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Epidemiological Analysis of the Heart Complications Related to Type 2 Diabetes *mellitus* in the Portuguese Hospital

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Abstract Type 2 Diabetes *mellitus* is considered one of the leading causes of heart disease. The aim of this study was to characterize the major cardiac complications and their incidence in Type 2 diabetic patients throughout hospitalization. The study involved 1321 patients with Type 2 diabetes coded as "principal diagnosis" in three Central Hospitals of the Portuguese National Health System, admitted from January 1st to December 31st of 2011. Data were collected from coded discharge summaries from each hospital. We observed significant incidence of congestive heart failure in the 3 institutions. A higher incidence of diabetes heart complications was observed among women than men in St. John of Porto and North Lisbon Hospital Centers (57,9% and 62,5%for women compared to 42,1% and 37,5% respectively, for men). , associated to diabetes mellitus (DM) with renal manifestations and DM without complication, type II, unspecified, about 37.24% and 36.5%, respectively. In contrast, at the University of Coimbra Hospital Center, diabetic men had higher incidence of heart complications (55,1% vs 49,9%). , approximately 42.3% associated to DM without complication, type II, unspecified. At Saint John of Porto and North Lisbon Hospital Centers, the 71 - 80 year age-group had the highest representation of heart complications, while at the University of Coimbra Hospital Center, the highest was in the 51 -80 years group. There was high incidence of cardiac complications in diabetic women associated to DM without complications and/or renal manifestations.

Keywords Type 2 Diabetes *mellitus*, Heart complications, Gender, Age

1. Introduction

Diabetes *mellitus*(DM) is a serious public health problem globally [1], because of its high morbidity and mortality [2] reducing the average life expectancy by up to 15 years [3]. DM affects approximately 25.8 million (8.3% of the population) and is the seventh cause of death in the United States [1]. In 2011, DM affected approximately 7.9 million Portuguese (12.7% of the total population), 6.1% of males and 4.3% female [4]. Among European countries, Portugal has the highest prevalence rate of DM. In 2011, the incidence rate was 652 new cases per 100,000 inhabitants, indicating an 80%, increase in the last decade [4]. Diabetes affects more than a quarter of the Portuguese population aged 60-79 years [4].

The type 2 Diabetes *mellitus* (T2DM), as a heterogeneous disease, is the leading cause of kidney failure (accounting for 44% of all new cases of kidney failure in 2008, 60% of non-traumatic lower limb amputation, and 28.5% of new cases of blindness among adults [3]. T2DM is considered as one of the leading causes of heart disease and stroke (60-70% of cases) in the United States [5].

1.1. Diabetes and Heart Disease

Cardiovascular disease (CVD) significantly increases mortality due to diabetes and is the leading cause of death of diabetic patients [6]. The risk of cardiovascular death is 2 times greater in patients with T2DM than non-diabetics [7, 8, 9]. Studies have further shown that diabetics, even without prior history myocardial infarction (MI), still have a have a higher risk of cardiovascular death than patients with a clinical history of AMI but without diabetes [10, 11]. In Portugal, about 31% of patients with T2DM are admitted for AMI [4].

The T2DM increases the risk of CVD three to four times in women [12] and three times in men, after adjusting for other risk factors [13] especially younger women aged less than 65 years of age [14]. In the United States, CVD represents 77% of T2DM hospitalizations [15]. In the last decade, several studies have documented some of the most frequent cardiac complications of diabetes, namely: AMI [16, 12]; congestive heart failure (CHF) affecting about 20 to 23% of diabetic patients [17]; and, coronary heart disease

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(CHD) [18, 19], responsible for multiple hospital admissions [20]. Observational studies have shown that, in the presence of microvascular disease, patients with T2DM, have an increased risk of developing cardiovascular events [21].

1.2. Diabetes and Kidney Disease

In a systematic review based on population studies, the average prevalence of chronic renal failure (CRF) was 7.2% in individuals 30 aged years or older, and it ranged from the 23.4-35.8% in patients aged over 64 years [22]. CRF and heart failure (HF), often coexist in the same patient [23].

Some studies suggest that a precautionary approach should be applied in the management of patients with CRF, in order to minimize the occurrence of episodes of AMI, HF, stroke and cardiovascular death, through proven therapies, such as: control of blood pressure, control of blood glucose levels and treatment of dyslipidemia, among others [24].

