As shown in Table 3: bivariate Weibull regression (95% CI of CHR) shows significant association of age, type of DM, CKD, DR, DBP, SBP, BMI, HDL, LDL, total cholesterol and triglyceride with risk of CVD. But after adjusting for other variable in multivariable Weibull regression, there are three independent variables (CKD, systolic HTN and triglyceride) that significantly determine the risk of CVD in diabetic patients. The risk of CVD was 2.53 times higher among diabetic patients with CKD as compared to those who has no CKD. The hazard of CVD among DM was 4.30 times higher for patients with systolic HTN as compared to their counter parts. Compared to patients with TG <150 mg/dl, diabetic patients with TG >/200 mg/dl had a 5.10-fold higher risk for the incident CVD.

Table 3: Multivariable Weibull regression for predictors of incident CVD among diabetes mellitus patients, 2020.
| Variables          | Categories | CHR [95% CI] | AHR [95% CI] | P-value |
|--------------------|------------|--------------|--------------|---------|
| Age                | <45        | 1            | 1            |         |
|                    | >/=45      | 2.21[1.27, 3.82] | 1.30[0.62, 2.74] | 0.483   |
| Type of DM         | TIDM       | 1            | 1            |         |
|                    | TIIDM      | 2.07[1.08, 3.97] | 0.43[0.17, 1.08] | 0.072   |
| CKD                | No         | 1            | 1            |         |
|                    | Yes        | 8.15[4.91, 13.51] | 2.53[1.36, 4.72] | 0.003** |
| DR                 | No         | 1            | 1            |         |
|                    | Yes        | 2.19[1.30, 3.69] | 1.07[0.59, 1.95] | 0.815   |
| DBP                | <90        | 1            | 1            |         |
|                    | >/=90      | 2.31[1.40, 3.82] | 0.82[0.46, 1.44] | 0.485   |
| SBP                | <140       | 1            | 1            |         |
|                    | >/=140     | 6.77[3.73, 12.30] | 4.30[2.12, 8.73] | <0.001*** |
| BMI                | <18.5      | 1            | 1            |         |
|                    | 18.5-24.9  | 1.36[0.18, 10.43] | 1.09[0.14, 8.39] | 0.937   |
|                    | >=25       | 11.27[1.55, 16.6] | 3.39[0.44, 5.86] | 0.239   |
| HDL                | >=40       | 1            | 1            |         |
|                    | <40        | 2.82[1.71, 4.67] | 0.69[0.37, 1.27] | 0.234   |
| LDL                | <100       | 1            | 1            |         |
|                    | >=100      | 2.46[1.47, 4.12] | 0.95[0.53, 1.72] | 0.869   |
| Total cholesterol  | <200       | 1            | 1            |         |
|                    | 200-239    | 0.95[0.45, 2.01] | 1.43[0.19, 1.97] | 0.063   |
|                    | >/=240     | 3.02[1.74, 5.24] | 1.82[0.44, 1.54] | 0.539   |
| Triglyceride       | <150       | 1            | 1            |         |
|                    | 150-199    | 2.83[1.17, 6.83] | 2.50[0.91, 6.88] | 0.075   |
|                    | >/=200     | 7.96[3.87, 16.38] | 5.10[2.02, 12.89] | 0.001*** |
Discussion

CVD among patients with diabetes is a life-threatening disease with poor survival rates and it is associated with high healthcare expenditure. Thus, the current study investigated the incidence of CVD and its predictors among type 1 and type 2 diabetes mellitus in Ethiopia. A total of three factors were identified to determine the incidence of CVD and these factors include: chronic kidney disease, systolic HTN and triglyceride.

