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THE IMPORTANCE OF THE TREATMENT STRATEGY CHANGES IN THE LONG-TERM EVOLUTION OF TYPE 2 DIABETIC PATIENTS WITH SUB-OPTIMAL GLYCAEMIC CONTROL AFTER ACUTE CORONARY SYNDROME

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Abstract

Background and Aims. *Several factors are associated with a heightened risk of subsequent events, morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) after an acute coronary syndrome (ACS). Improving the management of these patients is a challenge that requires urgent attention. We aimed to study the long-term effect of the change in treatment strategy depending on the HbA1c level detected during the hospitalization for ACS.* ***Material and methods.*** *The primary endpoints of this study were the major adverse cardiac events (MACE) at 12 months. From the originally included 221 patients 15 were lost (no response to follow-up phone calls). The sub-optimal glycaemic control group (HbA1c>7.0%, n=84) was divided in two subgroups: patients who completed a diabetological consult with further treatment changes (intervention group) and patients without this referral (control group).* ***Results.*** *No significant differences in baseline characteristics were found between the 2 subgroups. The second subgroup had a triple risk for a MACE in 1 year (HR=2.8704, 95% CI: 1.109-7.423, p=0.0296) compared to the intervention group. No significant differences were found in secondary endpoints.* ***Conclusion.*** *This study suggests that, after hospitalization for an ACS, diabetologist referral and treatment strategy changes are recommended for all T2DM patients whose HbA1c level is over 7% before discharge.*

key words: *acute coronary syndrome (ACS), type 2 diabetes mellitus, HbA1c, long-term evolution, major adverse cardiac events (MACE).*

Background and Aims

The importance of type 2 diabetes mellitus (T2DM) as a major risk factor for cardiovascular heart disease is well known and proven [1,2]. Type 2 diabetes can be assimilated with the ischemic coronary disease, based on a study made in 1998 reporting that, in 7 years, a patient with T2DM has the same risk for myocardial infarction (MI) with a non-diabetic patient who had a MI before [3]. A meta-analysis, conducted by the Emerging Risk Factors Collaboration,

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including almost 700,000 subjects with no history of MI, angina or stroke at baseline, revealed that diabetes confers an approximately twofold excess risk for coronary heart disease (CHD), major stroke and deaths attributed to other vascular causes [4]. This poor prognosis also extends to patients with diabetes following a revascularization procedure [5].

Several factors are associated with the increased risk for subsequent events, morbidity and mortality in patients with T2DM following an Acute Coronary Syndrome (ACS) [6]. Improving the management of these patients is a challenge that requires urgent attention. The Diabetes and Cardiovascular Disease study group of the French Society of Diabetes in collaboration with the French Society of Cardiology have devised a consensus statement on the care of the hyperglycaemic/diabetic patient during and in the immediate follow-up of acute coronary syndrome [7]. This consensus emphasizes the importance of the strict glucose control during the hospitalization for ACS, but also recommends that, during cardiac rehabilitation, any patient with unknown diabetes diagnosed by the oral glucose tolerance test (OGTT) and cases of uncontrolled diabetes (HbA1c $\geq$ 8%) or severe/repeated hypoglycaemia should be referred to a diabetologist to establish an adapted treatment strategy.

However, this treatment strategy is not very easy to establish. Because hypoglycaemia may augment the myocardial ischemia and provoke cardiac arrhythmias [8], drugs which can predispose to this adverse event should be avoided if possible. Because of the possible effects on the cardiac potassium channels, some sulfonylureas were mentioned to aggravate myocardial ischemia [9], but the clinical relevance of these effects remains unproven. Metformin may have some beneficial cardiovascular effects and seems to be an useful drug for patients with coronary disease if there are no other contraindications [10]. In one single study, pioglitazone proved to reduce major cardiovascular adverse events in patients with demonstrated macrovascular disease. Thus, it can be used in the absence of cardiac failure [11]. In preliminary reports, the therapy with GLP-1 receptor agonists and DPP-4 inhibitors was associated with decreased cardiovascular risk, but there is not enough data for the long-term clinical evolution [12]. There are limited data showing that alpha-glycosidase inhibitors [13] or bromocriptine [14] can reduce cardiovascular events. Thus, we are waiting for clear recommendations about treatment strategies for this group of patients.

Until then, we aimed to study the long-term effect of the change in treatment strategy depending on the HbA1c level detected during the hospitalization for ACS in T2DM patients. Although, the recommendations for diabetologist referral are clear, the compliance with these guidelines is still low. So, there are many T2DM patients who remain with their previous treatment scheme after hospitalization for ACS. We will compare their long-term evolution with those whom management strategy was updated by diabetologist immediately after the acute coronary event, taking into account also the HbA1c level at the discharge.