Approximately 25-30% of patients with T2DM have kidney disease (KD), usually presenting as typical diabetic glomerulosclerosis, but sometimes more prominently as a vascular nephropathy [25]. Diabetic Nephropathy (DN) is the most common cause of chronic kidney disease (CKD) in developed countries, and is the leading cause of end-stage kidney disease [21], most especially amongT2DM patients of advanced age [25]. Even when the T2DM is controlled, the disease can still lead to CRF and kidney failure [21]. A prevalence study of 415,910 United States Veterans with T2DM, showed that 10.7% had a renal disease in addition, but that 43.4% did not present with DN. More specifically, the prevalence of DN was approximately 4.2%-6% of patients with terminal renal failure (TRF) [26].

Due to the high degree of overlap of CVD and CRF, there has been a great interest in studying this complex bi-directional pathophysiological process that aggravates the function of both organs [27]. A large proportion of patients admitted to the hospital has varying degrees of cardiac and renal dysfunction [28]. Primary disorders of one of these two organs (heart and kidney) results, sometimes, into a secondary dysfunction or injury to the other [29].

In 2011, 7% of hospital admissions in Portugal were due to diabetic patients with T2DM who had renal manifestations, among which the prevalence of CRF was 27.2%, constituting 32% of new cases of CRF hemodialysis [4]. The present study sought to describe heart complications and their incidence in hospitalized patients with type 2diabetes.

2. Methods

The study was observational, descriptive and cross-sectional, involving 1321 type 2 diabetic patients admitted with T2DM as the principal diagnosis, from January 1stto December 31st of 2011. Data were collected from three public hospitals in different regions of Portugal i.e. Saint John of Porto Hospital Centre EPE, University of Coimbra Hospital Centre EPE and Lisbon North Hospital Centre EPE. The descriptive data were collected from the DRG hospital information systems database, called DREAM and SAM, with the approval of the Auditors and encoders. The principal registrycodes of diagnosis and procedures of Diabetes *mellitus* (DM) type II non-specified type DM was (ICD-9-CM: 250**.**x0 or 250**.**x2) were based on the classification of diagnoses and procedures according to the International Classification of Diseases 9th Revision, ICD 9 of the WHO. Therefore, the variables selected from the discharge summaries of each episode of encoded admission were: age, gender, a principal diagnosis of T2DM, and a second diagnosis of cardiac complications. The codes of heart complications included were the following: 426.13 – Atrio Ventricular Block 2º; 427.31 – Atrial Fibrillation; 427.89 – Other Specified Cardiac Arrhythmias; 428.23-Chronic Systolic Heart Failure; 428.33 – Chronic Diastolic Heart Failure; 42843 – Chronic Combined Systolic and Diastolic Heart Failure; 404.91-Hypertensive Heart disease and Chronic Renal Disease, N/C,/SPEC INSUF CARD, C/DRC EST.I-IV OR N/SPEC; 410.11- Acute Myocardial Infarction, Anterior, Initial Episode; 410.71 - Acute SubEndocardial Infarction of the Myocardium; 411.89 – Ischemic Heart Disease, Acute or Sub Acute; 411.1-Intermediate Coronary Syndrome; 413.9 - Angina Pectoris or unspecified; 426.0 – Auricular Ventricular Complete Block; 424.0 – Mitral Valve Diseases; 424.1 – Aortic Valve Diseases; and, 428.0 – Congestive Heart Failure, unspecified. Data were entered and analyzed using the statistical program *Statistical Package for Social Sciences* (SPSS©) for Windows® version 18.Univariate and bivariate analysis were applied to establish relationships between distinct variables. The analysis of variables was conducted mainly through counts and frequencies. Also Chi-Square Tests with a confidence interval (CI) of 95% were carried out to verify the existence of dependency relationships between variables.

3. Ethical Considerations

The study was approved by the ethics committees of the three hospitals The confidentiality and privacy of data collected were guaranteed in accordance with the Helsinki Declaration, using the most recently revised version of the World Medical Association.

4. Results

At **St. John of Porto Hospital Center,** of 536 T2DM patients who attended, 54% had cardiac complications, with a significant incidence of congestive heart failure (CHF) at 40.7%, followed by atrial fibrillation (AF) with 23.79%. At the **University of Coimbra Hospital Center,** of the 379 who attended, 21% had cardiac complications, with a significant incidence of CHF at 48.7%, followed by AF with 34.6%. At **Lisbon North Hospital Center,** of 406 who attended, 24% had cardiac complications, with a significant

incidence of AF at 37.5%, followed by CHF with 33.3% as shown in Table 1.

