eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/

Prevalence and relevance of abnormal glucose metabolism in acute coronary syndromes: insights from the PLATelet inhibition and patient Outcomes (PLATO) trial

Axel Åkerblom[1,2,3,16] · Daniel Wojdyla[3] · Philippe Gabriel Steg[4,5,6,7] · Lars Wallentin[1,2] · Stefan K. James[1,2] · Andrzej Budaj[8] · Hugo A. Katus[9] · Anders Himmelmann[10] · Kurt Huber[11,12] · Agneta Siegbahn[2,13] · Robert F. Storey[14] · Richard C. Becker[3,15] on behalf of the PLATO Investigators

Abstract

Diabetes mellitus (DM) and abnormal glucose metabolism are associated with cardiovascular (CV) disease. We investigated the prevalence and prognostic importance of dysglycaemia in patients with acute coronary syndromes (ACS) in the PLATelet inhibition and patient Outcomes (PLATO) trial. Diabetes was defined as known diabetes or HbA1c $\geq 6.5\%$ or non-fasting glucose ≥ 11.1 mmol/L on admission, prediabetes as HbA1c $\geq 5.7\%$ but $< 6.5\%$, and no diabetes as HbA1c $< 5.7\%$. The primary endpoint was the composite of CV death, spontaneous myocardial infarction type 1 (sMI) or stroke at 12 months. Multivariable Cox regression models, adjusting for baseline characteristics, and biomarkers NT-proBNP and troponin I, were used to explore the association between glycaemia and outcome. On admission, 16,007 (86.1%) patients had HbA1c and/or glucose levels available and were subdivided into DM 38.5% (6160) (1501 patients had no previous DM diagnosis), prediabetes 38.8% (6210), and no DM 22.7% (3637). Kaplan Meier event rates at 12 months for CV death, sMI or stroke per subgroups were 14.5% (832), 9.0% (522), and 8.5% (293), respectively with multivariable adjusted HRs, versus no diabetes, for diabetes: 1.71 (1.50–1.95) and for prediabetes 1.03 (0.90–1.19). Corresponding event rates for CV death were 6.9% (391), 3.4% (195) and 3.0% (102), respectively, with adjusted HRs for patients with DM of: 1.92 (1.42–2.60) and for prediabetes 1.02 (0.79–1.32). Abnormal glucose metabolism is common in ACS patients, but only patients with definite DM have an increased CV risk, indicating that prediabetes is not immediately associated with worse CV outcomes.

Keywords Diabetes · Pre-diabetes · Hemoglobin A1C · Acute coronary syndromes · Myocardial infarction · Risk prediction

✉ Axel Åkerblom
Axel.Akerblom@ucr.uu.se

1 Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden

2 Uppsala Clinical Research Center UCR, Uppsala University, Uppsala, Sweden

3 Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA

4 INSERM-Unité 1148, Paris, France

5 Assistance Publique-Hôpitaux de Paris, Département Hospitalo-Universitaire FIRE, Hôpital Bichat, Paris, France

6 Université Paris-Diderot, Sorbonne-Paris Cité, Paris, France

7 NHLI Imperial College, ICMS, Royal Brompton Hospital, London, UK

8 Postgraduate Medical School, Grochowski Hospital, Warsaw, Poland

9 Medizinishe Klinik, Universitätsklinikum Heidelberg, Heidelberg, Germany

10 AstraZeneca Research and Development, Mölndal, Sweden

11 Department of Cardiology and Intensive Care Medicine, Wilhelminen Hospital, Vienna, Austria

12 Medical School, Sigmund Freud University, Vienna, Austria

13 Department of Medical Sciences, Clinical Chemistry, Uppsala University, Uppsala, Sweden

14 Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK

15 Division of Cardiovascular Health and Disease, Heart, Lung and Vascular Institute, Academic Health Center, Cincinnati, OH, USA

16 Uppsala Clinical Research Center, Dag Hammarskjölds väg 38, 751 85 Uppsala, Sweden

Highlights

- Abnormal glucose metabolism is common in ACS patients.
- Patients with definite diabetes have a doubled CV risk during the first year after an ACS event.
- However, prediabetes is not immediately associated with worse CV outcomes during up to one year of follow up.
- Although prediabetes is important to diagnose, the CV risk is not increased, compared with normoglycemic patients, during the first year after ACS.

