Impact of diabetes duration on heart failure in Korean patients without clinical cardiovascular disease

Minsu Noh, MDa, Hyunwook Kwon, MDa, Chang Hee Jung, MD, PhDb, Seung-Whan Lee, MD, PhDb, Jong-Young Lee, MD, PhDd, Min-Ju Kim, MSc, Youngjin Han, MDa, Tae-Won Kwon, MD, PhDb, Yong-Pil Cho, MD, PhDa,

Abstract
We aimed to investigate the association between diabetes duration and the subsequent occurrence of heart failure (HF) in type 2 diabetes mellitus (T2DM) patients without clinical cardiovascular disease.

In this single-center, observational cohort study, a total of 3724 T2DM patients were stratified by diabetes duration into three 5-year interval subgroups. The primary outcomes were the occurrence of new-onset HF and all-cause mortality. HF incidence (P < .001) and mortality (P = .001) were significantly higher in patients with a longer duration of diabetes (≥10 years) than in those with a shorter duration (<5 years). On multivariate analysis, diabetes duration ≥10 years was not independently associated with all-cause mortality compared with duration <5 years, but there was a nonsignificant increased risk of HF in patients with a diabetes duration ≥10 years (P = .056). Poor glycemic control was associated with an increased risk of HF and mortality; statin use was associated with a significantly decreased risk of mortality.

Our study indicated that a longer duration of diabetes is associated with an increased risk of new-onset HF occurrence and all-cause mortality in T2DM patients without clinical cardiovascular disease.

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, EF = ejection fraction, HbA1c = glycated hemoglobin, HF = heart failure, HR = hazard ratio, LV = left ventricular, MI = myocardial infarction, T2DM = type 2 diabetes mellitus.

Keywords: cardiovascular diseases, diabetes mellitus, risk factors

1. Introduction
The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide, in parallel with increasing numbers of overweight and obese individuals and a growing population of older adults, who have the highest incidence of diabetes.1,2 Diabetes is associated with long-term cardiac and cerebrovascular morbidity and up to a 3-fold increase in mortality; however, improved medical treatment was shown to reduce the incidence of diabetes-related morbidity and mortality between 1990 and 2010.3,4 Despite this improvement, diabetes remains a significant risk factor for the development of cardiovascular disease (CVD).5–8 Although some studies have assessed the association between diabetes duration and risk of CVD,9,10 the impact of diabetes duration on the risk of new-onset heart failure (HF) in T2DM patients without previous clinical CVD is less understood. Specifically, few studies have examined the HF risk in T2DM patients receiving both medical treatment and risk factor modification with respect to diabetes duration.

This study investigated the association between diabetes duration and the subsequent occurrence of HF in Asian T2DM patients without clinical CVD who received both current medical treatment and risk factor modification. The clinical variables associated with new-onset HF in these patients were also investigated.

2. Subjects and methods
2.1. Study design and population
This single-center, retrospective, observational study analyzed data extracted from patient medical records. The present study protocol was reviewed and approved by the institutional review board of Asan Medical Center (IRB No. 2015–0691), which waived the need for informed consent. A total of 6485 consecutive Asian T2DM patients >30 years old who first visited the Diabetes Center outpatient clinic between January 2009 and December 2012 were eligible, regardless of diabetes duration. In this study, we excluded subjects fulfilling criteria for prediabetes based on American Diabetes Association guidelines.11 Only patients with baseline cardiovascular screening (cardiac enzyme levels, 12-lead electrocardiogram, and carotid...
Follow-up visits were scheduled at approximately 6-month intervals, and all medication adjustments were made by the patient’s health care provider in our Diabetes Center. Follow-up laboratory evaluations including cardiac enzyme levels and 12-lead electrocardiograms were performed depending on individual CVD risk factors.