Table 1. Stratification of Heart Complications

Hospital	ICD-9 Code				
	428.0	427.31	404.91	413.9	427.89
A	40,7%	23,8%	6,9%		
B	48,7%	34,6%		12,8%	
C	33,3%	37,5%			6,3%

A – St. John of PortoHospital Center**; B –** University of Coimbra Hospital Center**; C –**Lisbon North Hospital Center**;** 428.0 - Congestive Heart Failure; 427.31 - Atrial Fibrillation; 404.91 - Hypertensive Heart disease and Chronic Renal; 413.9 - Angina Pectoris; 427.89 - Specified Cardiac Arrhythmias.

At **St. John of Porto Hospital Center,** heart complications were more prevalent among diabetic women than men (57.9% and 42.1%, respectively). However, in males the incidence of heart complications, such as the Intermediate Coronary Syndrome (ICS), Angina Pectoris (AP) and the Atrio-ventricular Block -Complete (AVBc) were more observed. At the **University of Coimbra Hospital Center,** clinical cardiac complications were more prevalent in diabetic men than women (55.1% and 44.9%, respectively). However, AF, AVBc and the Specified Cardiac Arrhythmias (SpCA) were more prevalent in diabetic women. At **Lisbon North Hospital Center,** diabetic women had more heart complications than diabetic men (62.5% and 37.5%, respectively). However, the incidence of ICS, hypertensive heart disease with CRF-unspecified, with heart failure - chronic kidney disease stage I-IV or unspecified (DCHRC I-IV), and SpCA was more expressive. However, CHF-unspecified was equally prevalent in both diabetic men and women as shown in **Table 2.**

Table 2. Distribution of Heart Complications by Gender

Sex		ICD-9 Code				
		428.0	427.31	404.91	413.9	427.89
A	Men	17,2%	10,3%	2,8%		
	Women	23,5%	13,5%	4,1%		
B	Men	29,8%	16,7%		7,7%	
	Women	19,2%	17,9%		5,1%	
C	Men	10,4%	14,6%			4,2%
	Women	22,9%	22,9%			2,1%

Upon analyzing the stratification of complications by age group in each institution, it was observed that at **St. John of Porto Hospital Center,** the incidence of CHF was most prevalent in the age-group of 71-80 years (32.76%).For the age-group up to 40 years, the only two types of heart complications, even then with a very low percentage, were AF with 0.34% and the SpCA with 0.34%. At the **University of Coimbra Hospital Center,** incidence of CHF was greatest inthe 51 - 80 years age-group. Angina Pectoris not listed elsewhere or not specified presented in equal prevalence in diabetic patients aged 51 - 60 years. The younger diabetic patients (41-50 years) had only one type of cardiac event, AP not listed elsewhere or unspecified, a very low percentage of 1.3%. Diabetic patients aged 81 years or higher, had the greatest numbers of AF. It was noteworthy that there was no diabetics aged less than 40 years with heart complications. At **Lisbon North Hospital Center,** it was observed that the incidence of heart complications was highest inthe age group 71 - 80 years. This group had a larger representation in every heart complications except diseases of aortic valve which figured more in the 61 - 70 years age-group, and the AVB 2ndgrade in the 51 - 60 years age-group. Diabetic patients aged up to 40 years had only mitral valve disease, and diabetic patients aged between 41 and 50 years had only SpCA as shown in **Table 3**.

Table 3. Distribution of Heart Complications by Age

Age (years)		ICD-9 codes				
		428.0	427.31	404.91	413.9	427.89
A	Up to 40	0,0%	0,3%	0,0%		
	41 - 50	2,4%	1,0%	0,7%		
	51 - 60	4,8%	2,1%	0,3%		
	61 - 70	10,3%	5,5%	2,8%		
	71 - 80	14,1%	7,9%	2,1%		
	81 or more	9,0%	6,9%	1,0%		
B	Up to 40	0,0%	0,0%		0,0%	
	41 - 50	0,0%	0,0%		1,3%	
	51 - 60	3,8%	0,0%		3,8%	
	61 - 70	19,2%	7,7%		0,0%	
	71 - 80	15,4%	11,4%		6,4%	
	81or more	10,3%	15,4%		1,3%	
C	Until 40	0,0%	0,0%			0,0%
	41 - 50	0,0%	0,0%			1,0%
	51 - 60	3,1%	0,0%			2,1%
	61 - 70	5,2%	3,1%			0,0%
	71 - 80	15,6%	15,6%			2,1%
	81 or more	9,4%	18,8%			2,0%

