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# Antidiabetic therapy at admission and survival in diabetic patients with acute myocardial infarction

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A B S T R A C T

Introduction: Diabetes mellitus is frequently associated to cardiovascular disease. We aimed at studying the relations between anti-diabetic drugs in use at admission by diabetic patients with acute myocardial infarction and survival after a period of at least 36 and up to 52 months after admission.
Methods: Retrospective study based on electronic records. Data from a total number of 195 admissions corresponding to different patients were under analysis.
Results: Kaplan–Meier analysis, as well as Cox analysis, failed to show a difference in survival associated to the use of DPP-4 inhibitors ($n = 35$ patients). A non-significant trend toward increased survival was seen with metformin ($n = 92$ patients), and in the opposite direction with both insulin ($n = 51$ patients) and sulfonylureas ($n = 51$ patients).
Conclusions: The use of DPP-4 inhibitors at admission, in patients with Diabetes mellitus admitted for acute myocardial infarction, was not associated to a different survival after no less than 36 months and up to 52 months after admission.

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## Introduction

*Diabetes mellitus* is a highly prevalent disease, and is frequently associated to cardiovascular disease. Haffner et al. showed that diabetic patients without previous myocardial infarction had a risk of death from coronary heart disease similar to nondiabetic patients with previous myocardial infarction.[1] Using data from the Multiple Risk Factor Intervention Trial, Stamler et al. showed that the presence of *Diabetes mellitus* was associated to an increased risk of cardiovascular death.[2]

Anti-diabetic therapy, however, has failed to produce consistent results in decreasing cardiovascular risk in diabetic patients, and in some cases an increased risk was in fact seen, starting with the seminal University Group Diabetes Program study.[3] A particular concern was raised by the Action to Control Cardiovascular Risk in Diabetes Study, published in 2008, which showed an increased mortality associated to intensive anti-diabetic therapy.[4]

A considerable curiosity exists concerning the cardiovascular effects of newer anti-diabetic drug classes, including dipeptidyl peptidase 4 (DDP-4) inhibitor drugs. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 study, saxagliptin use was not associated to an increased incidence of major adverse cardiovascular events; however, an excess rate of hospitalization for heart failure was seen.[5] In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin study, the use of this latter drug was not associated to a change in the incidence of cardiovascular disease,[6] the same happening in the Examination of cardiovascular outcomes with alogliptin versus standard of care[7] study. In this latter case, the study was carried out in patients with a recent acute coronary syndrome.

In a previous report, we retrospectively studied data on the relation between peak plasma troponin levels and anti-diabetic drugs (insulin, metformin, sulfonylureas and DPP-4 inhibitors) in use, from the admissions with acute myocardial infarction that took place during 15 months in an acute coronary care unit.[8] In the present investigation, and using the same cohort, we aimed at studying the relations between anti-diabetic drugs in use at admission and survival after a period of at least 36 and up to 52 months after admission. The same cohort was previously studied using similar methods but addressing a different research question (the relation between plasma alkaline phosphatase and survival).[9]

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## Methods

The present study was retrospective, and part of the methods have been described in previous reports,[8,9] and are hereby reproduced. From all patients admitted to an intensive coronary care unit from January 2011 to March 2012, in a university hospital, in Porto, Portugal, patients with both acute myocardial infarction and diabetes mellitus were identified. A patient was considered to have diabetes mellitus if anti-diabetic therapy was being taken, if the diagnosis had been previously established on the basis of then current recommendations or if glycated hemoglobin greater than 6.5% was present at admission. Acute myocardial infarction was diagnosed following the recommendations in use. Patients with in-hospital acute myocardial infarction were excluded. Patients who were initially admitted to another hospital, and who were later transferred into our institution, were only included if the peak value for plasma troponin I could be clearly identified.

From the electronic files, the following data were obtained: age; gender; peak plasma cardiac troponin I levels; creatinine plasma levels at admission; presence of ST segment elevation in the electrocardiogram; previous history of myocardial infarction; previous coronary revascularization, either percutaneous or surgical; primary coronary angioplasty in the current episode. Troponin I was measured using the ARCHITECT STAT system, of Abbott Diagnostics (Abbott Park, IL, USA). The 99th percentile of troponin I in a normal population with this assay was established at 0.012 ng/ml.

