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Incremental role of glycaemic variability over HbA1c in identifying type 2 diabetic patients with high platelet reactivity undergoing percutaneous coronary intervention

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Abstract

Background: Diabetic patients with on-treatment high platelet reactivity (HPR) show an increased risk of thrombotic events. Whether measuring glycosylated haemoglobin (HbA1c) levels and/or glycaemic variability (GV) may help identifying diabetic patients at higher risk deserving tailored antiplatelet and/or glucose lowering strategies is unknown. We aimed to investigate the relationship between GV, HbA1c levels and platelet reactivity in patients with type 2 diabetes mellitus (DM) undergoing percutaneous coronary intervention (PCI).

Methods: Platelet reactivity was measured in type 2 DM patients using VerifyNow P2Y12 assay. HPR was defined as P2Y12 Reaction Unit (PRU) > 240. GV was expressed through mean amplitude of glycaemic excursions (MAGE) and coefficient of variance (CV) by using the iPro™ continuous glucose recorder.

Results: Thirty-five patients (age 70 ± 9 years, 86% male, mean HbA1c 7.2 ± 1.0%) on clopidogrel therapy were enrolled. HbA1c was independently associated with HPR (OR 7.25, 95% CI 1.55–33.86, $p = 0.012$). Furthermore, when factored into the model, GV indexes provided independent (OR 1.094, 95% CI 1.007–1.188, $p < 0.034$) and additional ($p < 0.001$) diagnostic significance in identifying diabetic patients with HPR.

Conclusions: Glyco-metabolic state significantly correlates with HPR in well-controlled type 2 DM patients on clopidogrel therapy. HbA1c identifies patients at higher thrombotic risk but the highest diagnostic accuracy is achieved by combining GV and HbA1c. Whether individualized antithrombotic and glucose-lowering therapies based on the assessment of these parameters may reduce the incidence of thrombotic events in patients undergoing PCI should be further investigated.

Keywords: Glycosylated haemoglobin, Glycaemic variability, Continuous glucose monitoring, Platelet reactivity, Percutaneous coronary intervention

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Background

Patients with type 2 diabetes mellitus (DM) are at higher risk of atherothrombotic events, accountable of about two-thirds of deaths [1, 2]. The enhanced thrombotic status of diabetic patients is related to multiple mechanisms such as endothelial dysfunction, activation of coagulation cascade and high platelet reactivity (HPR) [3]. The latter is considered to play a crucial role in the pathogenesis of macrovascular complications [3], as diabetic patients with HPR showed an over threefold increase in 2-years cardiovascular events recurrence although on steady-state dual antiplatelet therapy [4, 5].

Nevertheless, which glycometabolic parameter should be used in predicting HPR among diabetic patients is unknown. Previous studies investigated the effects of glycosylated hemoglobin (HbA1c) on platelet function with conflicting results [6–9]. This happens also because fasting blood glucose, fructosamine or HbA1c levels may not offer a complete assessment of glycaemic status [10]. Conversely, glycaemic variability (GV) includes an overall measure of patients' blood glucose fluctuations, taking into account all hypo- and hyperglycaemic episodes in a pre-determined period of monitoring. Long-term visit-to-visit GV has been shown to be a better risk predictor than mean HbA1c values for micro and macro-vascular complications and all-cause mortality [11]. Moreover, high levels of GV, assessed by continuous glucose monitoring (CGM), appear to have even more deleterious effects than sustained hyperglycaemia in the pathogenesis of cardiovascular autonomic neuropathy and other cardiovascular complications [12, 13]. Previous studies have already correlated an increased GV to the occurrence of adverse events in patients with acute coronary syndromes undergoing percutaneous coronary revascularization (PCI) [14–16]. Finally, critically ill patients admitted to intensive care unit with high GV have shown a significant increased mortality compared with those with less glycemic variability even with slight hyperglycaemia [17].

Notwithstanding, prospective studies investigating the effects of GV on platelet function are lacking. Moreover, whether GV assessment over HbA1c may improve antiplatelet and glucose-lowering management of diabetic patients is still undetermined.

Thus, in this study, we aimed to explore the possible correlation between HbA1c levels and HPR in patients undergoing PCI on clopidogrel therapy. Moreover, we aimed to examine the possible role of GV over HbA1c in identifying diabetic patients at higher thrombotic risk.