Introduction

Diabetes mellitus (DM) is associated with a two- to four-fold increased risk for cardiovascular (CV) events compared with non-diabetics [1]. In patients without diagnosed DM, but with borderline increased haemoglobin A1c (HbA1c), heightened fasting glucose or abnormal glucose tolerance test, an increased risk of CV events has been observed in a general population [2, 3]. The impact of dysglycaemia on CV risk in patients with acute coronary syndrome (ACS) is less clear with partly conflicting results [2–10]. In the PLATelet inhibition and patient Outcomes (PLATO) trial, we evaluated the effect of the antiplatelet drug ticagrelor, compared to clopidogrel, in patients with ACS [11, 12]. We have previously reported ticagrelor to be both more efficacious and of similar safety compared with clopidogrel, irrespective of diabetes status [8]. In the current substudy, we stratified patients into clinically accepted subgroups of glycaemia based on admission non-fasting glucose and HbA1c to explore the impact of dysglycaemia on CV outcomes [3, 8].

Methods

Study population

The PLATO trial (NCT00391872) enrolled 18624 patients with ACS, who were randomised to either clopidogrel or ticagrelor treatment in addition to optimal medical therapy, including aspirin, and optional invasive strategy [11, 12]. All patients were evaluated for diabetes at baseline, and baseline non-fasting glucose concentration and HbA1c were collected. All participants provided written informed consent and the study complied with the declaration of Helsinki. The study was approved by all local Ethics Committees and Institutional Review Boards.

Laboratory analysis

The details of laboratory sampling and handling have previously been published [11, 12].

Plasma glucose and HbA1c concentrations were determined with sandwich immunoassays on the Cobas® Analytics e601 Immunoanalyzer (Roche Diagnostics, Mannheim, Germany) at the Uppsala Clinical Research Center laboratory, Uppsala, Sweden.

### Definitions of outcome events and glycaemia subgroups

The primary endpoint of the present biomarker substudy was the composite of CV death, stroke or spontaneous myocardial infarction (sMI) within one year of follow up. sMI was defined in accordance with the universal definition of myocardial infarction (MI), hence a non-procedure-related, non-fatal, MI type 1 [13].

DM was defined as patients with known diabetes or admission HbA1c ≥ 6.5% (≥ 48 mmol/mol), or non-fasting venous glucose ≥ 11.1 mmol/L on admission. Pre-DM was defined as patients with HbA1c ≥ 5.7% but < 6.5% (≥ 39 mmol/mol but < 48 mmol/mol) [3]. Patients with HbA1c < 5.7% were considered to have neither DM nor pre-DM (referred to here as 'non-diabetes') [3].

Statistical analysis

Baseline characteristics were presented by subgroups of glycaemia, and compared using chi-square or Kruskal–Wallis tests. Kaplan Meier event rates at 1-year, overall and by glycaemic subgroups, were estimated. The associations between glycaemic subgroups, with the non-diabetes group as reference, and the outcomes were assessed by Cox proportional hazard models. Unadjusted and adjusted hazard ratios were derived. Adjustment variables included baseline characteristics (age, gender, smoking status, type of ACS, and history of angina, MI, hypercholesterolemia, diabetes, hypertension, chronic kidney disease, previous; percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG); stroke or transient ischemic attack (TIA), as well as log transformed biomarkers; NT-pro-BNP and hs-troponin I. p-values less than 0.05 were considered statistically significant results. Statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC) (Fig. 1).

