Original Article

Comparison of primary versus secondary prevention of cardiovascular disease in patients with type2 diabetes: Focus on achievement of ABC goals

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ABSTRACT

Background: Primary and secondary prevention of cardiovascular disease is of utmost importance in the management of patients with diabetes.
Objectives: We studied a group of Iranian patients with type2 diabetes to provide an overview of the current status of secondary prevention of cardiovascular disease in the Middle East.
Methods: This is a cross-sectional study of 2029 Patients with type2 diabetes including 323 patients with coronary artery disease (CAD) were recruited. Achievement of goals in HbA1c (A), blood pressure (B) and LDL-cholesterol(C) was assessed.
Results: The study showed 25.3% of CAD positive patients achieved HbA1c <7% compared to 30% in CAD negative patients. The achievement of blood pressure $\leq 140/90$ mmHg was 53.2% and 52.8% in CAD positive and CAD negative patients respectively. There was no difference in the achievement of all three ABC goals between the two groups (p = 0.733). After logistic regression analysis, history of hypertension had the highest odds ratio for CAD.
Conclusion: Although ABC control has an important impact on the prevention of cardiovascular outcomes, the ideal goal needs further efforts to be achieved.

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1. Introduction

Type2 diabetes mellitus is the most common form of diabetes in the world. There was a 35% increase in the prevalence of diabetes from 2005 to 2011 as reported from Iran [1].The proportion of ischemic heart disease in patients with diabetes is 23.9% in Iran [2]. The national estimate of the prevalence of coronary heart disease in Iran was 5.3% in 2011 [3]. Primary and secondary prevention of cardiovascular disease is of utmost importance in the management

of patients with diabetes. Framingham study revealed a two to three-fold increase in the risk of atherosclerotic disease in type2 diabetes patients compared to those without diabetes [4]. Mukamal et al. in their cohort study reported a hazard ratio of 1.5 for mortality risk after first myocardial infarction in patients with diabetes compared with those without diabetes. Cardiovascular events have a high health burden in patients with diabetes [5]. Modifiable Cardiovascular risk factors are hyperglycemia, dyslipidemia, hypertension, obesity, smoking, and physical inactivity. If a cardiovascular event occurs, preventing relapse is an important concern for clinicians. The recurrent cardiovascular disease is frequent in type2 diabetes, especially in women [6,7]. Carlo Giorda et al. in the study in 2008, showed that approximately 6% of patients with diabetes developed recurrent cardiovascular events every year [8]. Cardiovascular outcomes in patients with diabetes could be improved with secondary prevention. The aim of this study was to

investigate the state of cardiovascular risk management in type2 diabetes patients with and without coronary artery disease referred to our tertiary diabetes center.

2. Material and methods

We designed a cross-sectional study, as a part of a prospective cohort study; in Patients with type 2 diabetes mellitus referred to the diabetes clinic of Vali-AsrHospital affiliated with Tehran University of Medical Sciences. Patients with type 2 diabetes, according to the criteria of the American Diabetes Association (ADA2017) were included in the study. Before enrollment, written informed consents were taken from all participants. Exclusion criteria were age <30, type1diabetes, history of malignancy, GFR <30 cc/min and dialysis. 2029 patients were enrolled in the current study. Patients were divided into CAD negative and CAD positive groups (Fig. 1). CAD positive was defined as PCI (percutaneous coronary intervention), CABG (coronary artery bypass graft), acute coronary syndrome or myocardial infarction. Patient characteristics such as age, gender, height, weight, waist circumferences, blood pressure, smoking, duration of diabetes, medication and laboratory measurements, including fasting blood glucose (FBS), hemoglobin A1c (HbA1c), total cholesterol, low density lipoprotein (LDL), high density cholesterol (HDL), triglyceride (TG) and creatinine were extracted from medical records at first visit. Body mass index (BMI) (kg/m^2) was calculated by weight (kg) divided by the square height (m^2). Pulse pressure was calculated by systolic blood pressure minus diastolic blood pressure. We calculated the eGFR by the cackroftgult formula in each participant. Systolic blood pressure and diastolic blood pressure measurement were performed in the seated position after 10 min of resting with a standard sphygmomanometer. The measurement was repeated after 15 min and the average was reported. A (HbA1C), B (blood pressure) and C (LDL-Cholesterol) goals defined as HbA1c<7%, blood pressure<140/90 mmHg and LDL<100 mg/dl respectively. The ethical committee of the Tehran University of Medical Sciences approved the study protocol.