2.4. Statistical analysis

Categorical variables are reported as frequency or percentage, and continuous variables are reported as mean ± standard deviation. Categorical variables were compared using Chi-square tests with the Bonferroni correction for multiple comparisons, and continuous variables were compared using 1-way analysis of variance with Tukey test for multiple comparisons. Diabetes duration was stratified by 5-year increments, with groups of <5 years, 5 to 10 years, or ≥10 years, to evaluate threshold effects. The cumulative probability of events was estimated with Kaplan–Meier analysis and was compared with the cumulative probability estimated with the log-rank test. Univariate and multivariate analyses of the association of clinical variables with each endpoint were conducted with Cox proportional hazards modeling using the event of interest and period from study enrollment to the date of the event or last follow-up as the outcome. Univariate Cox proportional hazard regression models were fitted to calculate hazard ratios (HRs) with 95% confidence intervals (95% CIs) to estimate the association of clinical variables with the occurrence of primary outcomes. Variables with a P < .1 on univariate analysis were included in multivariate Cox proportional hazard regression models using the backward elimination method. P values were 2-tailed; P < .05 was considered statistically significant. Statistical analyses were performed using SPSS Version 21.0 (SSPS, Inc., Chicago, IL).

3. Results

3.1. Study population

Of the 6485 consecutive T2DM patients treated at our Diabetes Center who were >30 years old, we excluded 1704 patients (26.3%) with prior CVD, 74 (1.1%) with a history of coronary or carotid revascularization, 366 (5.6%) with known malignancy, and 73 (1.1%) with known chronic renal failure and dialysis. A further 544 patients (8.4%) were excluded from the analysis either because they were lost to follow-up (376 patients, 5.8%) or because of poor adherence to medication or risk factor modification (168 patients, 2.6%). The remaining 3724 patients (57.4%) without chronic CVD at baseline who had received both medical treatment for diabetes and risk factor modification with regular 6-month interval follow-up were included in the study evaluation. Eligible patients were stratified into 3 groups, based on diabetes duration <5, 5 to 10, and ≥10 years. The mean duration of diabetes at baseline was 8.8 ± 7.4 years.

Baseline characteristics are presented in Table 1. Patients with longer diabetes duration were more likely to be older (P < .001), female (P < .001), and obese (P = .001) than patients with shorter diabetes duration. Longer-duration patients also had a higher prevalence of hypertension (P < .001), chronic kidney disease (P < .001), and significant carotid artery stenosis (P = .033), and a lower prevalence of past smoking (P = .002). They showed worse glycemic control, reflected by the glycated hemoglobin (HbA1c) levels (P < .001), and worse chronic kidney disease, reflected by the serum creatinine (P < .001) and estimated glomerular
Table 1
Baseline characteristics of the study population stratified by diabetes duration.