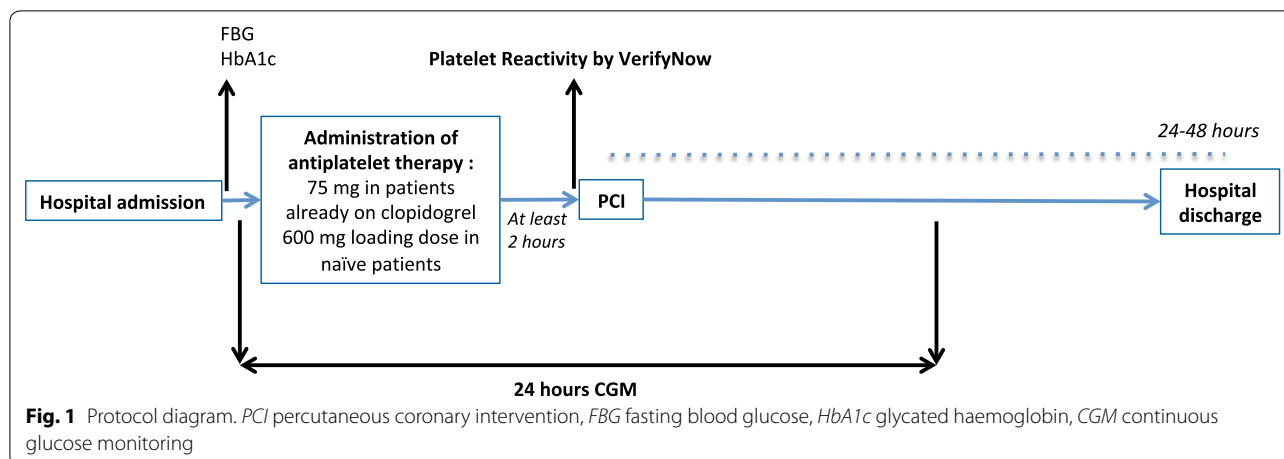
Research design and methods

Consecutive patients with type 2 DM scheduled for elective PCI were prospectively enrolled at our Institution between February and October 2016. Exclusion criteria were: primary intervention for ST-elevation acute myocardial infarction; acute coronary syndrome in the previous 72 h; use of glycoprotein IIb/IIIa inhibitors; platelet count $<70 \times 10^9/l$; severe renal failure (glomerular filtration rate $<30 \text{ ml/min/1.73 m}^2$); coexistent immunological, inflammatory or neoplastic disease at the time of enrolment; high bleeding risk or other contraindications to antiplatelet therapy; availability of glucose sensor for research purpose.

Presence of diabetes mellitus was defined as a history of diabetes controlled by diet or oral glucose-lowering agents or insulin. Coronary intervention was performed with standard technique. All patients were taking aspirin 100–325 mg at the time of the procedure; a 600 mg loading dose of clopidogrel was given at least 2 h before intervention in naïve patients, whereas, patients already on clopidogrel therapy for at least 5 days before the procedure continued to receive a standard dose of 75 mg. After PCI, all patients were maintained on aspirin and clopidogrel 75 mg/day. Our local Ethic Committee approved the study and all subjects enrolled provided written informed consent.

Platelet function and laboratory testing

A schematic diagram of the study protocol was reported in Fig. 1. We performed a blood sample in all patients immediately before the percutaneous procedure in the catheterization laboratory, right after the insertion of the radial/femoral sheath, for the assessment of platelet reactivity using the VerifyNow P2Y12 assay (Accumetrics Inc., San Diego, California). Results were expressed as P2Y12 reaction units (PRU) and HPR was defined as a PRU value >240 [18, 19]. Fasting blood glucose levels and HbA1c were also obtained before PCI in all patients. Furthermore, blood samples were drawn before and at 8 and 24 h after the procedure for creatine kinase-MB (CK-MB) and troponin I (TnI) levels detection; further values were obtained if symptoms suggested myocardial ischemia. These measurements were performed by standard enzymatic procedures (LOCI™ immunochemiluminometric assay—SIE-MENS); normal limits were considered 3.6 ng/ml for CK-MB and 0.06 ng/ml for TnI. PCI-related myocardial damage was defined by an elevation of TnI >5 the 99th percentile URL in patients with normal baseline values and by an increase of TnI $>20\%$ if the baseline values were elevated ($>0.06 \text{ ng/ml}$).



Glycaemic variability assessment

The glucose monitoring methods were previously reported [20]. Briefly, all enrolled patients were equipped with the iPro™ continuous glucose recorder (Medtronic, Northridge, CA) and a CGM sensor (Enlite® Sensor) was inserted into the subcutaneous abdominal fat tissue about 12 h before the revascularization procedure and platelet reactivity assessment. CGM measured subcutaneous tissue interstitial glucose levels every 5 min, within a range 40–400 mg/dl. The analysis was performed on data obtained in the entire peri-procedural period, from 12 h before to 12 h after PCI. During iPro™ CGM, patients also checked their capillary blood glucose levels with a self-monitoring at least 4 times per day. The FreeStyleLite (Abbott Laboratories, Abbott Park, IL) BG-monitoring system was used to calibrate the iPro™ continuous glucose recorder. After 24-h monitoring, the recorded data were downloaded for the analysis of the glucose excursion parameters using the CareLinkiPro System. Intraday GV was expressed by the GV indexes: standard deviation (SD); coefficient of variation (CV); mean amplitude of glycaemic excursions (MAGE), representing an average size of glycaemic fluctuations; MAGE-up, an average size of glycaemic fluctuations from nadirs to peaks, thus indicating hyperglycaemic excursions; MAGE-down, indicating glycaemic variations from peaks to nadirs, thus hypoglycaemic excursions; continuous overall net glycaemic action (CONGA) (1, 2 and 4) assessing magnitude and timing of blood glucose fluctuations captured over various time periods.

Statistical analysis

Data are presented as percentages and frequencies for categorical variables; whereas, continuous data are presented as mean ± standard deviation (SD). To identify

deviations from the normal distribution the Kolmogorov–Smirnov test was used. Comparisons between groups were evaluated using the Mann–Whitney U test, the Chi-square or the Fisher exact test according to distribution. Bivariate correlations between variables were performed and partial correlations were used to adjust for covariates (e.g., BMI and age). HPR and PCI-related myocardial damage were used as dependent variables and only variables which showed a p-value of <0.1 in the two-way analysis were tested in the hierarchical multivariate model. Results of logistic regression are expressed as odds ratios (ORs) with their 95% confidence intervals (95% CI). Two-tailed p-value <0.05 was considered statistically significant. The statistical analyses were performed using SPSS version 20.