2.1. Statistical analysis

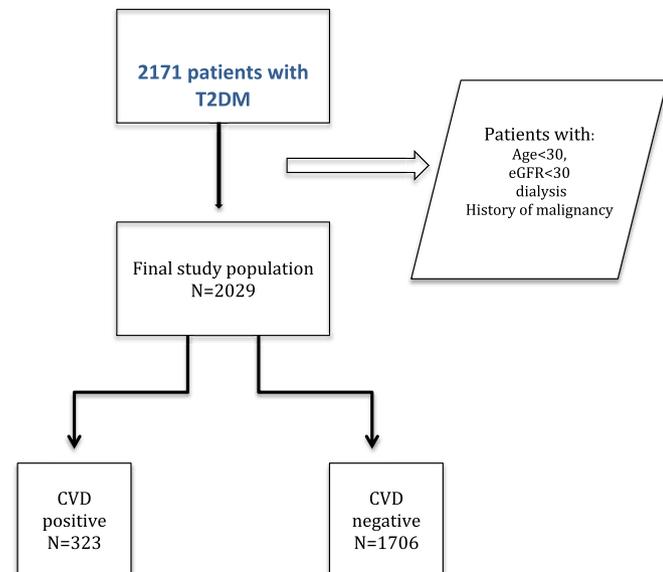We used statistical software IBM SPSS version 19 and STATA software version 12 for statistical analysis. Data were presented as a mean ± standard deviation for continuous variables and number (percentage) for categorical variables. One-way analysis of variances (ANOVA) and x^2test was used as appropriate for between group comparisons. Statistical significance was defined as a p-value less than 0.05.

Selection backward analysis with $\alpha = 0.2$ was used to identify the potential independent risk factors associated with CAD.

3. Results

In the present study 2029 type2 diabetic patients with and without coronary artery disease (CAD) were included, 323 (15.9%) CAD positive and 1706 CAD negative. Clinical and laboratory characteristics of patients with and without cardiovascular events are shown in Table 1. Mean age in the total population was 55.68 ± 11.42 years. Studied patients were 1224 females and 805 males. Hypertension was present in 44.4% of all participants, 62.8% in the CAD positive group versus 38.4%in CAD negative group.

BMI $\geq$30 kg/m^2 was present in 36.1% of CAD positive and 34.3% of CAD negative patients. One way analysis of variances (ANOVA) and x^2test was used as appropriate for between-group comparisons and summarized in Table 1. Out of 21 studied parameters, thirteen including age, sex, smoking, waist circumferences, systolic blood pressure, pulse pressure, duration of diabetes, history of hypertension, fasting blood glucose, total cholesterol, HDL-cholesterol, eGFR and antidiabetic agents were significantly different between CAD positive and CAD negative groups. There was no significant difference in BMI, diastolic blood pressure, HbA1c, LDL-cholesterol, triglyceride (TG) and statin use between CAD positive and CAD negative groups.

After logistic regression with backward elimination with $\alpha = 0.2$, older age, male gender, smoking, longer duration of diabetes, history of hypertension, HbA1c and insulin treatment remained as significant risk factors for cardiovascular events. Odds ratio, 95% CI, and P values are presented in Table 2.

Fig. 1. Study design.

Table 1
Comparisons of two groups of patients with type2 diabetes with and without CAD.