The survival of patients was established by the retrospective study of electronic health records, after a minimum period of 36 months had passed from each admission. In the case of dead patients, the date of death was recorded, when available, or alternatively the date of the last observation of each patient. In the case of patients not known to be dead, censoring was carried out in the date of the last observation. No attempt was made to study the causes of death or the medication in use after hospital discharge.

For each class of anti-diabetic drug – insulin, metformin, sulfonylureas and DPP-4 inhibitors – patients under each of these classes of drugs were compared to the remaining patients.

Kaplan–Meier study was carried out. The comparison between groups was made using the log-rank test. Cox-proportional hazards survival modeling was used. Covariates included gender, age, plasma creatinine, peak plasma troponin I, presence of ST segment elevation, and use of each of the 4 classes of anti-diabetic drugs mentioned above.

A significance level of 0.05 was considered statistically significant. Data analysis was performed using the SPSS 22 software program, from IBM (Amonk, NY, USA). The present protocol was approved by the ethics committee of our institution.

## Results

Data from a total number of 195 admissions corresponding to different patients were under analysis, out of an initial number of 954 patients admitted in the period under study, from which 200 admissions corresponded to diabetic patients (in the case of more than one admission for the same patient, only the initial admission was considered). 126 patients were of the male sex and 69 were female. The mean age was 67.6 ± 10.6 years.

ST segment elevation myocardial infarction was present in 62 patients. Primary coronary angioplasty was carried out in 44 patients. The mean peak plasma cardiac troponin I values for the 200 admissions was 49.5 ± 95.9 ng/ml.

After a period not inferior to 36 months and up to 52 months after each admission, the retrospective analysis of electronic records showed that 58 of the 195 patients had died (29.7%).

Most patients were taking at admission, alone or in combination, metformin, insulin, sulfonylureas and DPP-4 inhibitors. Thirty
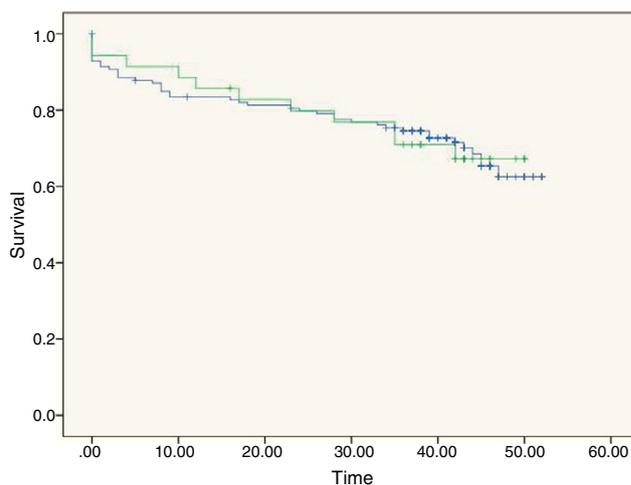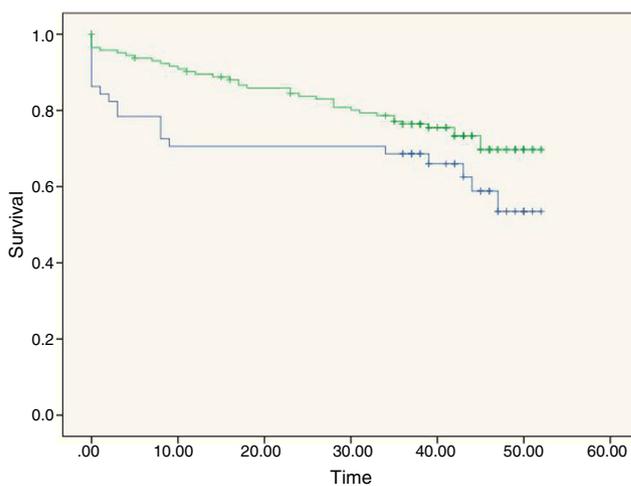


**Fig. 1.** Kaplan–Meier survival curves for 195 patients with *Diabetes mellitus* and acute myocardial infarction, according to DPP-4 inhibitors therapy at admission. Time measured in months. Green line – patients under DPP4-I therapy; blue line – patients not under DPP4-I therapy. Significance level in log-rank test 0.957.

one patients were taking no antidiabetic therapy at admission. Nineteen patients were taking oral antidiabetic drugs, but it was impossible to establish which drugs were in use (either the patients did not recall the names of the drugs in use or the record was incomplete).