Upon analyzing the sample to encode the types of DM and the incidence of heart complications in each one, at **St. John of Porto Hospital Center** there was higher incidence of heart complications in DM with renal manifestations, type II or unspecified, unspecified as uncontrolled (37.24%), followed by the DM with renal manifestations, type II or unspecified, uncontrolled (14.83%) and, in DM with specified manifestations, not classified elsewhere, type II or unspecified, unspecified as uncontrolled (7.24%). It was also found that the most incident cardiac complication in diabetic patients with renal manifestations, type II or n/specified, uncontrolled, and in DM with renal manifestations, type II or unspecified, unspecified as uncontrolled was CHF unspecified. At the **University of Coimbra Hospital Center,** there was a higher incidence of heart complications in DM without complications, type II or unspecified, not controlled with 42.3% of diabetic patients, followed by DM with peripheral circulatory changes, type II or unspecified, unspecified as uncontrolled with 12.8%. It was also found

that the most frequent cardiac complication in diabetic patients with DM without additional complication stype II or unspecified, uncontrolled was CHF unspecified (17.9%).

Table 4. Distribution of Diabetes *mellitus* type by Heart Complications

	ICD9 code	Heart Complications
A	250.40	37,2%
	250.42	14,8%
	250.80	7,2%
B	250.02	42,3%
	250.70	12,8%
	250.52	10,3%
	250.72	10,3%
C	250.02	36,5%
	250.42	17,7%
	250.82	19,8%

250.02 - Diabetes mellitus, without complication, type II or unspecified, uncontrolled; 250.40 - Diabetes mellitus with renal manifestations, type II or unspecified, not stated as uncontrolled; 250.42 - Diabetes mellitus with renal manifestations, type II or unspecified, uncontrolled; 250.52 - Diabetes mellitus with ophthalmic manifestations, type II or unspecified, uncontrolled; 250.70 - Diabetes mellitus with peripheral circulatory disorders, type II or unspecified, not stated as uncontrolled; 250.80 - Diabetes mellitus with specified manifestations, type II or unspecified, not stated as uncontrolled; 250.82 - Diabetes mellitus with specified manifestations, type II or unspecified, uncontrolled.

Table 5. Correlation of heart complications withrenal manifestations

Chi-Square Tests
St. John of PortoHospital Center

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	,467[a]	2	,792
Likelihood Ratio	,465	2	,793
Linear-by-Linear Association	,275	1	,600
N ofValid Cases	76		

Chi-Square Tests
University of Coimbra Hospital Center

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	16,386[a]	16	,426
Likelihood Ratio	18,768	16	,281
Linear-by-Linear Association	,362	1	,547
N ofValid Cases	59		

Chi-Square Tests
Lisbon North Hospital Center

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	2,933[a]	2	,231
Likelihood Ratio	3,701	2	,157
Linear-by-Linear Association	2,143	1	,143
N ofValid Cases	11		

At **Lisbon North Hospital Center,** there was higher incidence of heart complications in DM without complication, type II or unspecified, not controlled with 36.5% of diabetics, seconded by specific manifestations with DM, not classified elsewhere (NCE), type II or unspecified, not controlled with 19.8% and in DM with renal manifestations, type II or unspecified, not controlled with 17.7%. It was also found that the highest incidence of cardiac complication in diabetic patients with DM without complication, type II or unspecified, not controlled, was CHF - unspecified with 16.67%, followed by AF with 8.33% as shown in **Table 4.**

Analyzing of correlation between the presence of cardiac complications and the presence of renal manifestations revealed no correlation (significance value (SIG. 2-tailed) = 0.792, $p < 0.005$ at **St. John of Porto Hospital Center,** 0.426 at the **University of Coimbra Hospital Center** and 0.231 at North Lisbon **Hospital Center** as shown in **Table 5.**

5. Discussion

Some authors have found that one of the most frequent cardiac complications of diabetes is the CHF, with higher incidence in diabetic women than diabetic men [17]. That finding is also upheld by the findings in this three-hospital study, which also observed that the incidence of CHF was higher in women. Its incidence was higher with advancing age, being highest between 71-80 years at St. John of Porto and North of Lisbon Hospital Centers but starting at a younger age (51 – 80 years) at the University of Coimbra Hospital Center. These results agree with the findings of Vaur et al. [17] who found that, in 4912 diabetics requiring hospitalization, the annual incidence of CHF was 1% among patients with an average age of 71 years (cautioning that they excluded diabetic patients under treatment with insulin and angiotensin system inhibitors).