Variables	CAD + (n = 323)	CAD − (n = 1706)	P value
Age (years)	60.46 ± 9.69	54.77 ± 11.51	0.001
Female/male ratio	0.87	1.69	0.001
Smoking (%)	17.2	10	0.001
BMI(kg/m^2)	28.58 ± 4.71	28.29 ± 4.90	0.325
Waist circumference (cm)	97.54 ± 11.28	95.69 ± 12.33	0.014
Systolic BP(mmHg)	134.21 ± 23.68	130.93 ± 21.67	0.014
Diastolic BP(mmHg)	77.91 ± 13.42	78.62 ± 12.31	0.352
Pulse pressure (mmHg)	56.57 ± 17.35	52.36 ± 16.57	0.001
Duration of DM(years)	11.05 ± 8.13	7.51 ± 6.78	0.001
History of HTN (%)	62.8	38.4	0.001
FBS (mg/dl)	168.78 ± 74.48	179.21 ± 77.29	0.038
HbA1c (%)	8.64 ± 2.49	8.43 ± 2.24	0.212
Cholesterol (mg/dl)	154.34 ± 62.23	173.93 ± 56.39	0.001
LDL-C (mg/dl)	104.25 ± 56.38	110.07 ± 56.30	0.140
HDL-C (mg/dl)	41.49 ± 13.68	43.59 ± 13.12	0.028
TG (mg/dl)	159.17 ± 118.20	170.39 ± 116.58	0.179
eGFR (cc/min)	85.09 ± 37.52	96.93 ± 39.11	0.001
Medication			
OAD %	64	77.6	0.001
Insulin %	21.6	12.4	
Insulin + OAD %	14.4	10	
Statin use %	98.1	97	0.594

Values are presented as mean ± Standard deviation and percentage (%) as appropriate. CAD, Coronary artery disease; BMI, Body Mass Index; BP, Blood Pressure; HTN, Hypertension; FBS: Fasting Blood Sugar; HbA1c, hemoglobin A1c; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; TG, Triglyceride; eGFR, estimated Glomerular Filtration Rate; OAD, Oral Antidiabetic Drugs.

Table 2
Statistically significant Results of logistic regression analysis of CAD risk factors in patients with type2 diabetes.

Variables	OR	95% CI	P value
History of HTN	2.60	1.77–3.83	0.001
Insulin treatment	2.04	1.26–3.31	0.003
Male gender	1.89	1.30–2.75	0.001
Smoking	1.60	1.00–2.6	0.05
Age (per 10 years)	1.22	1.04–1.48	0.018
HbA1c	1.09	1.00–1.18	0.029
Duration of DM	1.02	1.00–1.05	0.018

OR, Odds Ratio; CI, Confidence Interval; CAD, Coronary artery disease; DM, Diabetes Mellitus; HTN, Hypertension; HbA1c, Hemoglobin A1c; eGFR, estimated Glomerular Filtration Rate.

Achievement of ABC goals presented in Table 3. The success rate for the achievement of HbA1c < 7% was 25.3% of CAD positive, and 30% of CAD negative patients. There was no statistically significant difference between the two groups (p = 0.336).

The success rate for the achievement of blood pressure ≤140/90 mmHg in hypertensive patients was 53.2% of the CAD positive patients compared to52.8% of the CAD negative ones. There was no statistically significant difference between the two groups (p = 0.274).

CAD positive patients achieved better LDL control, 58.4% had LDL lower than 100 mg/dl compared to 48.1% in CAD negative patients (p = 0.003).

There was no difference in the achievement of all three ABC goals between the two groups, 7.7% of the CAD positive and 7.4% of the CAD negative patients met all three targets.