Material and Methods

For this study we included 221 T2DM patients who required hospitalization for ACS (unstable angina, non-ST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction) in the Bihor County Emergency Clinical Hospital, Oradea, Romania and 6 Hospitals in the region of Darmstadt, Germany between 01.01.2013 and 31.12.2013. The diagnosis of ACS has been based on the

American College of Cardiology (ACC) / American Heart Association (AHA) guidelines [15]. Only the patients with known T2DM were included, if their medical records contained documentation of past history of T2DM or past laboratory results compatible with the diagnosis of T2DM, according to the American Diabetes Association (ADA) 2010 Revised Clinical Practice Guidelines for diabetes diagnosis [16].

We used an observational, prospective study design and we noted the patient's age, gender, cardio-vascular risk factors, vital signs on admission, laboratory tests, the type of the reperfusion therapy, left ventricular systolic function, HbA1c level at discharge and if they completed the diabetologist referral. HbA1c level was determined with a turbidimetric inhibition immunoassay method in both group of patients.

The primary endpoint of this study was the rate of major adverse cardiac events (MACE) at 12 months. MACE included cardio-vascular mortality, MI, malignant arrhythmia, cardiac arrest, cardiogenic shock, congestive heart failure (CHF), rehospitalization for angina, and rehospitalization for heart failure. Cardiogenic shock was defined as systolic blood pressure <90 mm Hg or a drop of mean arterial pressure >30 mm Hg with a pulse >60 beats per minute to exclude shock secondary to bradycardia and/or low urine output (<0.5 mL/kg/h) with or without evidence of organ congestion [17]. Malignant arrhythmia was defined as symptomatic sustained ventricular tachycardia and also ventricular fibrillation, irrespective of symptoms or hemodynamic stability. Secondary endpoints included cardio-vascular mortality rate, all-cause mortality rate, rehospitalization for angina and rehospitalization for heart failure in the 12-month follow-up period.

The clinical data was obtained from hospital records and the follow-up was made by telephone to exclude bias from losing data regarding the primary and secondary endpoints.

Various cut-off values for HbA1c were used by different authors to demonstrate the prognostic value of glycosylated haemoglobin in T2DM patient after ACS [18]. After reviewing the data of this meta-analysis [18] and the consensus recommendations from the French Society of Diabetes [7] we chose the cut-off value of 7.0% to investigate the prognostic value of the treatment strategy changes recommended by the diabetologist in the long-term evolution of this special group of T2DM patients.

Statistical analysis. We used MedCalc version 12.5.0.0 (MedCalc Software, Mariakerke, Belgium) for statistical analysis. The Kolmogorov-Smirnov test was applied to examine normal distribution. Continuous variables with normal distribution were presented as mean and standard deviation - SD (in brackets); those with skewed distribution as median and interquartile range (in brackets). Categorical variables were presented as number of patients and percentage. Baseline characteristics of the 2 groups were compared using the $\chi 2$ test or the Fisher exact test for categorical variables, the Student unpaired t test for continuous variables with normal distribution and the Mann-Whitney test for those with skewed distribution, as appropriate. The dates of all-cause death, CV-related death, and MACE were recorded. The hazard ratio (HR) of the study group related to 12-month MACE, 12-month all-cause mortality, and 12-month CV mortality, and other secondary endpoints were calculated. Twelve-month event-free survival was estimated by the Kaplan-Meier method and was compared with the log-rank test.

Results

From the originally included 221 patients 15 were lost (no response to follow-up phone calls).

The remaining 206 cases were divided in two groups depending on HbA1c level at discharge: optimal glycaemic control group (HbA1c≤7.0%, n=122) and sub-optimal glycaemic control group (HbA1c>7.0%, n=84). The median values of glycosylated haemoglobin for the two groups were: 6.0% (interquartile range: 5.8-6.4) vs 8.1% (interquartile range: 7.55-8.6) – p<0.0001.

To emphasize the importance of the treatment strategy changes in this special group of patients, in this first phase of a larger study we analysed only the cases with sub-optimal glycaemic control. Thus, according to the referral to a diabetologist, this group of patients was divided in two subgroups: patients who completed a diabetological consult with further treatment changes (intervention group) and patients without this referral (control group). Surprisingly, the second subgroup was more numerous than the first one (44 without diabetologist referral vs. 40 with diabetologist referral), but the median value of the glycosylated haemoglobin was significantly higher in the intervention subgroup (8.25% vs. 7.9%, p=0.0430).

The baseline characteristics for these subgroups are shown in Table 1.