| Risk factor                     | Diabetes duration |
|---------------------------------|-------------------|
|                                 | <5 y              | 5–10 y             | ≥10 y             |
|                                 | Number of patients| 1313 (35.3)        | 911 (24.5)        | 1500 (40.3)       |
|                                 | Diabetes duration, y | 1.8 ± 1.4         | 7.0 ± 1.4         | 15.9 ± 6.2        |
| Mean age, y                     | 60.0 ± 7.3        | 61.4 ± 7.5        | 63.6 ± 8.1        |
| Male sex                        | 843 (64.2)a       | 525 (56.7)b       | 848 (56.5)b       |
|                                 | 525 (62.0)b       | 494 (54.2)b       | 774 (51.6)b       |
| Body mass index, kg/m²          | 25.5 ± 3.2a       | 25.1 ± 3.1a       | 24.7 ± 3.2a       |
| Risk factor                     | Hypertension      | 588 (44.8)a       | 518 (56.9)a       | 896 (59.7)b       |
|                                 | 518 (56.9)a       | 494 (54.2)b       | 774 (51.6)b       |
|                                 | 15 (1.1)a         | 21 (2.3)a         | 79 (5.3)b         |
|                                 | 70 (5.3)a         | 54 (5.9)b         | 115 (7.7)b        |
| Laboratory data                 | HbA1c (%)         | 6.8 ± 0.9a        | 7.2 ± 1.0b        | 7.5 ± 1.0b        |
|                                 | Creatinine, mg/dL | 0.9 ± 0.3a        | 0.9 ± 0.3a        | 1.0 ± 0.3a        |
|                                 | eGFR, ml/min/1.73 m² | 76.8 ± 13.0a    | 75.2 ± 14.4a      | 72.0 ± 16.4a      |
|                                 | Total cholesterol, mg/dL | 177.0 ± 39.8a  | 165.4 ± 32.2a     | 163.1 ± 34.0b     |
|                                 | HDL, mg/dL        | 50.8 ± 13.3       | 50.6 ± 12.6       | 51.2 ± 13.5       |
|                                 | LDL, mg/dL        | 105.7 ± 34.0a     | 95.4 ± 27.6b      | 93.8 ± 28.2b      |
|                                 | TG, mg/dL         | 137.9 ± 82.0a     | 134.5 ± 73.2b     | 125.2 ± 74.5b     |
| Medication use                  | Antiplatelet      | 662 (50.4)a       | 565 (62.0)b       | 1010 (67.3)c      |
|                                 | Statin            | 586 (46.6)a       | 404 (48.2)a       | 774 (51.6)b       |
|                                 | Hypertension      | 539 (41.1)a       | 467 (51.3)b       | 816 (54.4)b       |
|                                 | ACE inhibitor     | 44 (3.4)a         | 36 (4.0)b         | 78 (5.0)b         |
|                                 | ARB               | 335 (25.3)a       | 343 (37.7)b       | 581 (38.7)b       |
|                                 | Insulin           | 108 (8.2)a        | 96 (10.4)a        | 419 (27.9)b       |
|                                 | Follow-up, mo     | 50.0 ± 20.4a      | 46.8 ± 17.3b      | 45.8 ± 15.2b      |

Continuous data are means ± standard deviations; categorical data are numbers (%).
ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, TG = triglycerides.
a,b,c Non-significant difference between groups.
Past smoking was defined as cessation within 6 months of enrollment.
≥50% luminal narrowing.
Mean values during follow-up.
Baseline values after study enrollment.

3.2. Association of diabetes duration and primary outcomes

During the mean follow-up period of 47.6 ± 17.8 months, the new-onset HF incidence was 3.0% in patients with a diabetes duration <5 years, 4.1% in those with a duration of 5 to 10 years, and 6.4% in those with a duration ≥10 years (Table 2). The difference between patients with ≥10 years’ duration of T2DM and <5 years’ duration was statistically significant (P < .001). The risks of both diastolic HF (P < .001) and all-cause mortality (P = .001) increased with a longer duration of diabetes (≥10 years) than a shorter duration of diabetes (<5 and 5–10 years). During the study period, 82 patients underwent prophylactic revascularizations (2.2%) for asymptomatic significant coronary or carotid artery stenosis; no instances of periprocedural major adverse cardiac events occurred in these patients. Kaplan–Meier analysis revealed that patients with a longer duration of diabetes had a higher risk of HF (P < .001) and all-cause mortality (P < .001) than those with a shorter duration (Fig. 1).

3.3. Analysis of clinical variables associated with primary outcomes

Multivariate Cox proportional hazard regression analyses adjusting for confounding variables indicated that a diabetes duration of ≥10 years compared with <5 years was not independently associated with all-cause mortality (HR 1.82;
95% CI 0.88–3.76; \( P = 0.105 \) (Table 3), but there was a nonsignificant increased risk of new-onset HF in patients with a diabetes duration \( \geq 10 \) years (HR 1.48; 95% CI 0.99–2.20; \( P = 0.056 \)) (Table 4). Poor glycemic control, as reflected by HbA1c level, was independently associated with HF (HR 1.19; 95% CI 1.07–1.33; \( P = 0.001 \)) and all-cause mortality (HR 1.32; 95% CI 1.04–1.68; \( P = 0.023 \)). Statin use was significantly associated with a decreased risk of mortality (HR 0.31; 95% CI 0.17–0.59; \( P < 0.001 \)).
4. Discussion

