

THE PREDICTION AND ASSESSMENT OF CARDIOVASCULAR AND RENAL DISEASE IN TYPE 2 DIABETES. A CURRENT REVIEW

**Loredana Mădălina Popa^{1,✉}, Amarin Remus Popa^{1,2}, Gabriela Florina Dale¹,
Mircea Ioachim Popescu^{2,3}**

¹ Clinic of Diabetes and Internal Diseases, Oradea Emergency Clinical County Hospital

² Faculty of Medicine and Pharmacy Oradea

³ Clinic of Cardiology, Oradea Emergency Clinical County Hospital

received: October 21, 2013

accepted: November 27, 2013

available online: December 15, 2013

Abstract

According to the current guidelines all type 2 diabetes (T2DM) subjects are at high cardiovascular (CV) risk. Scientists are researching the issue of further risk stratification among already high-risk patients, improved cost-effective risk stratification tools being under development. The assessment of the CV risk with the help of prediction models developed for the general population is considered to be not accurately enough for high risk individuals, therefore the current interest for identifying novel biomarkers and the development of specifically designed risk-scores for individuals with diabetes.

key words: type 2 diabetes, cardiovascular risk assessment, novel biomarkers, multimarker risk score

Risk scores for cardiovascular disease prediction in T2DM

Several risk-engines for estimation of the 10 year risk of cardiovascular disease in type 2 diabetes (T2DM) patients are currently available. The UKPDS (United Kingdom Prospective Diabetes Study) risk engine is the most commonly used [1]. It is diabetes specific and includes glycaemia, time since diagnosis, systolic blood pressure, lipid levels, age, sex, ethnic group and smoking status. Updating the risk equations is an important aspect, as new not previously considered data becomes available. The ZODIAC risk engine, validated in a 1353 Dutch cohort is a recently proposed alternative.

ZODIAC includes serum creatinine and albuminuria and excludes the lipid profile and the systolic blood pressure, as opposed to UKPDS [2]. A contemporary prediction model designed to quantify the CV risk in T2DM, the ADVANCE risk engine, was developed based on data assessed from 7168 T2DM participants in the ADVANCE (Action in Diabetes and Vascular Disease) clinical trial. In contrast to previous CV disease prediction equations, the ADVANCE risk engine estimates the 4-year probability of a major CV event - CV death, nonfatal stroke, nonfatal myocardial infarction (MI)- based on 10 risk factors: known duration of diabetes, age at diagnosis, sex, hypertension, pulse pressure, atrial fibrillation, retinopathy,

glycated hemoglobin (HbA1c), urinary albumin-creatinine ratio, non HDL cholesterol (HDL-c) [3]. A definitive model is not yet available and it remains to be seen which risk score proves to be more precise in clinical practice use.

Nevertheless there is evidence that the 10 year cardiovascular disease risk prediction models underestimate the actual risk in young adults and women. The 20 or 30 year CV risk assessment seems to be more accurate [4]. However, no algorithm to quantify the 20 or 30 year risk of CV disease in T2DM has been proposed, most likely because of the difficulty of following-up a statistically significant cohort for a sufficiently extended period of time.

Concerning sex-related differences, according to current knowledge, diabetes increases the risk for CV disease by 3 to 4 times in women in comparison to a twofold increase in male subjects, after adjustment for other CV disease related risk factors [5]. Sex-specific conditions such as a personal history of surgically induced menopause, polycystic ovary syndrome or gestational diabetes negatively influence the risk of CV events in T2DM women. Furthermore the outcomes after a major nonfatal CV event are more severe in women than in men [6]. Several trials have addressed the issue of CV risk reduction through postmenopausal sex-hormone replacement therapy, but no significant progress has been recorded, intervention trials such as WHI (Women Health Initiative) did not support any beneficial effects on CV disease risk reduction [5]. The use of intensive glucose-lowering treatment in women for CV protection purposes has also been researched. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial no differences in the effect of aggressive glycaemic-control (defined as HbA1c < 6%) between women and men have been observed. On the contrary, a significant increase in CV disease mortality in the intensive

treatment arm was reported [7], regardless of gender or treatment regimen selected in order to achieve the HbA1c target. Neither the DIGAMI trial succeeded to reveal any differences between the use of various glucose-lowering agents for tertiary CV disease prevention following an acute MI in women, but did sustain the hypothesis that the presence of diabetes chronic complications is a stronger CV disease predictor in women than in men [5]. However, in the UKPDS risk engine the female sex is considered to be protective for CV disease in comparison with male sex. Thus according with the new data there is the urgent need for improved risk-score systems particularly designed for women with known T2DM.