The current study revealed 15.29% 95%CI (12.07, 19.18) of cumulative incidence and 2.71 95%CI (2.11, 3.48) per 100PY of incidence density CVD among T1DM and T2DM patients during the median follow up time of 5.89 year. Incidence of CVD differs substantially across different populations with diabetes based on the study setting, inclusion criteria, CVD outcome definition, and duration of the follow-up. Unfortunately, to our knowledge there were no longitudinal studies found in the literature related to CVD incidence among diabetic patients in the near countries of Ethiopia. However, worldwide, some studies showed a higher and others a much lower incidence of CVD compared to our study. The incidence of CVD in our study is in line with a recent study conducted in Italian (incidence rates of 28.8 and 23.3 per 1000 person-years among men and women, respectively) (26), Sweden(25.4 per 1000 PY) (27) and Africa (22.5 per 1000 PY) (28). Our study revealed higher incidence of CVD among diabetic patients as compared with studies conducted in the world. Studies in China (29) and Oman (30) showed that 17.2 and 17.6 per 1000 PY of CVD among DM within median follow up periods of 5.3 and 5.6 years, respectively. This difference was probable because of the higher proportion of DM patients in our study had hypertension which contribute to the risk for developing CVD, compared to general population (6). Facility based study in Ethiopia (19) and population-based study Italy (26) revealed incidence rate of 16.7 per 1000 PY and a cumulative incidence of 7.6% respectively. Nevertheless, these two studies considered CHD alone as outcome which might be the reason for the lower incidence of CVD compared to our study. However, our estimates of incident CVD were lower than those reported in Finland (cumulative incidence of 20.2%) with mean age of 59.1 years (31) and New Zealand cohort (incidence rate of 44.5 per 1000 PY) with mean age of 59.2 years (32). The possible reason for this lower incidence of CVD in our study could be due to lower mean age of our study participants (43.93 years) compared to studies in Finland and New Zealand. Age plays important role in the deterioration of cardiovascular functionality (33). This functional changes in aging adult hearts have been characterized by diastolic, systolic and electrical dysfunction, resulting in an increased risk of CVD in older adults (34). For example, the American Heart Association (AHA) reported the incidence of CVD: approximately 40% among 40–59 years, 75% among 60–79 years, and 86% in those above the age of 80 years (35). The other possible reason might be, because our study included Coronary Heart Diseases, peripheral arterial disease and stroke as CVD outcome and excluded sudden death from the definition of the outcome. Due to methodological differences such as the methods of CVD diagnosis and study design, direct comparisons of study findings may not be feasible.

In our study, we found that, the presence of chronic kidney disease comorbid increased the incidence of CVD among diabetes by more than two-fold as compared with their counterparts. The finding of increased incident CVD among DM patients with CKD in our study is consistent with previous reports in
different parts of the world (14, 36, 37). Our finding also supports the current American Diabetes Association direction, that regular assessment of eGFR and urine ACR is part of routine care for DM patients and used for early identification of patients at high risk of CVD (38). This study also revealed that renal function impairment (low eGFR and increased albuminuria) can increase the risk of CVD by two to four-fold (39). CKD is not only associated with risk of CVD, but also increases the CVD mortality by two-fold in patients with stage 3 CKD and three-fold in patients with stage 4 CKD when compared to patients with normal renal function (40). CKD causes CVD through alteration of salt and water balance which predisposes to volume retention and alterations in vascular tone that together contribute to HTN (41). Elevation in blood pressure is initially causes extracellular fluid volume expansion and rise in cardiac output. Subsequently, arterial pressure remains elevated and increases peripheral resistance which leads to CVD (42). The other means of CVD in CKD is through activation of renin, angiotensin and aldosterone that contributes to abnormal vascular tone, HTN, nephron loss and finally leads to CVD (43).

Similarly, diabetic patients with systolic HTN comorbid had more than four-fold higher risk of developing CVD than those who had no systolic HTN which agrees with the findings from other longitudinal studies (14, 18, 44). Even though the recent guideline by American College of Cardiology and American Heart Association showed importance of detection, evaluation and management of high blood pressure in reducing the risk of CVD (45), a significant number of patients fail to achieve blood pressure targets in developing countries (46). As example, the findings from a regional survey of Middle East countries showed that, out of all HTN patients in the countries only 47% were being treated with antihypertensive and of these, only 19% had BPs < 140/90 mmHg (47). Though, there is no literature on how much of hypertensive patients achieved the target BPs in Ethiopia, it is expected that important number of patients target BPs are not being achieved. The other possible reason could be the damage of endothelial cell structure and functioning by high blood pressure that leads to abnormal growth of endothelial cell and vasoconstriction that predispose DM patients for vascular complication (48).