Results

Mean age of the overall population was 70 ± 9 years, 33 (94%) of patients underwent elective procedure for stable angina and 17 (49%) were treated by PCI for multivessel coronary disease. Other demographic and clinical characteristics are reported in Additional file 1: Table S1.

High platelet reactivity on clopidogrel therapy was observed in 14 patients (40%). Table 1 reports glycaemic parameters and glucose-lowering therapies of the whole population and according to HPR. At the time of the index procedure the vast majority of patients were treated with metformin and about one-third were on insulin; no difference was observed between the two groups with regard to pre-procedural oral glucose lowering strategies.

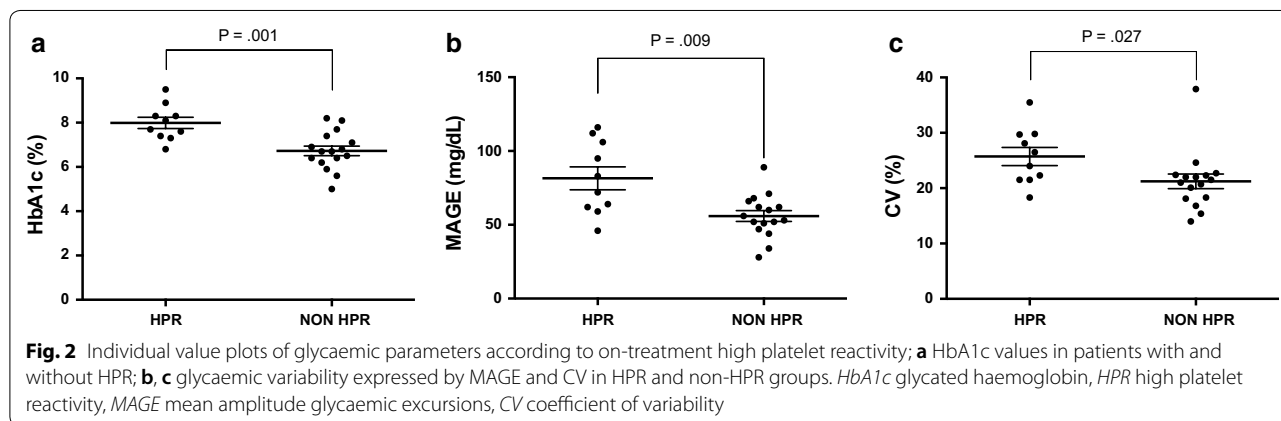
Mean HbA1c value was overall consistent with a well-controlled glycaemic status (Table 1). Nevertheless, significantly higher mean HbA1c levels were observed in patients with HPR indicating a worse glycaemic control (p < 0.001; Table 1) (Fig. 2a). Furthermore, increased

Table 1 Glycaemic parameters and glucose-lowering therapies in overall population and according to HPR

| Variable | Overall population | HPR | | p value |
|---|--------------------|--------------|--------------|---------|
| | | Yes (n = 14) | No (n = 21) | |
| PRU | 207 ± 82 | 284 ± 35 | 151 ± 57 | <0.001 |
| Hb1Ac (%) | 7.1 ± 1.0 | 7.9 ± 0.8 | 6.7 ± 0.8 | <0.001 |
| Hb1Ac (mmol/mol) | 54 ± 4 | 63 ± 2 | 50 ± 3 | |
| FBG (mg/dl) | 131.6 ± 50.8 | 145.5 ± 38.5 | 125.4 ± 63.6 | 0.551 |
| GV indexes | | | | |
| CONGA 1 (mg/dl) | 22.5 ± 8.4 | 22.7 ± 8.1 | 22.4 ± 8.9 | 0.816 |
| CONGA 2 (mg/dl) | 31 ± 9.1 | 30.5 ± 7.5 | 31.7 ± 11.0 | 0.856 |
| CONGA 4 (mg/dl) | 41.6 ± 13.9 | 41.9 ± 13.1 | 41.3 ± 15.4 | 0.857 |
| MAGE (mg/dl) | 66.8 ± 24 | 80.3 ± 26.9 | 55.9 ± 14.6 | 0.009 |
| MAGE-up (mg/dl) | 67.7 ± 27.6 | 71.2 ± 29.9 | 64.9 ± 26.2 | 0.938 |
| MAGE-down (mg/dl) | 61.4 ± 40.2 | 52.5 ± 49.4 | 68.7 ± 30.8 | 0.421 |
| SD (mg/dl) | 34.2 ± 11.4 | 34.9 ± 11.1 | 33.6 ± 12.0 | 0.586 |
| Average glycaemia (mg/dl) | 139.0 ± 35.0 | 140.8 ± 35.9 | 137.8 ± 36.2 | 0.897 |
| CV (%) | 23.3 ± 5.4 | 25.9 ± 4.6 | 21.2 ± 15.3 | 0.027 |
| Mean duration of diabetes mellitus (months) | 41 ± 34 | 51 ± 9 | 35 ± 8 | 0.027 |
| Insulin therapy | 12 (36) | 7 (21) | 5 (15) | 0.070 |
| Metformin | 20 (60) | 8 (23) | 12 (35) | 0.810 |
| Sulfonylureas | 11 (33) | 2 (6) | 9 (26) | 0.090 |

Values are given as mean ± SD or n (%)

HPR high platelet reactivity, PRU P2Y12 reaction unit, Hb1Ac glycated hemoglobin, FBG fasting blood glucose, GV glycaemic variability, CONGA continuous overall net glycaemic action, MAGE mean amplitude of glycemic excursions, SD standard deviation, CV coefficient of variation



values of MAGE and CV were also reported in this group (p values ≤ 0.027; Table 1 and Fig. 2b, c).