Irrespectively of gender, an accurate prediction is important in order to decide when to initiate and which is the appropriate medical treatment beneficial for the individual at risk. A group of scientists researched the consequences on individual cardiovascular risk of the delay in glucose-lowering treatment initiation and intensification in newly diagnosed T2DM [8]. A cohort of 110543 patients was selected for this study. Demographic and diabetes history data including the time interval between diagnosis, initiation and intensification of the hypoglycaemic therapy were assessed. The effects of the delay in treatment were evaluated periodically, examining the HbA1c value, as a marker of glycaemic control in relationship with the risk of MI, stroke and heart failure (HF). The conclusion was that early treatment intensification was protective for the patients with poor glycaemic control.

Prevention of cardiovascular disease in T2DM: evidence-based clinical trials

A significant number of clinical studies are currently ongoing, attempting to identify the most appropriate glucose-lowering agents, with the potential of lowering cardiovascular risk in

distinct T2DM groups. There are suggestions that incretins, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists may have a positive effect in CV risk reduction [9]. Linagliptin, a DPP-4 inhibitor apparently provides CV disease protection in addition to the glucose-lowering effect. Moreover there are no restrictions in chronic kidney disease (CKD), which is highly prevalent in T2DM, its metabolites being predominantly eliminated enterohepatically. The results from a large meta-analysis of linagliptin phase 3 studies data (including 3319 T2DM patients receiving linagliptin and 1920 controls) were recently reported [10]. A significantly reduced CV risk, which couldn't be explained by the intensive management of traditional CV risk factors was reported in the linagliptin treatment cohort. Additional data, referring to linagliptin's longterm CV outcomes in T2DM subjects will be provided by the currently ongoing CAROLINA (Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Early Type 2 Diabetes) clinical study, estimated to be completed in 2018 [11]. SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) clinical trial evaluated the beneficial CV effects of saxagliptin, another DPP-4 inhibitor, when added to the subject's previous antidiabetic therapy. According to the recently published results, treatment with saxagliptin improved the glycaemic control and reduced the progression of CKD in T2DM subjects, but did not show additional advantages in CV risk reduction, in comparison with placebo [12]. Concerning a new DPP-4 inhibitor, alogliptin, EXAMINE (Examination of Cardiovascular Outcomes: Alogliptin versus Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome) clinical trial enrolled 5380 T2DM subjects who had a recent acute coronary syndrome event, receiving alogliptin in addition to the antihyperglycaemic and cardiovascular treatment. In EXAMINE, the CV risk was

neither significantly higher, nor significantly decreased with alogliptin, as compared to placebo [13]. Thus far nor saxagliptin, neither alogliptin have shown superiority in CV risk reduction.

Regarding the GLP-1 receptor agonists, there is no consensus on a potential CV benefit. GLP-1 receptor agonists are known to be associated with weight reduction, which is already a great advantage in decreasing the risk of future CV events. The results of the EXCEL study evaluating the cardiovascular outcomes (nonfatal MI, nonfatal stroke, cardiovascular related death) after treatment with exenatide once weekly in T2DM subjects as an add-on therapy to the subject's previous treatment regimen, are supposed to clarify the impact of exenatide on cardiovascular risk. The estimated study completion date is 2017. It is expected that LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results) and ELIXA (Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes after Acute Coronary Syndrome during Treatment with Lixisenatide) clinical trials will provide conclusive data regarding GLP-1 receptor agonists CV outcomes in high risk T2DM patients. LEADER trial was designed to assess liraglutide CV outcomes in 9340 subjects, a percentage of 81.3 being diagnosed with prior CV disease [14]. In ELIXA trial, expected to be completed in 2015, approximately 6000 T2DM patients who had experienced an acute coronary syndrome event prior to recruitment and randomization, are followed-up until the occurrence of a major CV event (CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina) [15].