4. Discussion

Globally, there are minimal data reporting achievement of ABC goals as secondary prevention in patients with type2 diabetes and cardiovascular disease. Here, we have studied the Iranian population as a representative subpopulation of the region to provide an overview of the current status of secondary prevention in the Middle East. We have demonstrated about a third of patients with type2diabetes achieved the goal of HbA1c and there was no difference between CAD positive and CAD negative groups. Achievement of the blood pressure goal in the hypertensive patients was about 50% in both CAD positive and CAD negative groups and there was not any significant difference between the two groups. A higher proportion of patients with CAD events attained LDL goal which may be due to the intensive statin therapy. CAD positive and CAD negative patients were similar in meeting all three goals, including HbA1c, blood pressure, and LDL. Although 44.4% of study participants were hypertensive (62.8% in the CAD positive group and 38.4%in CAD negative group) only about 50% of them achieved blood pressure goal. Notably, history of hypertension, insulin treatment, and male gender were the main factors increasing the risk of cardiovascular events respectively. (OR: 2.6, OR: 2.04 and OR: 1.89 respectively).

The literature on the achievement of ABC goals in patients with type 2 diabetes and cardiovascular events are demonstrated in Table 4. In Ramon González -Juanatey et al. study in 2001, 74% of 1275 type2 diabetes patients with cardiovascular events (CVD) were hypertensive. Less than 30% of CVD positive patients achieved blood pressure ≤130/85, only 12% had LDL <100 and 39% of them received statin therapy [9]. In Mostaza et al. study in patients with type 2 diabetic and coronary artery events, 49.7% of patients had A1C control, 38% had blood pressure control, 29% had control of LDL and 7% of patients had optimal control of their risk factors [10].Anht Tran et al. in 2013 showed, among 1653 patients with type2 diabetes, 380 (23%) of them had CVD events. Achievement of treatment targets, including HbA1C<7.5%, systolic blood pressure <140 and Cholesterol/HDL ratio<4 were assessed. Their study revealed that among patients on pharmacological treatment for secondary prevention 65% reached to HbA1c goal, 64% reached to systolic blood pressure goal and 66% reached to lipid target that was comparable with the primary prevention group [11].EUROASPIRE IV survey of CAD patients in Europe reported that rates of blood pressure control were achieved in 54% of previously known diabetic patients, LDL goal <96 mg/dl was achieved in 66% of them and 53% had HbA1c <7% [12].The Euro heart survey on diabetes and heart showed about 30% achievement of blood pressure target (<140/90) in diabetic patients and LDL control also was not adequate in 57% of diabetic patients [13]. Pagidipati et al. in 2017 studied 13616 diabetic patients with cardiovascular events and HbA1C level 6.5%–8.0%, and reported blood pressure control as 57.9%, LDL control as 73.8% and statin treatment frequency as 85.8% [14].There is a wide variation in achievement of blood pressure goals ranging from <30% to 68%, according to earlier studies in Spain, Norway, and other European countries (Table 4).Few studies have investigated the ABC target in Middle Eastern countries especially in the CAD positive diabetic patients. Despite the strong evidence showing the benefit of ABC control in patients with diabetes, most patients did not achieve ABC targets and control remains suboptimal in the published literature. Also in this study, we observed that there was not any difference in all three target achievement between CAD positive and CAD negative groups. It means both primary and secondary prevention status is suboptimal. Formulation and discrimination of practice guidelines, improving access to health care and medicine, training of health care providers, financial support of quality improvement, infrastructure improvements, improve risk factor monitoring and improve treatment adherence may help improvement in the quality of care [15].

Our study showed the history of hypertension had the highest odds ratio for cardiovascular risk, but the modifiable component i.e. hypertension control was suboptimal in the published literature and also in our study. A meta-analysis in 2017 showed non-adherence to anti-hypertensive medications in 83.7% of patients with uncontrolled hypertension [16].A study in 2008 in Iran showed approximately 25% of Iranian aged 25–64 years were hypertensive and only 24% of treated subjects achieved blood pressure lower than 140/90 mmHg [17]. There seems to be an intense need for the public teaching and improving interventions for anti-hypertensive medication adherence.