At the bivariate analysis, PRU was significantly associated with HbA1c ($r^2=0.12$, $p<0.04$, Fig. 3a) and MAGE ($r^2=0.22$, $p<0.009$, Fig. 3b) levels. Those associations remained significant after controlling for age (HbA1c: Adj $r^2=0.12$, $p<0.05$; MAGE: Adj $r^2=0.23$, $p<0.01$) and BMI (HbA1c: Adj $r^2=0.13$, $p<0.04$; MAGE: Adj $r^2=0.19$, $p<0.017$).

At the multivariate analysis, HbA1c was demonstrated to be an independent predictor of HPR ($p<0.012$; Model 1, Table 2). Notably, when MAGE was introduced into the model, it also showed to be an independent marker of HPR even after the adjustment for HbA1c ($p<0.034$; Model 2, Table 2). Moreover, introducing MAGE in addition to HbA1c in the hierarchical multivariate model with HPR as the end point, the fit of the model was improved as compared with

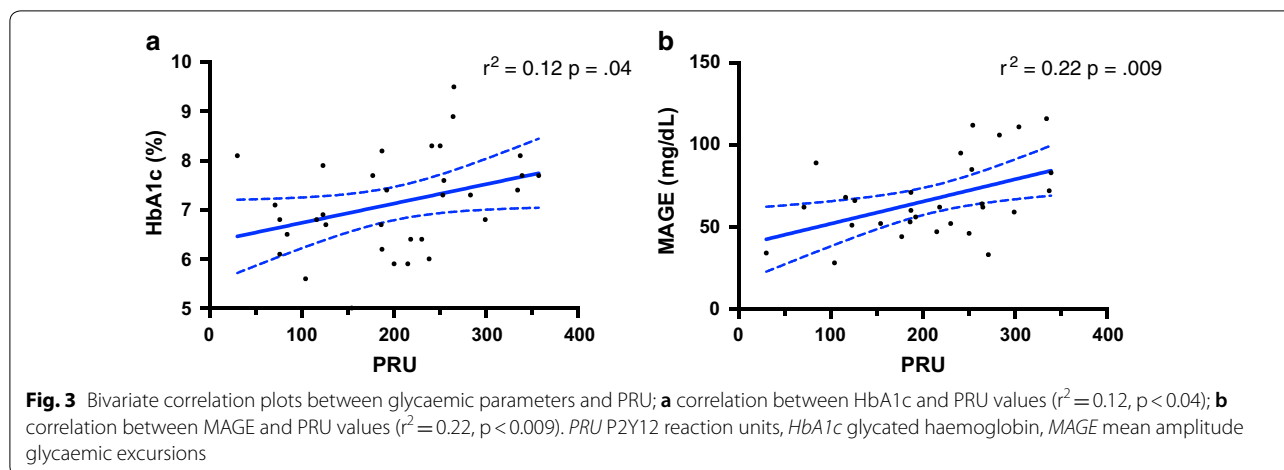


Table 2 Logistic regression models considering HPR as endpoint

| | p-value | OR (95% CI) |
|--|---------|---------------------|
| Model 1 (pseudoR2: 0.499, $p < 0.001$) | | |
| HbA1c | 0.012 | 7.25 (1.55–33.86) |
| Model 2 (pseudoR2: 0.757, $p < 0.0001$) | | |
| HbA1c | 0.019 | 13.21 (1.52–114.19) |
| MAGE | 0.034 | 1.094 (1.007–1.188) |
| Model 3 (pseudoR2: 0.618, $p < 0.0001$) | | |
| HbA1c | 0.018 | 9.13 (1.46–56.79) |
| CV | 0.071 | 1.22 (0.98–1.53) |

HPR high platelet reactivity, Hb1Ac glycated hemoglobin, MAGE mean amplitude glucose excursions, CV coefficient of variation

In the multivariate analysis (hierarchical enter method) HPR was entered in the model as dependent variable and as independent variables were included only the variables with $p < 0.10$ at the bivariate regression analysis: HbA1c, MAGE and CV. Excluded variables: fasting blood glucose, BMI, age, gender, weight, left ventricle ejection fraction, clopidogrel bolus (600 mg), chronic clopidogrel therapy, haemoglobin, haematocrit, platelet count number, white blood cells, total cholesterol, HDL, LDL, triglycerides and all the other glycaemic variability indexes (glycaemic average, SD, CONGA1, CONGA2, CONGA4, MAGE UP, MAGE DOWN); * $p < 0.05$

that including only HbA1c as single predictive variable (pseudoR2: 0.757, $p < 0.0001$; Model 2, Table 2). Indeed, the combination of MAGE and HbA1c explained the 75% of the variance of HPR compared with the 49% described with HbA1c only.