Biomarkers of cardiovascular disease assessment in T2DM: current utility, clinical considerations and future perspectives

Early detection of asymptomatic organ damage in high CV risk subjects followed by

initiation of preventive therapy delays the clinical onset of the vascular disease and improves the outcomes [16]. The intima-media thickness (IMT), the carotid-femoral pulse wave velocity (PWV) and urinary albumin excretion (UAE) are just a few of the multiple contemporary biomarkers potentially useful for predicting the risk of major cardiovascular events. The individual prognosis and appropriate treatment should be established after multiorgan risk assessment, in most cases high CV risk subjects benefiting from early applied and intensive interventions in order to achieve the strict therapeutic objectives conceived for this specific group.

IMT is a strong predictor of major cardiovascular events independently of traditional CV risk factors in hypertensive patients. In 2007, the ESC-ESH (European Society of Cardiology - European Society of Hypertension) guidelines [17] established a threshold IMT value > 0.9 , measured at the level of the common carotid artery as well as at the level of the carotid bifurcations. Knowing that individuals with diabetes have an accelerated development of atherosclerosis, investigating the predictive value of the IMT as a determinant of overall CV risk in T2DM would be of great value for the early detection of asymptomatic artery disease. Recently, the results of a clinical study, aiming to investigate whether the measurement of the carotid IMT improves cardiovascular risk assessment were published [18]. The primary objective was to evaluate the effectiveness of the common carotid segment IMT measurement in cardiovascular risk prediction in T2DM subjects. The cardiovascular risk stratification was applied in a large high-risk group including 4220 subjects with diabetes, without previously diagnosed cardiovascular disease. IMT measurements in other carotid segments were performed but not considered in the statistical analysis. After adjustment for the

traditional risk factors (smoking, hypertension, dyslipidemia), IMT measurement provided no improvement in risk prediction in T2DM subjects [18]. A Japanese group of researchers expressed a different opinion after comparing the predictability of Framingham risk score, UKPDS risk engine, IMT and LDL-c/HDL-c Ratio for asymptomatic vascular disease in T2DM [19]. Thus, data from 116 Japanese patients were collected and the 10 year risk of CV disease was calculated with the Framingham and UKPDS risk engines. A comparison between 5 different predicting models was performed, each risk score being combined with IMT value or LDL-c / HDL-c Ratio as well as with the combination of both parameters. The data suggested that the combination of Framingham risk score with IMT value was superior in predicting the probability of major CV events [19].

Most currently used predictive models exclude older adults, explaining the interest for developing a multimarker risk score designed for older adults with diabetes. A prediction algorithm specifically designed for older adults with diabetes was recently evaluated, including some traditional risk factors as well as novel biomarkers of subclinical atherosclerosis [20]. The subjects were selected from MESA (Multi-Ethnic Study of Atherosclerosis) and CHS (Cardiovascular Health Study) clinical trials. A total of 782 T2DM participants over 65 years of age fulfilled the inclusion criteria. A number of 3 predicting models were applied to each participant, the first one included traditional CV risk factors, the second one included novel circulating biomarkers and the third one subclinical atherosclerosis biomarkers. The addition of common carotid IMT, internal carotid IMT and other subclinical vascular disease biomarkers such as the ankle-brachial index (ABI) modestly improved the reclassification into greater or lesser risk of CV disease in already high risk subjects. The

improvement mostly derived from the down-classification of T2DM individuals without previous CV events. Even though statistically significant, the final results are not strong enough to sustain the use of the designed predictive model in clinical practice.

PWV is the gold standard for measuring aortic stiffness. Age-related degenerative alterations of arterial walls are responsible for the increase in vascular stiffness in the general population. In addition to age, arterial blood pressure is a powerful determinant of PWV [21]. The ESC-ESH 2013 Guidelines reported that PWV has independent predictive value for cardiovascular risk assessment in hypertensive patients [16]. After adjustment for age, vascular stiffness data obtained through non-invasive methods in T2DM subjects without previous CV disease, suggested that diabetes is independently associated with an increase in PWV. Consequently, the opportunity emerged that PWV may be used as a biomarker of early vascular dysfunction and a target for early intervention in overt CV disease in T2DM patients [22].