Another important finding of this study was to verify the coding of the typology of DM with heart complications, focusing on DM with renal manifestations and the degree of DM control. No data were found on this subject upon extensive search. However, some authors report that the incidence of kidney disease (KD) in these patients may, probably, be underestimated, since the concentration of serum creatinine in the period of hospitalization alone may not accurately reflect kidney function (KF) [30]. However, renal dysfunction as a co-morbidity can be a complication of the treatment of CHF, even when it was not present at the time of admission. Between 27 and 45% of diabetics admitted for CHF can develop an acute worsening of their KD throughout hospitalization [30]. A study showed that of 1.681 patients, over the age of 65 years admitted in hospitals for CHF, 21% presented with KD, and 41% had a baseline serum creatinine level increased [31]. Similar works have noted that 18% of 11,327 in-patients in 115 hospitals had renal dysfunction associated with CHF [32]. Finally, 30% of patients hospitalized with acute heart failure had clinical history of chronic renal failure in an assessment of 105,388 episodes of hospitalization in 274 hospitals reported in *Acute Decompensated Heart Failure National Registry* (ADHERE) [33].

Another cardiac event with high incidence observed in this study was the AF, agreeing with the result of an important meta-analysis (n = 1.686 .097) involving 108.703 cases of AF, where about 24 to 34% were diabetics with T2DM [34]. However, that review may have under-estimated the real association between DM and AF, due to the presence of other factors. For example, the body mass index and the

presence of prior heart disease varied between the studies included in the analysis, making it impossible to take account of their possible impact on the association [34]. Dublin et al. [35] also observed a causal association between DM and AF. In that study, the duration of DM and the risk of incidence of AF increased over time, in such a way, that for diabetics with over 10 years of DM, the risk of developing AF was approximately 64% compared to only 7% in those with DM less than 5 years of duration [35]. Watanabe et al. [36] who did work on records of 28,449 265 patients who presented episodes of AF, led the association between glucose tolerance and the risk of developing AF. The Framingham Heart Study also found that DM, insulin resistance and glucose tolerance are associated with left ventricular hypertrophy (LVH) which, itself, could be an important risk factor of AF [37].

The present study demonstrates that heart complications prevail more in females. This finding has been interpreted, analyzed and discussed in some earlier studies, albeit with some controversy. In one meta-analysis, the increased relative risk adjusted to age of coronary heart disease (CHD) was greatly reduced in female diabetics than in males. However, the same study, after allowance for the risk of more severe CVD, diabetic women presented a higher risk of developing CHD than diabetic men [38]. It concludes that gender could be a risk factor that should be considered and understood. Another explanation for this difference, for some authors, is that diabetic women are exposed to less aggressive preventive treatments than diabetic men [39]. Another important risk factor pointed out in woks is the impact of insulin resistance, differentially influenced by age, sex hormones and lifestyle [40]. Another reason, though, is the difference in the impact of risk factors, including hormone levels such as the loss of estrogens in the case of diabetes [41]. The INTERHEART study describes several risk factors which could explain the differences on gender related to CVD (such as high blood pressure, high alcohol consumption, stress, and weight gain and low physical activity) and which could have prevailed more in women than in men [42]. The improved levels of LDL cholesterol are related to CVD, in both men and women, but low levels of HDL cholesterol and increased levels of triglycerides have shown to be more intensely related to CHD in women than in men [13].

6. Conclusions

The high incidence of CHF among the Type II diabetic (T2DM) population with renal manifestations emphasizes the need of early identification of the disease and the aggressive treatment of risk factors of CHF and KD. Evidence of renal disease in the presence of heart failure should not be ignored. Instead, it should be sought for, and renal disease prevented in all CHF case management. Finally, given the steep climb in rate of CFH from that among those below 40 years to those above 70 years, there is strong indication that younger diabetics may benefit from more intensive monitoring of CHF risk factors, such as hypertension, dyslipidemia, microalbuminuria, anemia and others.