Comparable findings were observed when CV was introduced in the hierarchical multivariate model, although without statistical significance ($p < 0.071$; Model 3, Table 2).

With respect to the effects of GV on clinical outcomes, patients with higher MAGE-up levels showed an increased incidence of PCI-related myocardial damage ($p < 0.005$, Additional file 1: Table S2), whereas, no difference in HbA1c values were observed between

patients with and without post-procedural troponin release. Similarly, MAGE-down tended to increase in patients showing post-procedural myocardial injury, highlighting the unfavourable consequences of hypoglycaemia over hyperglycaemia on myocardial ischemia ($p = 0.053$, Additional file 1: Table S2). Finally, when MAGE-up was introduced in the hierarchical multivariate model with PCI-induced myocardial damage as the end point, it revealed to be an independent predictor of this complication ($p < 0.029$, Additional file 1: Table S3).

Discussion

Our findings indicate a remarkable influence of the glycaemic status on platelet reactivity in type 2 diabetic patients undergoing PCI on clopidogrel therapy. In our series, patients with HPR showed increased HbA1c values as well as higher GV expressed by elevated MAGE and CV levels. Finally, we found an additional prognostic role of GV over HbA1c in identifying diabetic patients at higher thrombotic risk.

HPR and diabetes

Guidelines recommend that patients with type 2 DM should be treated to achieve a HbA1c level between 7 and 8%, although an even less stringent target has been proposed in those with advanced macrovascular complications, such as established cardiovascular disease [21]. In our population, more than 70% of patients had an HbA1c value $\leq 7\%$, indicating a well-controlled glycaemic status; however, the incidence of HPR was still 40%. With respect to external validity of the present analysis, these findings are consistent with previous literature reporting reduced responsiveness to antiplatelet drugs in 36–60% of diabetic patients [22–24], with the highest values in those receiving insulin therapy [25]. The high prevalence of HPR among diabetic patients should be properly

taken into account on the clinical ground because HPR represents a recognized predictor of post-PCI long-term cardiovascular events, including death, MI and stent thrombosis in patients on antiplatelet therapy [26].

Glycated haemoglobin and HPR

In our study, HbA1c was observed to be an independent predictor of HPR, with each 1% increase in HbA1c levels translating into a seven-fold rise in the risk of PRU > 240. Previous studies investigating the impact of this glycaemic parameter on platelet reactivity have shown contradictory results [6–9]. Gaborit et al. [6] reported no correlation between ADP-induced platelet aggregation and glycaemic variables such as fasting blood glucose and glycated haemoglobin in a large cohort of diabetic patients. On the other hand, a specifically designed analysis of the prospective, multicenter Assessment of Dual AntiPlatelet Therapy With Drug-Eluting Stent (ADAPT-DES) Registry showed HPR prevalence increasing progressively with HbA1c levels [9]. Unfortunately, no previous study took into account the effects of GV on platelet reactivity.

While HbA1c represents a measure of chronic hyperglycaemia [10, 27], it does not reflect acute glucose fluctuations (hyper/hypoglycaemic spikes). Acute glycaemic variations are closely associated with cardiovascular complications and may be more adequately assessed by using GV [11–17]. Long-term GV has been demonstrated to represent a better glycaemic parameter than mean HbA1c for assessing the risk of micro and macrovascular complications in diabetic patients [11]. Moreover, HbA1c is characterized by several other shortcomings including worse diagnostic performance in different populations such as elderly, patients with iron deficiency anaemia or increased red blood cell turnover, those with end-stage renal disease or alcohol consumption [10].

Consequently, several studies described the clinical impact of GV in patients with coronary artery disease undergoing PCI [14–16]. A high MAGE value has been demonstrated an independent predictor of long-term poor prognosis in a large cohort of patients with acute coronary syndromes undergoing coronary stenting [15].

Glycaemic variability and HPR

According to our results, GV showed to be relevant in determining platelet reactivity despite an adequate HbA1c level: indeed, at the multivariate analysis, MAGE revealed to be an independent predictor of HPR even after the adjustment for HbA1c. Importantly, GV also exhibited an incremental value over HbA1c in detecting patients at higher thrombotic risk: adding MAGE over HbA1c to the hierarchical multivariate model significantly increases the chance to identify a non-responder

to clopidogrel (76% compared with 50% gained with HbA1c measurement only).

To the best of our knowledge, this is the first study investigating the correlation between GV assessed by CGM and platelet reactivity, particularly in the setting of percutaneous coronary revascularization. Previous studies only focused on hyper or hypoglycaemia at one time, failing to demonstrate the biological significance of the combined, which can be only expressed by GV. For instance, induced hypoglycaemia (50 mg/dl) in patients with type 2 DM has been demonstrated to enhance platelet hyperactivity by impairing sensitivity to prostacyclin [28]. On the other side, acute, short-term hyperglycaemia has been proposed to produce transient increased platelet activation after exposure to high shear stress both in vitro and in vivo in diabetic patients, possibly involving enhanced levels of Von Willebrand factor [29]. Furthermore, persistent in vivo platelet activation has been observed in response to postprandial hyperglycaemic spikes in patients with early diagnosed type 2 DM and with HbA1c levels < 7% [30]. Nevertheless, GV is the only measure including positive and negative acute glycaemic fluctuations and, therefore, it might play a more relevant role in promoting a prothrombotic state.