The carotid-femoral PWV is currently under extensive research, allowing the reclassification of T2DM subjects into a higher or lower CV risk subgroup. Apparently T2DM subjects with increased PWV have a higher risk to develop a major cardiovascular event independently of the traditional CV risk factors. Thus the authors of a clinical study conducted in Brazil recently published results confirming this hypothesis [23]. The investigators enrolled 565 T2DM subjects, previously diagnosed with microvascular or/and macrovascular complications of diabetes or other traditional cardiovascular risk factors (hypertension, dyslipidemia). After adjustment for the traditional risk factors, the cohort with increased aortic stiffness (defined as PWV above 10 m/s) had a higher risk for cardiovascular morbidity

and mortality in comparison with normal aortic stiffness subjects. As stated in a 2012 expert consensus document, the 10 m/s is the currently accepted threshold value as corresponding to significant alterations of aortic function [23]. Furthermore carotid-femoral PWV had a better predictive value in certain study subgroups such as subjects with microvascular complications and subjects with inadequate glycaemic control. According to the investigators the use of this method should be extended to routine clinical practice, in order to choose the appropriate pharmacological treatment for the reduction of the aortic stiffness, subsequently decreasing the individual cardiovascular risk. Several strategies to reduce arterial stiffness have been widely discussed. Namely angiotensin-converting-enzyme-inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) are the currently proposed alternatives, due to their positive effect on arterial stiffness, independently of blood-pressure lowering in T2DM patients [24]. However, large scale, prospective studies in T2DM subjects with repeated measurements of PWV are required before correctly understanding its precise relevance.

Cardiovascular disease, CKD and T2DM

Cardiovascular events are particularly frequent in T2DM patients previously diagnosed with CKD. Combinations of several biomarkers are investigated for the purpose of enhancing the prognostic value of traditional CV risk factors in this group of patients. Many studies examined the association between UAE as a biomarker of kidney injury and the risk for CV disease [25]. There is evidence that UAE rates below the current threshold value defining micro-albuminuria, (30 mg/g) predict the risk of CV events in T2DM patients [26]. Several evidence-based reports support also the importance of the estimated glomerular filtration rate (eGFR) as a

renal dysfunction biomarker [25]. Even though they are independent risk factors for CV disease, the assessment of both UAE and eGFR improves the risk stratification among high risk individuals. Even in subjects with normal range UAE and eGFR data is available regarding the relationship between increased serum levels of cystatin c and CV risk in T2DM [27]. Therefore, in order to upgrade the assessment of the individual CV risk in CKD patients, efforts are being made for the development of a predictive model, comprising several renal dysfunction biomarkers, including UAE, eGFR and cystatin c. In 2011, a group of researchers aimed to predict the CV disease risk, based on albuminuria and eGFR value in T2DM [28]. Data from the 9795 subjects participating in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study was extracted. Patients had T2DM, no CV event for the 3 months prior to recruitment and were followed-up for a period of over 5 years, all major cardiovascular events being reported. Patients were stratified in 3 subgroups, according to the eGFR levels: above 90 ml/min/1.73 m², between 60-89 ml/min/1.73 m² and between 30-59 ml/min/1.73 m². All subjects, irrespective of the eGFR group, were also stratified according to the UAE rates. Normoalbuminuric subjects were identified even in stage 3 of CKD while macroalbuminuria with normal eGFR was also present. As expected the highest CV risk category was encountered in stage 3 CKD subjects with coexistent albuminuria. During the study the progression or therapy-aided regression of renal dysfunction modified the CV risk, confirming once more the need for early detection and initiation of treatment. The authors concluded that a correct assessment of renal dysfunction requires the determination of both eGFR and albuminuria [28].