Fig. 1 Kaplan Meier plots of the composite endpoint per glycemic subgroups
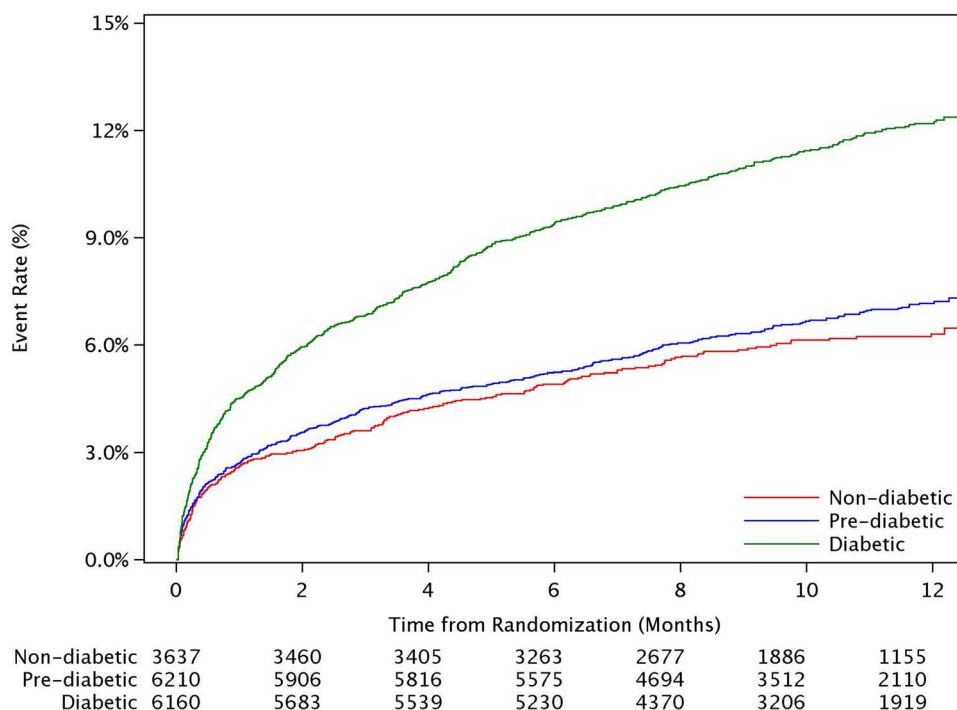
Results

Information on previous DM, non-fasting glucose and/or HbA1c, were available for 16,007 patients (85.9%). On admission, 6160 patients (38.5%) had DM according to our pre-specified criteria, of which 1501 patients (9.4%) had no previous DM diagnosis, consequently new-onset DM. In the new-onset DM subgroup, 1076 patients had an HbA1c $\geq 6.5\%$. Another 201 individuals had non-fasting blood glucose above 11.1 mmol/L, but with normal HbA1c. A total of 224 patients had both an elevated HbA1c and non-fasting blood glucose above 11.1 mmol/L.

Patients with DM were older, and had more comorbidities compared to patients without DM (Table 1). In patients with DM, normal HbA1c ($<5.7\%$) was observed in 146 patients (2.4%), while HbA1c was between 5.7 and 6.4% in 811 patients (13.2%) and 4346 patients (70.5%) had an HbA1c of $\geq 6.5\%$. HbA1c was not available in 857 patients (13.9%) classified as diabetic by other criteria.

In addition, 6210 (38.8%) patients had pre-DM defined as HbA1c concentrations of $\geq 5.7\%$ but $<6.5\%$. Normal HbA1c concentrations (HbA1c $<5.7\%$) were observed in 3637 (22.7%) of the study population.

Glycaemia subgroups and outcome

The Kaplan Meier event rates at 12 months for the combined endpoint of CV death, sMI or stroke per subgroups were 12.2% (694) for patients with DM, 7.2% (409) for pre-DM and 6.3% (213) for patients with no DM (Table 2 and Fig 1).