Glycaemic variability and peri-procedural myocardial damage

In our population higher GV values were observed in patients with PCI-related myocardial damage, confirming our previous evidence that diabetic patients with poor glycaemic control may have a significantly higher risk of suffering from this complication [17]. This is particularly relevant considering PCI-related myocardial injury associated with unfavourable long-term outcome [31]. Interestingly, high levels of MAGE were associated with increased myocardial damage, assessed by myocardial blush grade and ST-segment resolution, also in non-diabetic patients undergoing primary PCI [32].

MAGE-up confirmed to be an independent predictor of this ischemic complication as well as high white blood cells levels. These findings are consistent with experimental studies reporting acute blood glucose fluctuations significantly associated with increased oxidative stress, inflammation and endothelial dysfunction, all factors involved in the pathophysiology of myocardial damage during PCI [33]. Moreover, the occurrence of PCI-associated myocardial damage may reflect a more extensive and unstable atherosclerotic burden, as observed in patients with high GV. An intravascular ultrasound study reported increased MAGE levels in patients with larger plaque volumes and greater lipid plaque components [34].

Clinical implications

Since HPR is a well-described predictor of adverse thrombotic events [4, 5, 26], our findings underscore the clinical importance of maintaining an adequate glycaemic control, assessed by GV and HbA1c, in diabetic patients undergoing PCI.

For instance, our study generates the hypothesis that periprocedural GV and HbA1c assessment may help to identify those diabetic patients that should be moved towards more aggressive antiplatelet management, such as ticagrelor, also in the setting of an elective procedure [35, 36].

Similarly, given the impact of glycaemic control on HPR, efforts to reduce GV in diabetic patients undergoing PCI may have the same clinical relevance than an intensified platelet inhibition. Indeed, improvement in glucose metabolism assessed by fasting glucose levels, HbA1c and GV has been demonstrated to be associated with reduced oxidative stress, this latter playing an important role in the development of cardiovascular complications in diabetic patients [37]. Moreover, in the last decade, several novel oral glucose lowering drug classes (dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 agonists, and sodium-glucose cotransporter 2 inhibitors) have been demonstrated to improve GV indexes [38, 39] and to reduce adverse cardiovascular outcomes in large clinical trials [40]. Few studies have also investigated possible effects of these agents on platelet function with favourable results [41, 42]. Nevertheless, whether the use of these new glucose-lowering drugs may also provide antithrombotic effects improving GV and HbA1c in diabetic patients undergoing PCI should be investigated in further studies.

Strengths and limitations

The study population was limited, but this is the first study indicating a significant association between GV and HPR. There is not yet a consensus regards the appropriate methods and indexes for assessing GV; consequently our results showing that patients with higher MAGE-up levels had an increased incidence of PCI-related myocardial damage need further confirmation. Nevertheless, in our study we used CV and MAGE for the correlation with HPR, the most accepted metrics for GV according to the previous literature [11, 20]. Furthermore, CGM accuracy may be reduced during the first hours after sensor insertion due to local trauma; however, in our cohort, the mean absolute relative difference (MARD) value, an accepted metric of CGM precision, was < 10% indicating an adequate monitoring performance [43]. CGM was maintained for 24 h, within the 12 h before and the 12 h after PCI; even though a longer period of monitoring

might translate in a more precise assessment of GV, nevertheless it would be less applicable to current clinical practice where patients with stable coronary disease are admitted few hours before the procedure and discharged shortly after; we believe that been in keeping with current recommended clinical practice may represent a further strength of the present study. Additionally, GV is likely affected by several pre-, intra- and post-procedural factors in patients undergoing PCI; thus, a 24-h GV monitoring peri-procedural interval may be an adequate time frame taking into account all these aspects and potentially useful, on the clinical ground, for the tailored antiplatelet management of these patients.

Finally, our sample size did not allow to investigate the effects of different glucose lowering agents on GV and, consequently, on platelet reactivity. In addition, we did not explore the effects of glycaemic state on prasugrel or ticagrelor antiplatelet action. However, even if both these two agents are considered the first choice in the acute coronary setting according to guidelines, clopidogrel still remains the more frequently used antiplatelet drug in elective procedures, and we observed as glycaemic state significantly impact patients' responsiveness to this drug.

Conclusions

Our hypothesis-generating findings indicate a dangerous but modifiable relationship between glycaemic status assessed by HbA1c levels and GV indexes and HPR in diabetic patients undergoing PCI on clopidogrel therapy. Thus, the present study while underscoring the relevance of a tailored antiplatelet management, on the same time draws our attention to the maintenance of a well-controlled glycometabolic status. Further studies are needed to confirm these results in larger samples.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12933-019-0952-8>.

Additional file 1: Table S1. Demographic and clinical characteristics of the overall population. **Table S2.** Differences according to PCI-related myocardial damage. **Table S3.** Logistic regression models considering PCI-related myocardial damage as end point.

Abbreviations

CGM: continuous glucose monitoring; CK-MB: creatine kinase-MB; CONGA: continuous overall net glycemic action; CV: coefficient of variation; DM: diabetes mellitus; GV: glycaemic variability; HbA1c: glycated hemoglobin; HPR: high platelet reactivity; MAGE: mean amplitude of glycaemic excursions; PCI: percutaneous coronary revascularization; PRU: P2Y12 reaction units; SD: standard deviation; TnI: troponin I.