Table 1. Patient baseline characteristics.

Variable	Intervention group n=40	Control group n=44	p value
Demographics			
Age (years), Mean (SD)	60.7 (8.7)	64.0 (11.8)	0.1471
Male, n (%)	21 (52.5%)	27 (61.4%)	0.5491
CV risk factors			
Hypertension, n (%)	29 (72.5%)	30 (68.2%)	0.8466
Hyperlipidaemia, n (%)	16 (40.0%)	17 (38.6%)	0.9236
Previous CHD, n (%)	15 (37.5%)	17 (38.6%)	0.9062
Previous MI, n (%)	5 (12.5%)	6 (13.6%)	0.8653
Previous CHF, n (%)	4 (10.0%)	4 (9.1%)	0.8178
Previous stroke/TIA, n (%)	10 (25.0%)	8 (18.2%)	0.6210
Documented PVD, n (%)	2 (5.0%)	3 (6.8%)	0.9125
History of renal impairment, n (%)	9 (22.5%)	6 (13.6%)	0.4388
Active smokers, n (%)	9 (22.5%)	15 (34.1%)	0.3510
Vital signs on admission			
Systolic BP (mmHg), Mean (SD)	150.1 (34.3)	147.4 (30.1)	0.6913
Diastolic BP (mmHg), Mean (SD)	77.1 (19.4)	77.3 (18.7)	0.9619
Heart rate (BPM), Mean (SD)	86.8 (23.2)	82.7 (19.1)	0.3775
Lab results			
HbA1c (%), Median (interquartile range)	8.25 (7.7-8.95)	7.9 (7.5-8.4)	0.0430
Total haemoglobin(g/dl), Mean (SD)	12.2 (2.3)	13.1 (2.1)	0.0644
Total cholesterol (mg/dl), Median (interquartile range)	210.5 (184.5-238)	207 (179-244)	0.9643
Triglycerides (mg/dl), Median (interquartile range)	186.5 (120-239)	202 (139-279)	0.2148
Blood glucose on admission (mg/dl), Mean (SD)	247.2 (64.4)	227.7 (51.7)	0.1282
TnT peak (pg/ml), Mean (SD)	1.45 (3.3)	1.42 (3.4)	0.9674
Serum Creatinine (mg/dl), Mean (SD)	2.0 (1.9)	1.43 (1.3)	0.1907

Abbreviations: BPM, Beats Per Minute; CV, cardio-vascular; CHF, congestive heart failure; HbA1c, glycosylated haemoglobin; CHD, coronary heart disease; MI, myocardial infarction; PVD, peripheral vascular disease; SD, standard deviation; TIA, transient ischemic attack; TnT, troponin T.

No significant differences were found between the 2 subgroups, except for the HbA1c level at discharge. Slightly higher blood glucose on admission and lower total haemoglobin in

patients who were referred for diabetological consult were recorded, but without statistical significance.

Other potential clinical outcome predictors such as vital signs and blood tests on admission (as shown in Table 1), respectively type of ACS, treatment modality and left ventricular systolic function at discharge (as shown in Table 2) were also well-balanced.

Table 2. Patient ACS clinical data.

Variable	Intervention group n=40	Control group n=44	p value
Type of ACS			
Unstable angina, n (%)	10 (25.0%)	15 (34.1%)	0.3976
NSTEMI, n (%)	18 (45.0%)	21 (47.7%)	
STEMI, n (%)	12 (30.0%)	8 (18.2%)	
Treatment modality			
Conservative, n (%)	15 (37.5%)	17 (38.6%)	0.3231
PCI, n (%)	23 (57.5%)	27 (61.4%)	
CABG, n (%)	2 (5.0%)	0 (0.0%)	
Left ventricular systolic function at discharge			
Ejection Fraction (%), Mean (SD)	50.02 (14.48)	50.32 (16.47)	0.9299

Abbreviations: ACS, acute coronary syndrome; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