In a sensitivity analysis, all MIs (not only sMI) were evaluated in the composite endpoint (CV death, MI and stroke), with event rates at 12 months per subgroups of 14.5% (832) for patients with DM, 9.0% (522) for pre-DM and 8.5% (293) for patients with no DM.

The association between glycaemia subgroups and the combination of CV death, sMI or stroke is presented in Table 2.

The Kaplan Meier event rates for CV death alone were: 6.9% (391), 3.4% (195) and 3.0% (102), with adjusted HRs presented in Table 2.

The individual components of the composite endpoint were evaluated in secondary analysis and are presented in Table 2.

Discussion

DM is independently associated with CV events, but there are conflicting reports on the impact of pre-DM on outcomes [2–7, 9]. This may be due to differences in the identification, classification, follow-up and, in some cases, a lack of other important prognostic variables in ACS, including hs-troponin and NT-proBNP [5]. DM is a multifaceted syndrome, and the pathogenesis for CV disease may include macrovascular changes, endothelial cell dysfunction and accelerated atherosclerosis, with a subsequent increased risk for plaque rupture, thrombus formation and ultimately vessel occlusion [3].

Table 1 Baseline characteristics by glycemic subgroups

Characteristic	Diabetic (N = 6160)	Pre-diabetic (N = 6210)	Non-diabetic (N = 3637)	Overall (N = 16,007)	p-value
Female gender	2074 (33.7%)	1703 (27.4%)	854 (23.5%)	4631 (28.9%)	< 0.0001
Age, years (median, 25th–75th)	64 (56–72)	62 (54–71)	60 (51–68)	62 (54–71)	< 0.0001
Weight, kg (median, 25th–75th)	81.0 (70.0–92.0)	80.0 (70.0–90.0)	78.0 (68.0–86.0)	80.0 (70.0–90.0)	< 0.0001
Smoking status					< 0.0001
Non-smoker	2794 (45.4%)	2285 (36.8%)	1273 (35.0%)	6352 (39.7%)	
Ex-smoker	1674 (27.2%)	1481 (23.8%)	875 (24.1%)	4030 (25.2%)	
Habitual smoker	1692 (27.5%)	2444 (39.4%)	1489 (40.9%)	5625 (35.1%)	
Systolic blood pressure (mmHg)	135 (120–150)	130 (120–150)	130 (120–149)	133 (120–150)	< 0.0001
Diastolic blood pressure (mmHg)	80 (70–88)	80 (70–90)	80 (70–90)	80 (70–90)	0.0222
Medical history					
Angina pectoris	3211 (52.1%)	2734 (44.0%)	1361 (37.4%)	7306 (45.6%)	< 0.0001
Myocardial infarction	1565 (25.4%)	1180 (19.0%)	585 (16.1%)	3330 (20.8%)	< 0.0001
Percutaneous coronary intervention	1049 (17.0%)	738 (11.9%)	385 (10.6%)	2172 (13.6%)	< 0.0001
Coronary artery bypass graft	546 (8.9%)	293 (4.7%)	137 (3.8%)	976 (6.1%)	< 0.0001
Non-haemorrhagic stroke	324 (5.3%)	206 (3.3%)	99 (2.7%)	629 (3.9%)	< 0.0001
Hypertension	4827 (78.4%)	3787 (61.0%)	1977 (54.4%)	10,591 (66.2%)	< 0.0001
Dyslipidaemia	3389 (55.0%)	2706 (43.6%)	1446 (39.8%)	7541 (47.1%)	< 0.0001
Peripheral artery disease	514 (8.3%)	335 (5.4%)	165 (4.5%)	1014 (6.3%)	< 0.0001
Chronic renal disease	416 (6.8%)	180 (2.9%)	99 (2.7%)	695 (4.3%)	< 0.0001
Treatment approach					< 0.0001
Invasive	4184 (67.9%)	4489 (72.3%)	2718 (74.7%)	11,391 (71.2%)	
Type of ACS					< 0.0001
STEMI	2183 (35.4%)	2628 (42.3%)	1582 (43.5%)	6393 (39.9%)	
Medications at the time of randomization					
Aspirin	5800 (94.2%)	5834 (93.9%)	3387 (93.1%)	15021 (93.8%)	0.1056
Beta blockers	4307 (69.9%)	4382 (70.6%)	2545 (70.0%)	11234 (70.2%)	0.7072
ACE inhibitors	3885 (63.1%)	3400 (54.8%)	186 (51.1%)	9145 (57.1%)	< 0.0001
Angiotensin II receptor blockers	764 (12.4%)	445 (7.2%)	247 (6.8%)	1456 (9.1%)	< 0.0001
Statins	4936 (80.1%)	4978 (80.2%)	2865 (78.8%)	12,779 (79.8%)	0.1904
Biochemistry (median, 25th–75th)					
Creatinine clearance[a] (mL/min)	76.9 (58.8–96.5)	80.8 (64.1–98.5)	84.3 (67.2-102.3)	80.4 (63.0–99.0)	< 0.0001
Glucose (mmol/L)	9.3 (7.0–12.5)	6.4 (5.6–7.5)	6.1 (5.4–7.1)	6.9 (5.7–8.8)	< 0.0001
Haemoglobin A1c (%)	7.2 (6.5–8.5)	5.9 (5.8–6.1)	5.5 (5.3–5.6)	6.0 (5.7–6.6)	< 0.0001
NT-proBNP (pmol/L)	76 (24–244)	53 (18–164)	49 (17–147)	59 (19–184)	< 0.0001
High sensitivity troponin I (ng/Lµg/L)	2.0 (0.2–11.8)	2.0 (0.2–12.0)	2.2 (0.2–12.2)	2.1 (0.2–12.0)	0.4910