Diabetes duration is a well-known indicator for future CVD risk,[20–23] and indeed, we show that new-onset HF incidence and all-cause mortality are significantly higher in patients with a longer duration of diabetes. Furthermore, our multivariate analyses indicate that a diabetes duration of ≥10 years compared with a duration of <5 years was not independently associated with HF and all-cause mortality in T2DM patients with no prior

### Table 3
Clinical variables associated with all-cause mortality.

|                     | Univariate analysis | Multivariate analysis |
|---------------------|---------------------|-----------------------|
|                     | HR (95% CI)         | P                     | HR (95% CI)         | P                     |
| Age                 | 1.07 (1.04–1.11)    | < .001                | 1.06 (1.02–1.09)    | .001                  |
| Male sex            | 1.49 (0.82–2.69)    | 1.88                  | NA                  | NA                    |
| BMI                 | 1.01 (0.92–1.09)    | 0.902                 | NA                  | NA                    |
| Hypertension        | 1.06 (0.61–1.84)    | 0.839                 | NA                  | NA                    |
| Dyslipidemia        | 0.41 (0.19–0.92)    | 0.029                 | NA                  | NA                    |
| Past smoking *      | 1.40 (0.63–3.12)    | 0.405                 | NA                  | NA                    |
| CKD                 | 5.09 (2.29–11.33)   | < .001                | 3.23 (1.43–7.32)    | .005                  |
| Carotid stenosis †  | 0.65 (0.16–2.66)    | 0.546                 | NA                  | NA                    |
| Hypertension medication | 1.01 (0.59–2.07)  | 0.961                 | NA                  | NA                    |
| ACE inhibitor       | 0.05 (0.00–18.56)   | NA                    | NA                  | NA                    |
| ARB                 | 1.18 (0.67–2.07)    | 0.578                 | NA                  | NA                    |
| Antithrombotic       | 0.87 (0.50–1.52)    | 0.632                 | NA                  | NA                    |
| Statin              | 0.33 (0.18–0.62)    | 0.001                 | 0.31 (0.17–0.59)    | < .001                |
| Insulin             | 2.05 (1.12–3.74)    | 0.020                 | NA                  | NA                    |
| HbA1c               | 1.41 (1.13–1.76)    | 0.003                 | 1.32 (1.04–1.68)    | 0.023                 |
| Creatinine          | 2.03 (1.31–3.15)    | 0.002                 | NA                  | NA                    |
| eGFR                | 0.98 (0.97–1.00)    | 0.027                 | NA                  | NA                    |

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, HR = hazard ratio, NA = not applicable.

* Past smoking was defined as cessation within 6 months of enrollment.

† ≥ 50% luminal narrowing.

### Table 4
Clinical variables associated with heart failure.

|                     | Univariate analysis | Multivariate analysis |
|---------------------|---------------------|-----------------------|
|                     | HR (95% CI)         | P                     | HR (95% CI)         | P                     |
| Age                 | 1.08 (1.06–1.10)    | < .001                | 1.07 (1.05–1.09)    | < .001                |
| Male sex            | 0.50 (0.37–0.68)    | < .001                | 0.57 (0.42–0.78)    | < .001                |
| BMI                 | 1.02 (0.97–1.06)    | 0.501                 | NA                  | NA                    |
| Hypertension        | 2.11 (1.52–2.92)    | < .001                | 1.46 (1.04–2.05)    | .029                  |
| Dyslipidemia        | 0.90 (0.64–1.26)    | 0.543                 | NA                  | NA                    |
| Past smoking *      | 0.86 (0.52–1.44)    | 0.572                 | NA                  | NA                    |
| CKD                 | 4.46 (2.77–7.19)    | < .001                | 2.58 (1.57–4.24)    | < .001                |
| Carotid stenosis †  | 2.64 (1.75–3.90)    | < .001                | 1.75 (1.14–2.69)    | .011                  |
| Hypertension medication | 2.06 (1.50–2.82)  | < .001                | NA                  | NA                    |
| ACE inhibitor       | 1.24 (0.63–2.42)    | 0.534                 | NA                  | NA                    |
| ARB                 | 1.46 (1.08–1.98)    | 0.015                 | NA                  | NA                    |
| Antithrombotic       | 2.29 (1.63–3.28)    | < .001                | NA                  | NA                    |
| Statin              | 1.45 (1.07–1.96)    | 0.018                 | NA                  | NA                    |
| Insulin             | 2.60 (1.88–3.61)    | < .001                | NA                  | NA                    |
| HbA1c               | 1.38 (1.21–1.56)    | 0.001                 | 1.19 (1.07–1.33)    | .001                  |
| Creatinine          | 1.84 (1.37–2.47)    | < .001                | NA                  | NA                    |
| eGFR                | 0.97 (0.96–0.98)    | < .001                | NA                  | NA                    |