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Authors' contributions

AN contributed to the conception and design of the study, to the interpretation of the data and wrote the manuscript. DT contributed to statistical analysis and data interpretation and supported the writing of the manuscript. CP, RM and SM contributed to data acquisition. AN and AC interpreted the results and supported the statistical analysis. PP and GPU reviewed the manuscript. FG and GDS contributed to the writing of the manuscript and reviewed/edited the manuscript. AN is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Availability of data and materials

The authors declare that all data supporting the findings of this study are available within the article and its Additional file.

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and has been approved by our local Ethic Committee (Ethical Committee of Campus Bio-Medico University of Rome). All subjects enrolled provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

- Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, REACH Registry Investigators, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA*. 2010;304(12):1350–7.
- Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjörnsdóttir S, et al. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015;373:1720–32.
- Vazzana N, Ranalli P, Cucurullo C, Davi G. Diabetes mellitus and thrombosis. *Thromb Res*. 2012;129(3):371–7.
- Angiolillo DJ, Bernardo E, Sabaté M, Jimenez-Quevedo P, Costa MA, Palazuelos J, et al. Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. *J Am Coll Cardiol*. 2007;50(16):1541–7.
- El Ghannudi S, Ohlmann P, Jesel L, Radulescu B, El Adraa E, Crimzade U, et al. Impaired inhibition of P2Y₁₂ by clopidogrel is a major determinant of cardiac death in diabetes mellitus patients treated by percutaneous coronary intervention. *Atherosclerosis*. 2011;217(2):465–72.
- Gaborit B, Frère C, Cuisset T, Alessi MC, Dutour A. Enhanced post-clopidogrel platelet reactivity in diabetic patients is independently related to plasma fibrinogen level but not to glycemic control. *J Thromb Haemost*. 2009;7(11):1939–41.
- Singer J, Weissler Snir A, Leshem-Lev D, Rigler M, Kornowski R, Lev E. Effect of intensive glycemic control on platelet reactivity in patients with long-standing uncontrolled diabetes. *Thromb Res*. 2014;134(1):121–4.
- Mangiaccapra F, Peace AJ, Wijns W, Barbato E. Lack of correlation between platelet reactivity and glycaemic control in type 2 diabetes mellitus patients treated with aspirin and clopidogrel. *J Thromb Thrombolysis*. 2011;32(1):54–8.
- Schoos MM, Dangas GD, Mehran R, Kirtane AJ, Yu J, Litherland C, et al. Impact of hemoglobin A1c levels on residual platelet reactivity and outcomes after insertion of coronary drug-eluting stents (from the ADAPT-DES study). *Am J Cardiol*. 2016;117(2):192–200.
- Hirsch IB, Brownlee M. Beyond hemoglobin A1c—need for additional markers of risk for diabetic microvascular complications. *JAMA*. 2010;303(22):2291–2.
- Cardoso CRL, Leite NC, Moram CBM, Salles GF. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study. *Cardiovasc Diabetol*. 2018;17(1):33.
- Matsutani D, Sakamoto M, Iuchi H, Minato S, Suzuki H, Kayama Y, et al. Glycemic variability in continuous glucose monitoring is inversely associated with baroreflex sensitivity in type 2 diabetes: a preliminary report. *Cardiovasc Diabetol*. 2018;17(1):36.
- Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. *Lancet Diabetes Endocrinol*. 2019;7(3):221–30.
- Gerbaud E, Darier R, Montaudon M, Beauvieux MC, Coffin-Boutreux C, Coste P, et al. Glycemic variability is a powerful independent predictive factor of midterm major adverse cardiac events in patients with diabetes with acute coronary syndrome. *Diabetes Care*. 2019;42(4):674–81.
- Takahashi H, Iwashita N, Kirigaya J, Kataoka S, Minamimoto Y, Gohbara M, et al. Glycemic variability determined with a continuous glucose monitoring system can predict prognosis after acute coronary syndrome. *Cardiovasc Diabetol*. 2018;17(1):116.
- Nusca A, Lauria Pantano A, Melfi R, Proscia C, Maddaloni E, Contuzzi R, et al. Glycemic variability assessed by continuous glucose monitoring and short-term outcome in diabetic patients undergoing percutaneous coronary intervention: an observational pilot study. *J Diabetes Res*. 2015;2015:250201.
- Singh M, Upreti V, Singh Y, Kannapur AS, Nakra M, Kotwal N. Effect of glycemic variability on mortality in ICU settings: a prospective observational study. *Indian J Endocrinol Metab*. 2018;22(5):632–5.
- Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) study. *J Am Coll Cardiol*. 2008;52(14):1128–33.
- Bonello L, Tantry US, Marcucci R, Blindt R, Angiolillo DJ, Becker R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *J Am Coll Cardiol*. 2010;56(12):919–33.
- Nusca A, Tuccinardi D, Albano M, Cavallaro C, Ricottini E, Manfrini S, et al. Glycemic variability in the development of cardiovascular complications in diabetes. *Diabetes Metab Res Rev*. 2018;34(8):e3047.
- American Diabetes Association. Glycemic targets: standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(Suppl 1):S55–64.
- Mangiaccapra F, Patti G, Peace A, Gatto L, Vizzi V, Ricottini E, et al. Comparison of platelet reactivity and periprocedural outcomes in patients with versus without diabetes mellitus and treated with clopidogrel and percutaneous coronary intervention. *Am J Cardiol*. 2010;106(5):619–23.
- Angiolillo DJ, Shoemaker SB, Desai B, Yuan H, Charlton RK, Bernardo E, et al. Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. *Circulation*. 2007;115(6):708–16.
- Singla A, Antonino MJ, Bliden KP, Tantry US, Gurbel PA. The relation between platelet reactivity and glycemic control in diabetic patients with cardiovascular disease on maintenance aspirin and clopidogrel therapy. *Am Heart J*. 2009;158(5):784.e1–6.
- Angiolillo DJ, Bernardo E, Ramirez C, Costa MA, Sabaté M, Jimenez-Quevedo P, et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. *J Am Coll Cardiol*. 2006;48(2):298–304.
- Brar SS, ten Berg J, Marcucci R, Price MJ, Valgimigli M, Kim HS, et al. Impact of platelet reactivity on clinical outcomes after percutaneous coronary