The effect of insulin on cardiovascular events in diabetes still remains controversial. In the current study insulin treatment led to

Table 3
Achievement of ABC targets alone or in combination in patients with type2 diabetes with and without CAD.

	CAD + (n = 323)	CAD − (n = 1706)	P value
A			
HbA1c ≤ 7	25.3%	30.0%	0.336
7 < HbA1c < 8	32.3%	29.3%	0.329
HbA1c ≥ 8	42.4%	40.7%	0.286
B			
BP ≤ 140/90 [a]	53.2%	52.8%	0.274
C			
LDL≤100	58.4%	48.1%	0.003
A & B & C			
HbA1c ≤ 7 and BP ≤ 140/90 and LDL≤100	7.7%	7.4%	0.733

Values are presented as percentage (%). CAD, Coronary artery disease; A: HbA1c; B: Blood pressure; C, Cholesterol (LDL-Cholesterol); HbA1c, Hemoglobin A1c; BP, Blood Pressure; LDL, Low Density Lipoprotein cholesterol.

[a] Blood pressure control in hypertensive patients.

Table 4
Comparison of different studies in achievement of goals in patients with type2 diabetes and CVD events.

Study	Patients with DM& CVD		HbA1c (A)goal	BP(B) goal	LDL or Cholesterol (C) goal	All three goals
Ramon González-Juanatey et al 2001. Spain	1275		NA	<30%	12%	NA
Mostaza-prieto et al. 2006. Spain	2884		49.7%	38%	29%	7%[a]
MatteoAnselmino et al., 2007 25 European countries	1524		NA	30%	43%	NA
Anht Tran et al., 2013 [b] Norway	1653 T2DM	380 CVD positive	65%	64%	66%	NA
		1273 CVD negative	66%	62%	62%	NA
Gyberg et al., 2015 24 European countries	2183		53%	54%	66%	NA
Pagidipati et al., 2017 38 countries	13616		NA	57.9%	73.8%	NA
Our study 2017 Tehran-Iran	2029 T2DM	323CVD positive	25.3%	53.2%	58.4%	7.7%
		1706 CVD negative	30%	52.8%	48.1%	7.4%

NA: not available, DM: diabetes mellitus, CVD: cardiovascular events.
[a] All three target and not smoking.
[b] Achievement of treatment targets including HbA1C<7.5%, systolic blood pressure <140 and Cholesterol/HDL ratio<4 were assessed.

a twofold increase in cardiovascular events. The high dose of insulin regimens can lead to increased cardiovascular morbidity and mortality in high risk type2 diabetes patients. Insulin in high dose can promote oxidative stress [18,19].Although some studies supported the anti-atherosclerotic effects of insulin [20,21],There are other studies showing pro-atherogenic effects [18]. Monnier L et al. study in 2011 demonstrated that in type2 diabetes patients received insulin, the 24 h urinary excretion rates of 8-iso PGF2α were normal in those receiving a low dose of insulin. But in those treated with a higher dose, urine excretion rate of 8-iso PGF2α was elevated [22]. This means that insulin is a hormone with anti-atherogenic effect at a lower dose, but with proatherogenic action at the high dose. An animal study in 1973 by Stout.R.W et al., showed chickens that received a normal diet and insulin injection developed lipid containing lesions of the aorta [23]. Also in another study by Cruz.A.B et al. infusion of insulin into diabetic dogs leads to lipid infiltration and medial proliferation in one injected femoral artery [24]. A systematic review in 2015 showed that insulin treatment in type2 diabetes was associated with higher adverse cardiovascular outcomes after PCI compared to non-insulin treated patients [25]. Iatrogenic hyperinsulinemia can affect the progression of atherogenesis and disturb cardiovascular function by impairing the balanced synthesis and release of endothelial mediators and promote a proinflammatory macrophage response [26—28].Also, treatment with insulin has been associated with a rise in platelet aggregation [29]. In the ORIGIN trial, insulin glargine had a neutral effect on cardiovascular outcomes [30]. Our study was cross sectional and the etiological effect of insulin therapy on cardiovascular events could not be concluded.