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, HR = hazard ratio, NA = not applicable.

* Past smoking was defined as cessation within 6 months of enrollment.

† ≥ 50% luminal narrowing.
clinical CVD, who also received medical treatment and risk factor modification for diabetes. Poor glycemic control was significantly associated with an increased risk of new-onset HF and all-cause mortality; statin use was significantly associated with a decreased risk of mortality.

Our study cohort was chosen to reflect healthy T2DM patients, and our results may therefore not apply to the general T2DM population. For this reason, we could not compare our findings to those of other population-based studies.\[24,25\] Compared with the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial cohort with a similarly aged population of adults with both T2DM and no prior CVD\[26\] our rate of death from any cause was extremely low, because we analyzed only the first event of each outcome.

DM is known to have independent adverse effects on diastolic dysfunction and increase the risk of HF.\[19\] Framingham Heart Study data have shown that HF is 2 to 5 times more frequent in diabetes patients than in age-matched control subjects.\[19\] Diabetes duration may also be associated with worsening LV diastolic dysfunction, but data on the impact of medication or risk factor modification are not yet available.\[15] Predisposing conditions for diastolic HF include older age, female sex, diabetes and obesity, arterial hypertension, and LV hypertrophy.\[17\] As the present study population includes more predisposing conditions with a longer duration of diabetes, and as no therapy has been shown to improve outcomes in patients with diastolic HF,\[18\] the incidence of diastolic HF significantly increased in patients with a longer duration of diabetes, despite medical treatment and risk factor modification. Diabetes duration ≥10 years showed a trend toward an increased risk of HF but was not associated with all-cause mortality. The presence of DM alone may be associated with diastolic dysfunction and loss of diastolic reserve, possibly increasing susceptibility to diastolic HF.\[17\]

Controversy persists regarding the target HbA1c level and its impact on the subsequent occurrence of CVD in diabetic patients. Two previous large trials failed to find any cardiovascular benefit from intensive control (HbA1c < 6.0–6.5%) compared with standard control (HbA1c: 7.0–7.9%).\[26,28\] Because intensive control was not shown to reduce CVD occurrence, the American Heart Association, American College of Cardiology, and American Diabetes Association recommend a HbA1c goal of 7% and leave the decision to pursue tighter control on an individualized basis up to the physician.\[29\] Although we did not determine a target HbA1c level to prevent the subsequent occurrence of HF and increased mortality, the association of poor glycemic control with HF and increased mortality suggests that the degree of hyperglycemia may be involved in HF pathogenesis in our patients. Patients with T2DM have an increased prevalence of lipid abnormalities, which increases their risk of CVD.\[16\]

Multiple clinical trials have demonstrated beneficial effects of statin therapy on CVD outcomes in subjects with and without MI.\[30\] Recently updated guidelines recommend that moderate-intensity statin therapy be considered in addition to lifestyle therapy for all diabetes patients ≥40 years old.\[15,16\] In our analysis, statin use was associated with a decreased risk of all-cause mortality. A prospective trial is needed to determine whether better glycemic control and statin use can improve clinical outcomes in T2DM patients without clinical CVD.