Another important finding of this study was, DM patients with triglyceride (TG) >/= 200 mg/dl were around five times at higher risk of developing CVD than triglyceride <150 mg/dl and the association between CVD and TG 150 to 199 mg/dl was not significant. Such studies showing the high risk of developing CVD among diabetes with high triglyceride has been previously reported (15, 49). Due to scarce of studies on causal associations between triglycerides and CVD, attention was not given by researchers and physicians, mainly from cardiologists who should carefully assess patients at risk of CVD (50). However, high levels of TG is common in DM patients due to the overproduction of TG-rich and reduced hepatic clearance for TG (51). Mendelian randomization studies showed a significant association of triglyceride with the risk of CVD (52). Remarkably, the gene-based testing indicated that a rare genetic variation with lower triglycerides were consistently associated with reduced risk for CVD (53). Despite the above facts, study reported that significantly elevated triglyceride level (>1000 mg/dL) is not always associated with CVD (54). Therefore, further investigation about this issue is needed.

In spite of its strength, this study was not done without limitations. First, due to the retrospective nature of data, we have not considered other potential predictors such as exercise, smoking, alcohol drinking and
diet due to their unavailability in the patients’ card. Despite, a longer follow-up of 10 years and above would be required to determine long-term predictors of CVD, our study participants were only followed for a median of 5.89 years.

**Conclusion**

In conclusion, CVD is being a public health problem among diabetic patients in Ethiopia and systolic HTN, chronic kidney disease and high triglyceride were found to be independent modifiable predictors of incident CVD among DM patients. More attention should be given to diabetic patients, who had HTN, CKD and high triglyceride level. Studies with longer follow-up period using prospective study design are required to determine the long-term effects of predictors of CVD among diabetic patients.

**Abbreviations**

AHR: Adjusted Hazard Ratio, AIC: Akakie Information Criterion, AHA: American Heart Association, BMI: Body Mass Index, CI: Confidence Interval, CHR: Crude Hazard Ratio, CKD: Chronic Kidney Disease, CHD: Cardiac Heart Disease, CVD: Cardiovascular Disease, DBP: Diastolic Blood Pressure, DM: Diabetes Mellitus, FBS: Fasting Blood Sugar, HbA1c: Glycosated Hemoglobin, HDL-C: High-Density Lipoprotein Cholesterol, HTN: Hypertension, IDF: International Diabetic Federation, IHD: Ischemic Heart Disease, JUMC: Jimma University Medical center, Kg/m$^2$: Kilogram per Square Meters, KM: Kaplan Meier, LDL-C: Low-Density Lipoprotein Cholesterol, NCDs: Noncommunicable Diseases, OHA: Oral Hypoglycemic Agent, PAD: Peripheral Arterial Disease, PHA: Proportional Hazard Assumption, PY: Person Years, SSA: Sub-Saharan African, SBP: Systolic Blood Pressure, TG: Triglyceride, T1DM: Type One Diabetes Mellitus, T2DM: Type Two Diabetes Mellitus, WHO: World health organization

**Declarations**

**Acknowledgments**

Our heartfelt gratitude goes to the University of Gondar, and Mettu University for support by all necessary services. Additionally, we appreciate the support from Hospitals administrations and data collector.

**Ethical approval and consent to participate**

Ethical approval for the study was obtained from the Ethical Review Board of University of Gondar and permission letter was obtained from the medical directors of Jimma University medical center. Data confidentiality was kept during all phases of research activities and held on secured password protected system.

**Availability of data and material**

Data will be available from the corresponding author upon request.
Funding

The University of Gondar has covered the costs of data collectors and supervisors per diem. However, the University had no role in study design, data collections, and analysis, decision to publish, or preparation of the manuscript.

Authors’ contributions

All authors equally participated in all stage of thesis. All authors read and approved the final manuscript and agree to be accountable for all the contents of the work in the manuscript.

Consent for publication

Not applicable

Competing interests

There is no competing of interests related to this work

References

1. Dalal S, Beunza JJ, Volmink J, Adebamowo C, Bajunirwe F, Njelekela M, et al. Non-communicable diseases in sub-Saharan Africa: what we know now. International journal of epidemiology. 2011;40(4):885-901.

2. International Diabetes federation DIABETES ATLAS, Ninth edition 2019.

3. Members ATF, Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). European heart journal. 2013;34(39):3035-87.

4. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: have all risk factors the same strength? World journal of diabetes. 2014;5(4):444.