Novel biomarkers of early renal dysfunction are also required in order to improve knowledge

about the underlying mechanisms involved and to establish the ideal timing of treatment, aiming to delay the onset and slow the progression of renal impairment. In an attempt to identify a urinary peptide biomarker set suitable to predict the onset and the subsequent progression of albuminuria in T2DM subjects, a group of researchers conducted a clinical trial on subjects from the PREVEND (Prevention of Renal and Vascular End-Stage Disease) study [29]. Knowing that albuminuria is a sign of vascular dysfunction (which in most cases progresses despite appropriate therapy) the purpose was to identify other proteins/peptides associated with an earlier stage of the disease. A number of 44 cases who transitioned from normo to albuminuria and 44 controls who had a stable UAE levels throughout the follow-up period were enrolled. The final results showed that evaluation of a 273 urinary peptide biomarker set (named CKD 273 classifier) enabled early renal risk assessment. The CKD 273 biomarker set included proteins and peptides, such as type I and type III collagen, uromodulin and glycoproteins related with T2DM renal dysfunction. Despite the small size of the study group, the authors concluded that a multibiomarker set is more precise for risk estimation than a single peptide and that the CKD 273 classifier might accurately predict the onset of albuminuria. The CKD 273 classifier might be clinically meaningful if utilized for distinguishing the patients at risk of developing albuminuria. Hopefully, further evidence will be provided by several currently ongoing clinical studies.

Another reliable biomarker of early renal impairment, specifically linked to vascular renal dysfunction is the renal resistive index (RI) [30]. Newly diagnosed T2DM subjects without previous CKD were recruited in a clinical trial, aiming to evaluate the value of RI for quantifying alterations in renal blood flow [30].

A dynamic evaluation of RI was performed and the RI values were significantly higher in T2DM participants than in hypertensive patients or age and sex-matched controls. An elevated RI was associated with a negative prognostic for renal disease progression in diabetic patients, even though no reference values of RI have been unanimously approved. In the same cohort, carotid-femoral PWV was assessed and higher values were recorded in diabetic patients than in controls. The assumption that a high RI value in T2DM is linked with carotid IMT wasn't sustained by a recent trial despite previous positive data available for hypertensive patients [31].

Large-scale GWA (Genome Wide Association) studies currently in progress are hoped to identify CV disease candidate genes [32]. There is hope that in the forthcoming future, the advances in uncovering CV disease

genetic markers, will clarify the issue of interindividual CV risk variability. Furthermore, genetic risk scores for CVD with clinical relevance will be probably available, leading to improvements of the CV risk prediction [32].

Conclusions

The conflicting results, regarding the predictive value of contemporary biomarkers in T2DM clinical trial cohorts are delaying the development of cost-effective prevention strategies addressed for T2DM patients. Different methods of statistical analysis, sample sizes, certain racial or ethnic features are just a few of the factors affecting the relevance of the results. Despite these limitations, periodically reviewing the clinical trials findings is mandatory in order to evaluate to what degree the published results have applicability for clinical practice.

REFERENCES

1. Stevens RJ, Kothari V, Adler AI, Stratton IM; 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). *Clinical Science* 101: 671-679, 2001.
2. Kleefstra N, Landman GWD, van Hateren KJJ, Gans ROB, Groenier KH, Bilo HJG. Calculating risk in patients with type 2 diabetes in the Netherlands: UKPDS versus ZODIAC risk engine performance (ZODIAC-26). *Diabetologia* 54[Suppl. 1]:S8-S9, 2011. (Abstract)
3. Kengne AP, Patel A, Marre M et al. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. *Eur J Cardiovasc Prevent Rehabil* 18: 393-398, 2011.
4. Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the Framingham heart study. *Circulation* 119: 3078-3084, 2009.
5. Norhammar A, Schenck-Gustafsson K. Type 2 diabetes and cardiovascular disease in women. *Diabetologia* 56: 1-9, 2013.
6. Venskutonyte L, Malmberg K, Norhammar A, Wedel H, Rydén L. Effect of gender on prognosis in patients with myocardial infarction and type 2 diabetes. *J Intern Med* 268: 75-82, 2010.
7. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycaemia in type 2 diabetes : a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 55: 1577-1596, 2012.
8. Paul S, Thorsted BL, Wolden M et al. Delay in treatment intensification increases the risk of cardiovascular events in patients with type 2 diabetes. *Diabetologia* 56[Suppl.1]: S534-S535, 2013. (Abstract)
9. Perk J, De Backer G, Gohlke H et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 33: 1635-1701, 2012.
10. Neubacher D, Johansen OE, von Eynatten M et al. Low cardiovascular (CV) risk hazard ratio observed with linagliptin in type 2 diabetes: further insights from a predefined CV meta-analysis. *Diabetologia* 55[Suppl. 1]: S500, 2012. (Abstract)