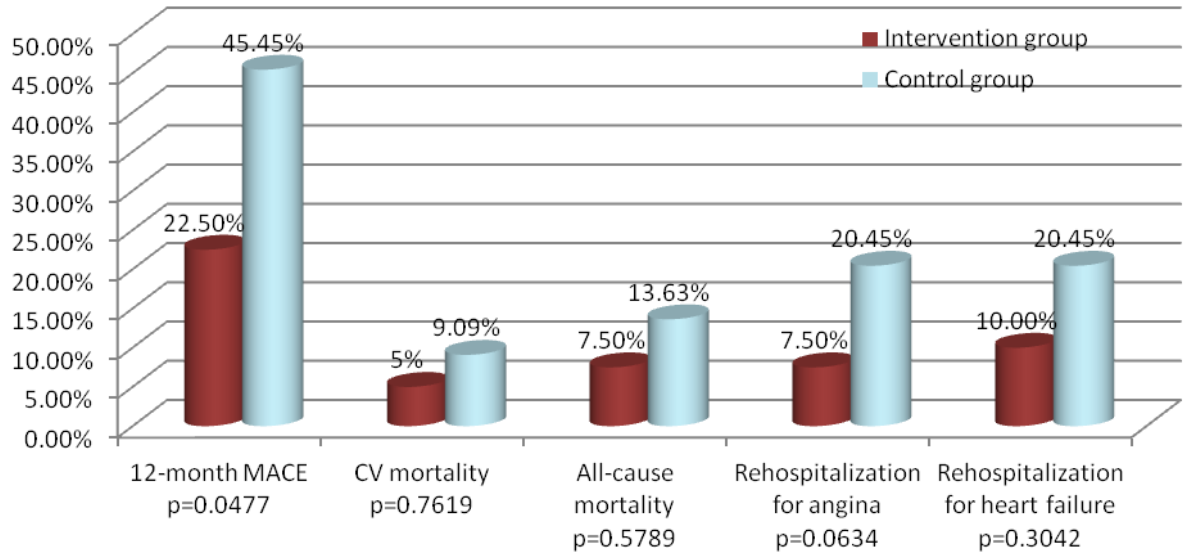

Figure 1. *Rates of 12-month MACE, 12-month CV mortality, 12-month all-cause mortality, rehospitalization for angina and rehospitalization for heart failure for both sub-groups of patients.*

As shown in Figure 1, there was a significant difference between the 2 subgroups in the primary endpoint - 12-month MACE rate. Thus, the patients without diabetologist referral and subsequent treatment strategy changes were more at a higher risk for a MACE in the 12 month follow-up period. For the secondary endpoints, these differences were not so marked, and were not significant.

The corresponding hazard ratios are given in Table 3. According to these results, the absence of referral to a diabetologist with subsequent

management changes in glycaemic control can almost triple the risk for a major adverse cardiac event in the next year after an ACS in this group of patients with T2DM.

Table 3. Hazard ratio for primary and secondary endpoints in diabetologist referral subgroup compared to subgroup without diabetologist referral.

	Hazard ratio (CI 95%)	p value
12-month MACE	2.8704 (1.109-7.423)	0.0296
12-month CV mortality	1.9000 (0.328-10.98)	0.4734
12-month all-cause mortality	1.9474 (0.453-8.368)	0.3703
Rehospitalization for angina	3.1714 (0.793-12.68)	0.1026
Rehospitalization for heart failure	2.3143 (0.652-8.211)	0.1940