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REFERENCES

[1] Heron M. Deaths: Leading Causes for 2009. National Vital Statistics Reports; Vol. 61, No. 7, October 26, 2012. http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_07.pdf.

[2] Egede, L. E., Gebregziabher, M., Lynch, C.P., et al., 2011, Longitudinal ethnic differences in multiple cardiovascular risk factor control in a cohort of US adults with diabetes, Diabetes Research and Clinical Practice, 385-394.

[3] National Institute of Diabetes and Digestive and Kidney Diseases. Advances and Emerging Opportunities in Diabetes Research: A strategic planning report of diabetes mellitus interagency coordinating committee, February, 2011. http://www.niddk.nih.gov/search/pages/Results.aspx?k=deaths%20of%20diabetes%20kid.

[4] Sociedade Portuguesa de Diabetologia. Relatório Anual do Observatório Nacional da Diabetes. Diabetes: Factos e Números,2012.http://www.spd.pt/index.php/observatrio-mainmenu-330.

[5] International Diabetes Federation. Diabetes Atlas: sixth edition, 2013. http://www.idf.org/diabetesatlas/content/diabetes-andimpaired-glucose-tolerance.

[6] Seshasai, S. R. , Kaptoge, S., Emerging Risk Factors Collaboration et al., 2011, Diabetes mellitus, fasting glucose, and risk of cause-specific death, N Engl J Med., 364, 829-841.

[7] Buse, J. B., Ginsberg, H. N., Bakris, G. L., et al., 2007, Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association, Circulation, 115, 114-26.

[8] Emerging Risk Factors Collaboration, Sarwar, N., Gao, P., Seshasai, S. R., et al., 2010, Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies, Lancet, 375, 2215-2222.

[9] Ahmad, K. A., Clarke, P. M., Gerdtham, U. G., et al., 2013, Predicting Changes in Cardiovascular Risk Factors in Type 2 Diabetes in the Post-UKPDS Era: Longitudinal Analysis of the Swedish National Diabetes Register, Journal of Diabetes Research, article ID 241347. http://dx.doi.org/10.1155/2013/241347.

[10] Evans, J. M. M., Wang, J., Morris, A. D., 2002, Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross

sectional and cohort studies, BMJ, 324, 939-42.

[11] Malmberg, K., Yusuf, S., Gerstein, H. C., et al., 2000, Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q wave myocardial infarction: results of the Oasis Registry, Circulation, 102, 1014-1019.

[12] Venskutonyte, L., Malmberg, K., Norhammar, A., et al., 2010,Effect of gender on prognosis in patients with myocardial infarction and type 2 diabetes.J Intern Med., 268(1), 75-82. doi: 10.1111/j.1365-2796.2010.02215.x. Epub2010 Jan 20.

[13] Norhammar, A., Gustafsson-Schenck, K., 2013, Type 2 diabetes and cardiovascular disease in women,Diabetology, 56, 1-9.

[14] Norhammar, A., Stenestrand, U., Lindbäck, J., et al., 2008, Women with diabetes mellitus younger than 65 years are a high risk group after myocardial infarction. A report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA), Heart, 94, 1565-70.

[15] Mody, R., Kalsekar, I., Kavookjian, J., et al., 2007, Economic impact of cardiovascular co-morbidity in patients with type 2 diabetes.J Diabetes Complications, 21(2), 75-83.

[16] Lopez-de-Andres, A., Hernández-Barrera, V., Carrasco-Garrido, P., et al., 2010,Trends of hospitalizations, fatality rate and costs for acute myocardial infarction among Spanish diabetic adults, 2001-2006,BMC Health Serv Res., 8;10-59. doi: 10.1186/1472-6963-10-59.

[17] Vaur, L., Gueret, P., Lievre, M., et al.,DIABHYCAR Study Group (type 2 DIABetes, Hypertension, CARdiovascular Events and Ramipril) study, 2003, Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 DIABetes, Hypertension, CArdiovascular Events and Ramipril) study,Diabetes Care, 26(3), 855-60.

[18] Carnethon, M. R., Biggs, M. L., Barzilay, J., et al., 2010, Diabetes and coronary heart disease as risk factors for mortality in older adults,Am J Med., 123(6), 556.e1-9. doi: 10.1016/j.amjmed.2009.11.023.