11. **Rosenstock J, Marx N, Kahn SE et al.** Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. *Diab Vasc Dis Res* 10: 289-301, 2013.
12. **Scirica BM, Bhatt DL, Braunwald E et al.** Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 369: 1317-1326, 2013.
13. **White W, Cannon CP, Heller SR et al.** Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 369: 1327-1335, 2013.
14. **Marso SP, Poulter NR, Nissen SE et al.** Design of the liraglutide effect and action in diabetes: Evaluation of cardiovascular outcome results (LEADER) trial. *Am Heart J* 5: 823-830, 2013.
15. **Barnett AH.** Lixisenatide: evidence for its potential use in the treatment of type 2 diabetes. *Core Evid* 6: 67-79, 2011.
16. **Mancia G, Fagard R, Narkiewicz K et al.** 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 34: 2159-2219, 2013.
17. **Mancia G, De Backer G, Dominiczak A et al.** 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 28: 1462-1536, 2007.
18. **Den Ruijter HM, Peters SAE, Groenewegen KA et al.** Common carotid intima-media thickness does not add to Framingham risk score in individuals with diabetes mellitus: the USE-IMT initiative. *Diabetologia* 56: 1494-1502, 2013.
19. **Fujihara K, Suzuki H, Sato A et al.** Comparison of Framingham risk score, UKPDS risk engine, maximum IMT and LDL-c/ HDL-c ratio for predicting coronary plaque in asymptomatic patients with type 2 diabetes. *Diabetologia* 55[Suppl. 1]: S494, 2012. (Abstract)
20. **Mukamal KJ, Kizer JR, Djousse L et al.** Prediction and classification of cardiovascular disease risk in older adults with diabetes. *Diabetologia* 56: 275-283, 2013.
21. **Laurent S, Boutouyrie P.** Recent advances in arterial stiffness and wave reflection in human hypertension. *J Hypertens* 49: 1202-1206, 2007.
22. **Van Bortel LM, Laurent S, Boutouyrie P et al.** Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 30: 445-448, 2012.
23. **Cardoso CRL, Ferreira MT, Leite NC, Salles GF.** Prognostic impact of aortic stiffness in high risk type 2 diabetic patients. The Rio de Janeiro type 2 diabetes cohort study. *Diabetes Care* 36: 3772-3778, 2013.
24. **Karralliedde J, Smith A, DeAngelis L et al.** Valsartan improves arterial stiffness in type 2 diabetes independently of blood pressure lowering. *Hypertension* 51: 1617-1623, 2008.
25. **Delles C, Jardine AG.** Renal function and cardiovascular events: relevance of eGFR and albuminuria in patients with diabetes. *Diabetologia* 54: 4-6, 2011.
26. **Weir MR.** Microalbuminuria and cardiovascular disease. *Clin J Am Soc Nephrol* 2: 581-590, 2007.
27. **Shlipak MG, Matsushita K, Arnlov J et al.** Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med* 369: 932-943, 2013.
28. **Drury PL, Ting R, Zannino D et al.** Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetologia* 54: 32-43, 2011.
29. **Roscioni SS, De Zeeuw D, Hellemons ME et al.** A urinary peptide biomarker set predicts worsening of albuminuria in type 2 diabetes mellitus. *Diabetologia* 56: 259-267, 2013.
30. **Bruno RM, Daghini E, Landini L et al.** Dynamic evaluation of renal resistive index in normoalbuminuric patients with newly diagnosed hypertension or type 2 diabetes. *Diabetologia* 54: 2430-2439, 2011.
31. **Florczak E, Januszewicz M, Januszewicz A et al.** Relationship between renal resistive index and early target organ damage in patients with never-treated essential hypertension. *Blood Press* 18: 55-61, 2009.
32. **Musunuru K, Kathiresan S.** Genetics of coronary artery disease. *Annu Rev Genomics Hum Genet* 11: 91-108, 2010.