5. Morrish N, Wang S-L, Stevens L, Fuller J, Keen H, Group WMS. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia. 2001;44(2):S14.

6. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation. 1999;100(10):1134-46.

7. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abers SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. Journal of the American College of Cardiology. 2017;70(1):1-25.
8. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics—2017 update. 2017.

9. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovascular diabetology. 2018;17(1):83.

10. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive summary: heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation. 2016;133(4):447-54.

11. Salama S, Mullany EC. A systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2017.

12. Moran A, Forouzanfar M, Sampson U, Chugh S, Feigin V, Mensah G. The epidemiology of cardiovascular diseases in sub-Saharan Africa: the global burden of diseases, injuries and risk factors 2010 study. Progress in cardiovascular diseases. 2013;56(3):234-9.

13. Keates AK, Mocumbi AO, Ntsekhe M, Sliwa K, Stewart S. Cardiovascular disease in Africa: epidemiological profile and challenges. Nature Reviews Cardiology. 2017;14(5):273-93.

14. Wan EYF, Fong DYT, Fung CSC, Lam CLK. Incidence and predictors for cardiovascular disease in Chinese patients with type 2 diabetes mellitus – a population-based retrospective cohort study. Journal of Diabetes and its Complications. 2016;30(3):444-50.

15. Bonakdaran S, Ebrahimzadeh S, Noghabi S. Cardiovascular disease and risk factors in patients with type 2 diabetes mellitus in Mashhad, Islamic Republic of Iran. EMHJ-Eastern Mediterranean Health Journal, 17 (9), 640-646, 2011. 2011.

16. Umamahesh K, Vigneswari A, Surya Thejaswi G, Satyavani K, Viswanathan V. Incidence of cardiovascular diseases and associated risk factors among subjects with type 2 diabetes - an 11-year follow up study. Indian Heart J. 2014;66(1):5-10.

17. Avogaro A, Giorda C, Maggini M, Mannucci E, Raschetti R, Lombardo F, et al. Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. Diabetes Care. 2007;30(5):1241-7.

18. Al-Shamsi S, Regmi D, Govender RD. Incidence of cardiovascular disease and its associated risk factors in at-risk men and women in the United Arab Emirates: a 9-year retrospective cohort study. BMC Cardiovasc Disord. 2019;19(1):148.

19. Wolde HF, Atsedeweyen A, Jember A, Awoke T, Mequenant M, Tsegaye AT, et al. Predictors of vascular complications among type 2 diabetes mellitus patients at University of Gondar Referral Hospital: a retrospective follow-up study. BMC Endocr Disord. 2018;18(1):52.

20. Organization WH. Prevention of cardiovascular disease: World Health Organization; 2007.

21. Kariuki JK, Stuart-Shor EM, Leveille SG, Hayman LL. Methodological challenges in estimating trends and burden of cardiovascular disease in sub-Saharan Africa. Cardiology Research and Practice. 2015;2015.
22. Mendis S, Thygesen K, Kuulasmaa K, Giampaoli S, Mähönen M, Ngu Blackett K, et al. World Health Organization definition of myocardial infarction: 2008–09 revision. International journal of epidemiology. 2011;40(1):139-46.

23. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-society consensus for the management of peripheral arterial disease (TASC II). Journal of vascular surgery. 2007;45(1):S5-S67.

24. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. Geneva;. World Health Organization technical report series. 1995;854:1-452.

25. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. Biometrics. 1983;499-503.

26. Avogaro A, Giorda C, Maggini M, Mannucci E, Raschetti R, Lombardo F, et al. Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. Diabetes care. 2007;30(5):1241-7.

27. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Nilsson PM, Gudbjörnsdottir S. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. Diabetes care. 2008;31(10):2038-43.

28. Franco OH, Steyerberg EW, Hu FB, Mackenbach J, Nusselder W. Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. Archives of internal medicine. 2007;167(11):1145-51.

29. Wan EYF, Fong DYT, Fung CSC, Lam CLK. Incidence and predictors for cardiovascular disease in Chinese patients with type 2 diabetes mellitus—a population-based retrospective cohort study. Journal of Diabetes and its Complications. 2016;30(3):444-50.