DPP4-inhibitor drugs (either vildagliptin or sitagliptin) were used at admission by 35 patients, 32 of whom were also using metformin. Kaplan–Meier analysis showed that the use of DPP4-inhibitor drugs at admission was not associated to a significant change in survival, when compared to patients not taking that type of drugs, with a significance level in log-rank test of 0.957 (Fig. 1).

Concerning the other three other major types of antidiabetic drugs used by the patients, insulin (Fig. 2), metformin (Fig. 3) and sulfonylureas (Fig. 4), significant differences were also not seen in Kaplan–Meier analysis, however non-significant trends were seen in the direction of increased mortality with the use of insulin (*n* = 51 patients; significance level in log-rank test of 0.074) and of sulfonylureas (*n* = 51 patients; significance level in log-rank test of 0.167) at admission, whereas the opposite was seen with metformin (*n* = 92



**Fig. 2.** Kaplan–Meier survival curves for 195 patients with *Diabetes mellitus* and acute myocardial infarction, according to insulin therapy at admission. Time measured in months. Blue line – patients under insulin therapy; green line – patients not under insulin therapy. Significance level in log-rank test 0.074.
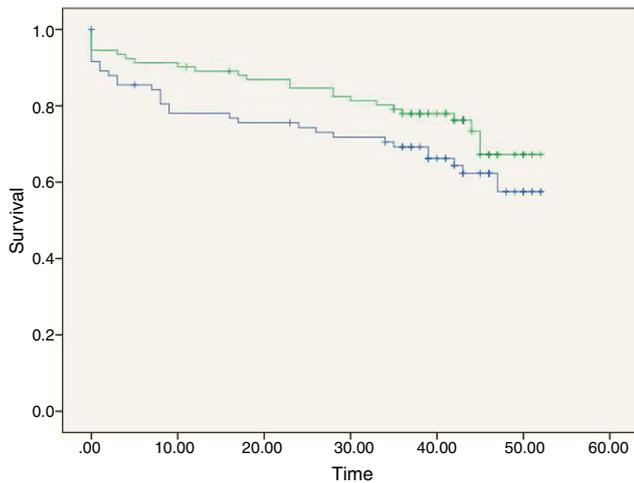
**Fig. 3.** Kaplan–Meier survival curves for 195 patients with *Diabetes mellitus* and acute myocardial infarction, according to metformin therapy at admission. Time measured in months. Green line – patients under metformin therapy; blue line – patients not under metformin therapy. Significance level in log-rank test 0.135.
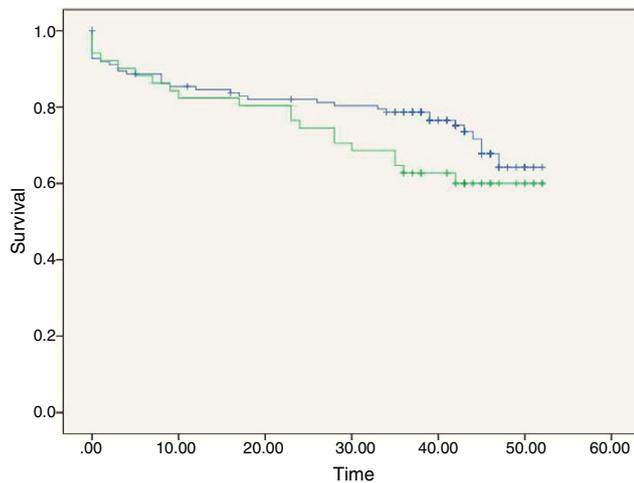


**Fig. 4.** Kaplan–Meier survival curves for 195 patients with *Diabetes mellitus* and acute myocardial infarction, according to sulfonylurea therapy at admission. Time measured in months. Green line – patients under sulfonylurea therapy; blue line – patients not under sulfonylurea therapy. Significance level in log-rank test 0.167.

patients; significance level in log-rank test of 0.135), in each case when compared to patients not taking the given type of drugs.