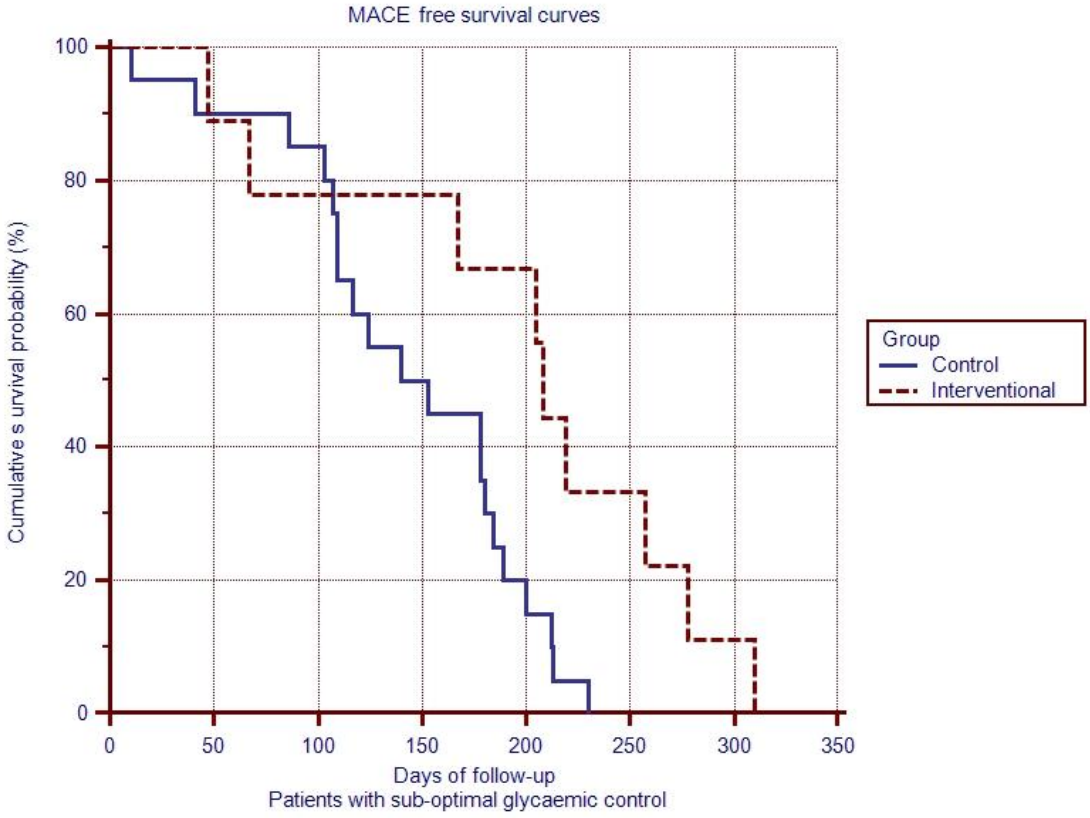

Figure 2. *MACE free Kaplan-Meier survival curves for patients with sub-optimal glycaemic control at inclusion.*

The MACE-free Kaplan-Meier survival curves also demonstrate significant differences between the 2 subgroups as shown in Figure 2 (logrank test: p=0.0173).

Discussion

The main finding of this study is the importance of the glycaemic control changes for T2DM patients after an ACS. Thus, our data show that, in poorly controlled patients, the absence of treatment change recommended by a diabetologist can triple the chance of MACE in 1 year.

One of the secondary results revealed that there are numerous cases, also in the sub-optimal glycaemic control group, that did not complete

the diabetological consult before discharge or immediately after that. This observation strengthens the presumption that the compliance with the recommendations of the French Diabetes Society is low in both countries; however the cut-off value for the selection of patients who benefit from diabetologist referral in these guidelines is much higher than in our study.

Numerous previous reports [19,20] have found that elevated admission glucose levels were associated with adverse short-term outcome in patients presenting with ACS. The predictive effect of admission glucose level is valid across the whole spectrum of patients presenting with ACS, including elderly patients [21], and also irrespective of the treatment modality, whether primary PCI [22] or lytic [21] or conservative management [23]. This observation was further confirmed by a large multinational observational registry, the Global Registry of Acute Coronary Events (GRACE) [24]. The relationship was extended to patients presenting with STEMI, NSTEMI, and unstable angina. However, a high glucose level may only be the marker of stress hyperglycaemia, and not represent the general glucometabolic state.

The measurement of glycated haemoglobin provides a reliable reflection of the degree of general glucometabolic state in the previous 8–12 weeks. It serves as a marker for diabetic control. There has been conflicting evidence about the prognostic value of HbA1c levels on short-term outcomes in ACS. Thus, the prognostic relationship between HbA1c and mortality after STEMI in patients with or without DM has been demonstrated in a small-scale trial [25]. However, other trials which included diabetic and non-diabetic patients did not show such a relationship [23,26]. Elevated HbA1c level is likely the result of long term insulin resistance. Metabolic disturbances associated with insulin resistance including hyperglycaemia, dyslipidaemia, hypercoagulability and inflammation might represent the major pathologic mechanism for the adverse impact of elevated HbA1c in the setting of CVD [27]. A recent meta-analysis concluded that HbA1c level is an independent predictor of total mortality in CVD patients without diabetes but not in patients with established diabetes [18].

Our study aimed to investigate the effect of the treatment strategy changes in T2DM patients with sub-optimal glycaemic control after hospitalization for ACS. The results suggest that these changes (targeting a tighter glycaemic control) can improve the long-term outcome for this special group of patients.

Study limitations. This study was an observational and nonrandomized study. Only patients with HbA1c levels checked before discharge were included. This might result in a selection bias. However, it was the standard practice to check HbA1c in every diabetic patient to optimize patient management. Apart from that, the study population was relatively small. This might result in inadequate power to detect a slight difference in clinical outcomes between the 2 subgroups. Therefore, it will be more informative if a larger sample size is studied. Moreover, there are some risk factors that were not evaluated related to the primary and secondary endpoints because the lack of data: low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) profiles, median values of blood pressure during the follow-up period, compliance to the recommended cardiologic treatment. These can constitute limitations for the present study.

Conclusions

In conclusion, our study suggests that, after hospitalization for an ACS, diabetologist referral

and treatment strategy changes are recommended for all T2DM patients whose HbA1c level before discharge is higher than 7%.

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***Duality of interest* -** no conflicts of interest.

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