30. Al Rawahi AH, Lee P, Al Anqoudi ZA, Al Busaidi A, Al Rabaani M, Al Mahrouqi F, et al. Cardiovascular disease incidence and risk factor patterns among Omanis with type 2 diabetes: a retrospective cohort study. Oman medical journal. 2017;32(2):106.

31. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. New England journal of medicine. 1998;339(4):229-34.

32. Elley CR, Robinson E, Kenealy T, Bramley D, Drury PL. Derivation and validation of a new cardiovascular risk score for people with type 2 diabetes: the new zealand diabetes cohort study. Diabetes care. 2010;33(6):1347-52.

33. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circulation research. 2012;110(8):1097-108.

34. Steenman M, Lande G. Cardiac aging and heart disease in humans. Biophysical reviews. 2017;9(2):131-7.

35. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18-e209.
36. Yang C, Wang J, Yang Y, Bai K, Gao B, Zhao M, et al. Impact of anemia and chronic kidney disease on the risk of cardiovascular disease and all-cause mortality among diabetic patients. Beijing da xue xue bao Yi xue ban= Journal of Peking University Health sciences. 2018;50(3):495-500.
37. Meisinger C, Döring A, Löwel H. Chronic kidney disease and risk of incident myocardial infarction and all-cause and cardiovascular disease mortality in middle-aged men and women from the general population. European heart journal. 2006;27(10):1245-50.
38. Association AD. Standards of medical care in diabetes—2015 abridged for primary care providers. Clinical diabetes: a publication of the American Diabetes Association. 2015;33(2):97.
39. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJL, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. The Lancet. 2013;382(9889):339-52.
40. Van Der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey AS, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney international. 2011;79(12):1341-52.
41. Koomans HA, Roos J, Dorhout Mees E, Delawi I. Sodium balance in renal failure. A comparison of patients with normal subjects under extremes of sodium intake. Hypertension. 1985;7(5):714-21.
42. Guyton A. Kidneys and fluids in pressure regulation. Small volume but large pressure changes. Hypertension. 1992;19(1_supplement):I2.
43. Tomey MI, Winston JA. Cardiovascular pathophysiology in chronic kidney disease: opportunities to transition from disease to health. Annals of global health. 2014;80(1):69-76.
44. Trialists'Collaboration BPLT. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. Bmj. 2008;336(7653):1121-3.
45. Carey RM, Whelton PK. Prevention, detection, evaluation, and management of high blood pressure in adults: synopsis of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline. Annals of internal medicine. 2018;168(5):351-8.
46. Xu W, Goldberg SI, Shubina M, Turchin A. Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: population based retrospective cohort study. bmj. 2015;350:h158.
47. Yusufali AM, Khatib R, Islam S, Alhabib KF, Bahonar A, Swidan HM, et al. Prevalence, awareness, treatment and control of hypertension in four Middle East countries. Journal of hypertension. 2017;35(7):1457-64.
48. Hsueh WA, Anderson PW. Hypertension, the endothelial cell, and the vascular complications of diabetes mellitus. Hypertension. 1992;20(2):253-63.
49. Lee JS, Chang P-Y, Zhang Y, Kizer JR, Best LG, Howard BV. Triglyceride and HDL-C dyslipidemia and risks of coronary heart disease and ischemic stroke by glycemic dysregulation status: the strong heart study. Diabetes care. 2017;40(4):529-37.
50. Madsen CM, Varbo A, Nordestgaard BG. Unmet need for primary prevention in individuals with hypertriglyceridaemia not eligible for statin therapy according to European Society of Cardiology/European Atherosclerosis Society guidelines: a contemporary population-based study. European heart journal. 2018;39(7):610-9.

51. Vergès B. Pathophysiology of diabetic dyslipidaemia: where are we? Diabetologia. 2015;58(5):886-99.

52. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, et al. Mendelian randomization of blood lipids for coronary heart disease. European heart journal. 2015;36(9):539-50.

53. Tada H, Kawashiri M-a. Genetic variations, triglycerides, and atherosclerotic disease. Journal of atherosclerosis and thrombosis. 2019;26(2):128-31.

54. Tada H, Takamura M, Kawashiri M-a. Genomics of hypertriglyceridemia. Advances in Clinical Chemistry. 97: Elsevier; 2020. p. 141-69.