5. Conclusions

Although control of HbA1c, hypertension, and LDL-cholesterol has an important impact on primary and secondary prevention of cardiovascular outcomes, the ideal goal needs further efforts to be achieved. As the prevalence of diabetes increases in the world, coordination, and involvement of the health and education systems are needed for a fundamental change. In this study, history of hypertension had the highest odds ratio for the cardiovascular risk among all of the risk factors.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.03.043.

References

[1] Esteghamati A, Etemad K, Koohpayehzadeh J, Abbasi M, Meysamie A, Noshad S, et al. Trends in the prevalence of diabetes and impaired fasting glucose in association with obesity in Iran: 2005—2011. Diabetes Res Clin Pract 2014;103(2):319—27.

[2] Esteghamati A, Larijani B, Aghajani MH, Ghaemi F, Kermanchi J, Shahrami A, et al. Diabetes in Iran: prospective analysis from first nationwide diabetes report of national program for prevention and control of diabetes (NPPCD-2016). 2017/10/18 Sci Rep 2017;7(1):13461.

[3] Abbasi M, Neishaboury M, Koohpayehzadeh J, Etemad K, Meysamie A, Asgari F, et al. National prevalence of self-reported coronary heart disease and chronic stable Angina pectoris: factor Analysis of the underlying cardiometabolic risk factors in the fourth round of the SuRFNCD-2011. Global Heart 2018;13(2):73—82.

[4] Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. May 11 Jama 1979;241(19):2035—8.

[5] Mukamal KJ, Nesto RW, Cohen MC, Muller JE, Maclure M, Sherwood JB, et al. Impact of diabetes on long-term survival after acute myocardial infarction. Diabetes Care 2001;24(8):1422—7.

[6] Farkouh ME, Boden WE, Bittner V, Muratov V, Hartigan P, Ogdie M, et al. Risk factor control for coronary artery disease secondary prevention in large randomized trials. J Am Coll Cardiol 2013;61(15):1607—15.

[7] Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. Jama 2004;291(3):335—42.

[8] Lorber D. Importance of cardiovascular disease risk management in patients with type 2 diabetes mellitus. Diabetes, Metab Syndrome Obes Targets Ther 2014;7:169.

[9] Abbott RD, Donahue RP, Kannel WB, Wilson PW. The impact of diabetes on survival following myocardial infarction in men vs women: the Framingham Study. Jama 1988;260(23):3456—60.

[10] Giorda CB, Avogaro A, Maggini M, Lombardo F, Mannucci E, Turco S, et al. Recurrence of cardiovascular events in patients with type 2 diabetes. Diabetes Care 2008;31(11):2154—9.

[11] Ramón G-JJ, Alegría EE, María GAJ, González MI, Vicente LJ. The role of diabetes mellitus in cardiac disease in Spain. THe CARDIOTENS study 1999. Med Clin 2001;116(18):686—91.

[12] Mostaza-Prieto JM, Martín-Jadraque L, López I, Tranche S, Lahoz C, Taboada M, et al. Evidence-based cardiovascular therapies and achievement of therapeutic goals in diabetic patients with coronary heart disease attended in primary care. Am Heart J 2006;152(6):1064—70.

[13] Tran AT, Straand J, Dalen I, Birkeland KI, Claudi T, Cooper JG, et al. Pharmacological primary and secondary cardiovascular prevention among diabetic patients in a multiethnic general practice population: still room for improvements. BMC Health Serv Res 2013;13(1):182.