This study has some limitations of note. First, its retrospective design is subject to selection and information biases. Hence, the primary outcome may have been underestimated. In addition, the baseline differences may have affected the incidence of primary outcome between the study populations stratified by diabetes duration. Patients with a longer duration of diabetes were older with a higher prevalence of comorbidities and poorer glycemic control than those with a shorter duration; in addition, they were more often female, and had a lower prevalence of past smoking in addition to significantly lower low-density lipoprotein cholesterol levels and a higher proportion of antiplatelet medication and statin use. Moreover, despite efforts to optimize risk factor variables, we sometimes failed to achieve management goals defined by the annually updated Standards of Medical Care in Diabetes by the American Diabetes Association\[15,16\] during the study period. Second, our study cohort included only patients of Asian descent, and because there may be racial or ethnic differences in the prevalence of HF and mortality in T2DM patients, our findings should be interpreted with caution when generally applied. Third, the baseline diabetes duration was estimated using self-reported ages, which may have included some inaccuracies from patient recall. Patients may have met criteria for prediabetes, which also increases the risk of CVD, for varying numbers of years. Furthermore, the analysis of the association between diabetes duration and the risk of primary outcome occurrence is complicated by the association of longer diabetes duration with older age, and residual confounding effects of this association cannot be excluded. Fourth, Doppler echocardiography was performed when any signs or symptoms suggestive of new-onset HF were identified, but we could not evaluate subclinical diastolic dysfunction, which may decrease the generalizability of the results. Lastly, the mean duration of follow-up was 47.6 ± 17.8 months, which may not have been long enough to accurately assess the primary outcomes.

In conclusion, a longer duration of diabetes is not a significant risk factor associated with an increased occurrence of new-onset HF and all-cause mortality in T2DM patients without previous clinical CVD. However, despite medical treatment for diabetes and risk factor modification for atherosclerotic CVD, patients with a longer duration of diabetes have an increased likelihood of new-onset HF and greater all-cause mortality.

Author contributions
Conceptualization: Minsu Noh, Hyunwook Kwon, Chang Hee Jung, Yong-Pil Cho.
Data curation: Minsu Noh, Hyunwook Kwon, Chang Hee Jung, Youngjin Han, Tae-Won Kwon, Yong-Pil Cho.
Formal analysis: Minsu Noh, Hyunwook Kwon, Min-Ju Kim, Yong-Pil Cho.
Investigation: Minsu Noh, Hyunwook Kwon, Chang Hee Jung, Seung-Whan Lee, Jong-Young Lee, Min-Ju Kim, Youngjin Han, Tae-Won Kwon, Yong-Pil Cho.
Methodology: Seung-Whan Lee, Jong-Young Lee, Min-Ju Kim, Yong-Pil Cho.
Validation: Minsu Noh, Hyunwook Kwon, Chang Hee Jung, Seung-Whan Lee, Jong-Young Lee, Min-Ju Kim, Youngjin Han, Tae-Won Kwon, Yong-Pil Cho.
Writing – original draft: Yong-Pil Cho.
Writing – review & editing: Chang Hee Jung, Seung-Whan Lee, Jong-Young Lee, Tae-Won Kwon, Yong-Pil Cho.
Yong-Pil Cho orcid: 0000-0002-0639-451X.

References
[1] Stam-Slob MC, van der Graaf Y, de Borst GJ, et al. SMART Study GroupEffect of type 2 diabetes on recurrent major cardiovascular events for patients with symptomatic vascular disease at different locations. Diabetes Care 2015;38:1528–35.
[2] Beckman JA, Paneni F, Cosentino F, et al. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. Eur Heart J 2013;34:2444–52.

[3] Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1930 to 2005. Circulation 2009;119:1728–35.

[4] Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990–2010. N Engl J Med 2014;370:1514–23.

[5] Kim JJ, Hwang BH, Choi II, et al. Impact of diabetes duration on the extent and severity of coronary atheroma burden and long-term clinical outcome in asymptomatic type 2 diabetic patients: evaluation by coronary CT angiography. Eur Heart J Cardiovasc Imaging 2015;16:1065–73.