- intervention. A collaborative meta-analysis of individual participant data. *J Am Coll Cardiol*. 2011;58(19):1945–54.
27. Kohnert KD, Augstein P, Heinke P, Zander E, Peterson K, Freyse EJ, et al. Chronic hyperglycemia but not glucose variability determines HbA1c levels in well-controlled patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2007;77(3):420–6.
 28. Kahal H, Aburima A, Spurgeon B, Wraith KS, Rigby AS, Sathyapalan T, et al. Platelet function following induced hypoglycaemia in type2 diabetes. *Diabetes Metab*. 2018;44(5):431–6.
 29. Gresle P, Guglielmini G, De Angelis M, Ciferri S, Ciofetta M, Falcinelli E, et al. Acute, short-term hyperglycemia enhances shear stress-induced platelet activation in patients with type II diabetes mellitus. *J Am Coll Cardiol*. 2003;41:1013–20.
 30. Santilli F, Formoso G, Sbraccia P, Averna M, Miccoli R, Di Fulvio P, et al. Postprandial hyperglycemia is a determinant of platelet activation in early type 2 diabetes mellitus. *J Thromb Haemost*. 2010;8(4):828–37.
 31. Prasad A, Singh M, Lerman A, Lennon RJ, Holmes DR Jr, Rihal CS. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. *J Am Coll Cardiol*. 2006;48(9):1765–70.
 32. Oka A, Deyama J, Umetani K, Harama T, Shimizu T, Makino A, et al. Glycemic variability is associated with myocardial damage in nondiabetic patients with ST-elevation myocardial infarction. *Cardiovasc Endocrinol Metab*. 2018;7:47–53.
 33. Lansky AJ, Stone GW. Periprocedural myocardial infarction: prevalence, prognosis, and prevention. *Circ Cardiovasc Interv*. 2010;3(6):602–10.
 34. Okada K, Hibi K, Gohbara M, Kataoka S, Takano K, Akiyama E, et al. Association between blood glucose variability and coronary plaque instability in patients with acute coronary syndromes. *Cardiovasc Diabetol*. 2015;14:111.
 35. Zafar MU, Baber U, Smith DA, Sartori S, Contreras J, Rey-Mendoza J, et al. Antithrombotic potency of ticagrelor versus clopidogrel in type 2 diabetic patients with cardiovascular disease. *Thromb Haemost*. 2017;117(10):1981–8.
 36. Franchi F, Rollini F, Aggarwal N, Hu J, Kureti M, Durairaj A, et al. Pharmacodynamic comparison of prasugrel versus ticagrelor in patients with type 2 diabetes mellitus and coronary artery disease: the OPTIMUS (optimizing antiplatelet therapy in diabetes mellitus)-4 study. *Circulation*. 2016;134(11):780–92.
 37. Ohara M, Nagaike H, Goto S, Fukase A, Tanabe Y, Tomoyasu M, et al. Improvements of ambient hyperglycemia and glycemic variability are associated with reduction in oxidative stress for patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2018;139:253–61.
 38. Marfella R, Barbieri M, Grella R, Rizzo MR, Nicoletti GF, Paolisso G. Effects of vildagliptin twice daily vs. sitagliptin once daily on 24 hour acute glucose fluctuations. *J Diabetes Complicat*. 2010;24(2):79–83.
 39. Frías JP, Nakhle S, Ruggles JA, Zhuplatov S, Klein E, Zhou R, et al. Exenatide once weekly improved 24-hour glucose control and reduced glycaemic variability in metformin-treated participants with type 2 diabetes: a randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2017;19(1):40–8.
 40. Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2018;319(15):1580–91.
 41. Cameron-Vendrig A, Reheeman A, Siraj MA, Xu XR, Wang Y, Lei X, et al. Glucagon-like peptide 1 receptor activation attenuates platelet aggregation and thrombosis. *Diabetes*. 2016;65(6):1714–23.
 42. Barale C, Buracco S, Cavalot F, Frascaroli C, Guerrasio A, Russo I. Glucagon-like peptide 1 related peptides increase nitric oxide effects to reduce platelet activation. *Thromb Haemost*. 2017;117(6):1115–28.
 43. Ajjan RA, Cummings MH, Jennings P, Leelarathna L, Rayman G, Wilmot EG. Accuracy of flash glucose monitoring and continuous glucose monitoring technologies: implications for clinical practice. *Diabetes Vasc Dis Res*. 2018;15(3):175–84.

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