[14] Gyberg V, De Bacquer D, De Backer G, Jennings C, Kotseva K, Mellbin L, et al. Patients with coronary artery disease and diabetes need improved management: a report from the EUROASPIRE IV survey: a registry from the Euro-Observational Research Programme of the European Society of Cardiology. Cardiovasc Diabetol 2015;14(1):133.

[15] Anselmino M, Bartnik M, Malmberg K, Rydén L, Investigators EHS. Management of coronary artery disease in patients with and without diabetes mellitus. Acute management reasonable but secondary prevention unacceptably poor: a report from the Euro Heart Survey on Diabetes and the Heart. Eur J Cardiovasc Prev Rehabil 2007;14(1):28—36.

[16] Pagidipati NJ, Navar AM, Pieper KS, Green JB, Bethel MA, Armstrong PW, et al.

Secondary prevention of cardiovascular disease in patients with type 2 diabetes mellitus: international insights from the TECOS trial (trial evaluating cardiovascular outcomes with sitagliptin). Sep 26 Circulation 2017;136(13): 1193–203.

[17] Esteghamati A, Abbasi M, Alikhani S, Gouya MM, Delavari A, Shishehbor MH, et al. Prevalence, awareness, treatment, and risk factors associated with hypertension in the Iranian population: the national survey of risk factors for noncommunicable diseases of Iran. J Clin Hypertens 2008;21(6):620–6.

[18] DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58(4):773–95.

[19] Rensing K, Reuwer A, Arsenault B, von der Thüsen J, Hoekstra J, Kastelein J, et al. Reducing cardiovascular disease risk in patients with type 2 diabetes and concomitant macrovascular disease: can insulin be too much of a good thing? Diabetes Obes Metab 2011;13(12):1073–87.

[20] Dandona P, Chaudhuri A, Ghanim H, Mohanty P. Insulin as an anti-inflammatory and antiatherogenic modulator. J Am Coll Cardiol 2009;53(5 Supplement):S14–20.

[21] Dandona P, Chaudhuri A, Ghanim H, Mohanty P. Effect of hyperglycemia and insulin in acute coronary syndromes. Am J Cardiol 2007;99(11):S12–8.

[22] Monnier L, Colette C, Michel F, Cristol JP, Owens DR. Insulin therapy has a complex relationship with measure of oxidative stress in type 2 diabetes: a case for further study. Diabetes Metabol Res Rev 2011;27(4):348–53.

[23] Stout R, Buchanan K, Vallance-Owen J. The relationship of arterial disease and glucagon metabolism in insulin-treated chickens. Atherosclerosis 1973;18(1): 153–62.

[24] Cruz AB, Amatuzio DS, Grande F, Hay LJ. Effect of intra-arterial insulin on tissue cholesterol and fatty acids in alloxan-diabetic dogs. Circ Res 1961;9(1): 39–43.

[25] Bundhun PK, Li N, Chen M-H. Adverse cardiovascular outcomes between insulin-treated and non-insulin treated diabetic patients after percutaneous coronary intervention: a systematic review and meta-analysis. Cardiovasc Diabetol 2015;14(1):135.

[26] Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. Endocr Rev 2007;28(5):463–91.

[27] Potenza MA, Addabbo F, Montagnani M. Vascular actions of insulin with implications for endothelial dysfunction. Am J Physiol Endocrinol Metabol 2009;297(3):E568–77.

[28] Wang M-Y, Yu X, Lee Y, McCorkle SK, Clark GO, Strowig S, et al. Iatrogenic hyperinsulinemia in type 1 diabetes: its effect on atherogenic risk markers. J Diabet Complicat 2013;27(1):70–4.

[29] Annadurai T, Vasanthakumar A, Geraldine P, Thomas PA. Variations in erythrocyte antioxidant levels and lipid peroxidation status and in serum lipid profile parameters in relation to blood haemoglobin A1c values in individuals with type 2 diabetes mellitus. Diabetes Res Clin Pract 2014;105(1):58–69.

[30] Investigators TOT. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367(4):319–28.