[6] Rassi CH, Churchill TW, Tavares CA, et al. Use of imaging and clinical data to screen for cardiovascular disease in asymptomatic diabetics. Cardiovasc Diabetol 2016;15:28.

[7] Cea Soriano L, Johansson S, Stefansson B, et al. Cardiovascular events and all-cause mortality in a cohort of 37,946 patients with type 2 diabetes: associations with renal function and cardiovascular risk factors. Cardiovasc Diabetol 2015;14:38.

[8] Li MF, Zhao CC, Li TT, et al. The coexistence of carotid and lower extremity atherosclerosis further increases cardio-cerebrovascular risk in type 2 diabetes. Cardiovasc Diabetol 2016;15:43.

[9] Fox CS, Sullivan L, D’Agostino RB Sr, et al. Framingham Heart Study. The significant effect of diabetes duration on coronary heart disease mortality: the Framingham Heart Study. Diabetes Care 2004;27:704–8.

[10] Banerjee C, Moon YP, Paik MC, et al. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. Stroke 2012;43:1212–7.

[11] American Diabetes Association. Classification and Diagnosis of Diabetes. Sec. 2. In Standards of Medical Care in Diabetes—2016. Diabetes Care 2016;39(suppl 1):S1–22.

[12] Noh M, Kwon H, Jung CH, et al. Impact of diabetes duration and degree of carotid artery stenosis on major adverse cardiovascular events: a single-center, retrospective, observational cohort study. Cardiovasc Diabetol 2017;6:74.

[13] Irie Y, Katakami N, Kaneto H, et al. The risk factors associated with glomerular function and aging. Diabetes Res Clin Pract 2014;105(Suppl 1):S110–6.

[14] Levey AS, Coresh J, Greene T, et al. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–54.

[15] American Diabetes Association. Approaches to glycemic treatment. Sec. 7. In Standards of Medical Care in Diabetes—2016. Diabetes Care 2016;39 (suppl 1):S52–9.

[16] American Diabetes Association. Cardiovascular disease and risk management. Sec. 8. In Standards of Medical Care in Diabetes—2016. Diabetes Care 2016;39(suppl 1):S60–71.

[17] Paulus WJ, Tschape C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–50.

[18] Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med 2016;375:1866–77.

[19] From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction: a population-based study. J Am Coll Cardiol 2010;55:300–5.

[20] Stevens RJ, Kothari V, Adler AL, et al. United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:871–9.

[21] Cederholm J, Eeg-Olofsson K, Eliasson B, et al. Swedish National Diabetes Register. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. Diabetes Care 2008;31:2038–43.

[22] Nanayakkara N, Ranasingha S, Gadowki A, et al. Age, age at diagnosis and diabetes duration are all associated with vascular complications in type 2 diabetes. J Diabetes Complications 2018;32:279–90.

[23] Zoungas S, Woodward M, Li Q, et al. ADVANCE Collaborative Group. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia 2014;57:2465–74.

[24] Wannamethee SG, Shaper AG, Whincup PH, et al. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. Arch Intern Med 2011;171:404–10.

[25] Yeap BR, McCaul KA, Flicker L, et al. Diabetes, myocardial infarction and stroke are distinct and duration-dependent predictors of subsequent cardiovascular events and all-cause mortality in older men. J Clin Endocrinol Metab 2015;100:1038–47.

[26] Gerstein HC, Miller ME, Byington RP, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–59.

[27] Seferović PM, Paulus WJ. Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. Eur Heart J 2015;36:1718–27, 1727a–1727c.

[28] Patel A, MacMahon S, Chalmers J, et al. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72.

[29] Skysler JS, Bergenstal R, Bonow RO, et al. American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glyemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. J Am Coll Cardiol 2009;53:298–304.

[30] Mihaylova B, Emberson J, Blackwell L, et al. Cholesterol Treatment Trials’ (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581–90.