[19] Fhärm, E., Cederholm, J., Eliasson, B., et al., 2012, Time trends in absolute and modifiable coronary heart disease risk in patients with Type 2 diabetes in the Swedish National Diabetes Register (NDR) 2003-2008,Diabet Med.,29(2), 198-206. doi: 10.1111/j.1464-5491.2011.03425.x.

[20] Bo, S., Ciccone, G., Grassi, G., et al., 2004, Patients with type 2 diabetes had higher rates of hospitalization than the general population,J ClinEpidemiol.,57(11), 1196-201.

[21] Karnib, H. H., and Ziyadeh, F. N., 2010, The cardiorenal syndrome in diabetes mellitus, Diabetes Research and Clinical Practice, 89, 201-209.

[22] Zhang, Q. L., and Rothenbacher, D., 2008, Prevalence of chronic kidney disease in population-based studies: systematic review, BMC Public Health, 8, 117.

[23] Longhini, C., Molino, C., and Fabbian, F., 2010, Cardiorenal syndrome: still not a defined entity. ClinExpNephrol., 14, 12-21.

[24] McCullough, P. A., Haapio, M., Mankad, S., 2010, Prevention of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference,Nephrol Dial Transplant, 1-8. doi: 10.1093/ndt/gfq180.

[25] Blicklé, J. F., Doucet, J., Krummel, T., et al., 2007, Diabetic nephropathy in the elderly. Diabetes & Metabolism, 33, S40-S55.

[26] Young, B. A., Pugh, J. A., Maynard, C., et al., 2004, Diabetes and renal disease in Veterans, Diabetes Care, 27(Suppl.2), B45-B49.

[27] McCullough, P. A., 2002, Cardiorenal risk: an important clinical intersection, Rev Cardiovasc Med., 3, 71-76.

[28] Dar, O., Cowie, M. R., 2008, Acute heart failure in the intensive care unit: epidemiology, Crit Care Med., 36, S3-8.

[29] Ronco, C., Haapio, M., House, A. A., et al., 2008, Cardiorenalsyndrome, J Am CollCardiol., 52(19), 1527-39. doi: 10.1016/j.jacc.2008.07.051. Review.

[30] Forman, D. E., Butler, J., Wang, Y., et al., 2004, Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure,J Am CollCardiol., 43, 61-7.

[31] Krumholz, H. M., Chen, Y. T., Vaccarino, V., et al., 2000, Correlates and impact on outcomes of worsening renal function in patients >65 years of age with heart failure, Am J Cardiol.,85, 1110-3.

[32] Cleland, J. G., Swedberg, K., Follath, F., et al., 2003, The EuroHeart Failure survey programme – a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis,Eur Heart J., 24, 442-63.

[33] Adams, K. F. Jr, Fonarow, G. C., Emerman, C. L., et al., 2005, Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Failure National Registry (ADHERE), Am Heart Journal, 149, 209-16.

[34] Huxley, R. R., Filion, K. B., Konety, S., et al., 2011, Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation, Am J Cardiol., 108, 56-62.

[35] Dublin, S., Glazer, N. L., Smith, N. L., et al., 2010, Diabetes mellitus, glycemic control, and risk of atrial fibrillation, J Gen Intern Med., 25, 853-858.

[36] Watanabe, H., Tanabe, N., Watanabe, T., et al., 2008, Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study, Circulation, 117, 1255-1260.

[37] Rutter, M. K., Parise, H., Benjamin, E. J., et al.,2003, Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study, Circulation, 107, 448-454.

[38] Huxley, R., Barzi, F., Woodward, M., 2006, Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies, BMJ, 332, 73-78.

[39] Rautio, A., Lundberg, V., Messner, T., et al., 2005, Favourable trends in the incidence and outcome of

myocardial infarction in non diabetic, but not in diabetic subjects: finding from the MONICA myocardial infarction registry in northern Sweden in 1989-2000, J Intern Med., 258, 369-377.

[40] Mittendorfer, B., 2005, Insulin resistance: sex matters, Curr Opin Clin NutrMetab Care, 8, 367-372.

[41] Berg, G., Mesch, V., Boero, L., et al., 2004, Lipid and lipoprotein profile in menopausal transition. Effects of hormones, age and fat distribution, Horm Metab Res., 36, 215-220.

[42] Anand, S. S., Islam, S., Rosengren, A., on behalf of the INTERHEART Investigators et al., 2008, Risk factors for myocardial infarction in women and men: insights from the INTERHEART study, Eur Heart Journal, 29, 932-940.