Cox analysis showed that peak plasma troponin I, age and plasma creatinine at admission were independent predictors of mortality (Table 1). On the contrary, gender, presence of ST-segment elevation in the electrocardiogram, and the use of either

**Table 1**
Cox regression analysis of survival of 195 patients with *Diabetes mellitus* admitted for acute myocardial infarction. Retrospective analysis of survival based on electronic health records after no less than 36 months after admission for each patient, and up to 52 months.

| Parameter | Significance level |
| --- | --- |
| Peak troponin I plasma level | <0.001 |
| Age | <0.001 |
| Gender | 0.144 |
| Plasma creatinine at admission | 0.012 |
| ST segment elevation in electrocardiogram | 0.101 |
| DPP-4 inhibitor use at admission | 0.543 |
| Insulin use at admission | 0.079 |
| Sulfonylurea use at admission | 0.315 |
| Metformin use at admission | 0.816 |

DPP-4 inhibitors, insulin, metformin or sulfonylureas at admission were not predictors of mortality (Table 1).

## Discussion

In the present report, survival of patients admitted for acute myocardial infarction was studied, according to the type of antidiabetic drugs in use at admission. The evaluation was made retrospectively, after a period not inferior to 36 months, and up to 52 months, had passed since admission. Four different types of anti-diabetic therapy were under study: metformin, insulin, sulfonylureas and DPP-4 inhibitors.

No attempt was made to evaluate the anti-diabetic therapy used by the patients after hospital discharge, however the standard policy at our institution was to use insulin (adjusted to plasma glucose) during the in-hospital stay, returning to the previous anti-diabetic therapy at discharge, except in cases previously not treated or with markedly elevated plasma glucose/glycated hemoglobin. It is therefore probable that a significant degree of overlap exists between anti-diabetic drugs used at admission and after discharge (especially in the case of patients treated with insulin). Any effect that might be observed could be due to: effects of anti-diabetic therapy during the index acute myocardial infarction episode; effects from further anti-diabetic treatment after discharge; indication bias, with a differential use of different types of anti-diabetic drugs in patients with different clinical condition (insulin being predominantly used in patients with long-standing disease). Standard therapy for these patients at discharge included double antiplatelet therapy and a statin.

Metformin use at admission was associated to a non-significant trend toward increased survival. This is not unexpected, since a consensus exists that metformin is one of the anti-diabetic drugs with the most favorable profile, given, namely, the data reported in the "overweight" study from the United Kingdom Prospective Diabetes Study (UKPDS 34).[10] Metformin was otherwise shown to be associated to a survival benefit in patients with incident cancer, both in comparison with other anti-diabetic drugs and in comparison with a nondiabetic population.[11]

Insulin use at admission was associated to a non-significant trend toward decreased survival. This likely reflects, at least in part, a possible indication bias, since insulin is currently used is patients with long-standing *Diabetes mellitus*, often with end-organ disease. In the Outcome Reduction with an Initial Glargine Intervention study, rates of incident cardiovascular outcomes were in fact similar in the insulin-glargine and standard-care groups.[12]

Sulfonylureas use at admission was also associated to a non-significant trend toward decreased survival. Sulfonylureas may not alter mortality of diabetic patients, when compared to metformin therapy.[13] Sulfonylureas may interact with myocardial ATP-sensitive potassium channels[14]; these drugs were noted to be associated with an increased risk of in-hospital mortality among diabetic patients undergoing coronary angioplasty for acute myocardial infarction.[15] It is however possible that different sulfonylureas elicit different cardiovascular effects. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation study, the use of gliclazide was associated to a decrease in nephropathy.[16]

Experimental data point in the direction of a favorable effect of DPP4 inhibition on infarct size.[17] In a previous study, we failed to show any difference in peak plasma troponin levels when patients either treated or not treated with DPP4 inhibitors at admission were compared.[8] In the present study, the use of DPP-4 inhibitor drugs at admission was notably devoid of any association to a difference in survival, since the Kaplan–Meier curves for patients either taking or not taking this type of drugs were nearly identical. This pattern is remarkably similar to what has been reported in the

Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study,[6] but the present data were obtained in a "real-world" situation, and not in the context of a controlled clinical trial, meaning that the whole range of patients was under analysis. In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care study, diabetic patients with a recent acute coronary syndrome did not have different rates of major adverse cardiovascular events if treated with alogliptin, as compared with placebo.[7]

*Study limitations* – The present study has significant limitations: it is a retrospective study; the small dimension of the sample limits the strength of conclusions; no attempt was made to characterize the drugs in use after the admission or the causes of death.

## Conclusions

In conclusion, the use of DPP-4 inhibitors at admission, in patients with *Diabetes mellitus* admitted for acute myocardial infarction, was not associated to a different survival after no less than 36 months and up to 52 months after admission.

## Conflict of interest

None declared.

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