[a]Cockcroft Gault

In the current substudy, we found comorbidities to be more common in patients with DM, including disadvantageous biomarker levels such as elevated serum creatinine and NT-proBNP, indicating underlying organ dysfunction. We did not, however, observe any differences between patients with pre-DM and patients without DM.

Pre-DM, defined as blood glucose concentrations higher than normal but not meeting the definition of diabetes, is associated with an approximately 5–10% annual risk of developing type 2 DM [14]. When diagnosed with DM, the patient momentarily is considered to have heightened risk for adverse events, and the indication for cardiac revascularisation, medical treatments e.g. ACE inhibitors, and fluid therapy with angiography uses the presence of DM as a dichotomous condition [2, 3, 15]. It is, however, unknown if the observed heightened CV risk starts even at moderate levels of dysglycaemia or if abnormal glucose metabolism below a certain threshold may be non-pathogenic [3, 14].

In the current cohort, the proportion of patients with DM and at the same time a normal HbA1c was 2.5%, indicating that medical and lifestyle treatments still are not able to maintain normal HbA1c in patients with diabetes.

Table 2 Proportions, event rates and hazard ratios (HR) per glycemic subgroups

	Diabetes	Pre-diabetes	No diabetes
Proportion and number of patients	38.5% (6160)	38.8% (6210)	22.7% (3637)
of which were new diagnosed	9.4% (1501)		
Event rates at 12 months			
CV death, sMI or stroke	12.2% (694)	7.2% (409)	6.3% (213)
CV death	6.9% (391)	3.4% (195)	3.0% (102)
	HR (95%CI)	HR (95%CI)	
HR versus no diabetes			
CV death, sMI or stroke	1.97 (1.69–2.29)	1.12 (0.95–1.32)	1
CV death	2.30 (1.85–2.86)	1.12 (0.88–1.42)	1
Adjusted HR vs no diabetes (n = 14,033)			
CV death, sMI or stroke	1.39 (1.11–1.74)	1.02 (0.86–1.22)	1
CV death	1.92 (1.42–2.60)	1.02 (0.79–1.32)	1

The increased CV risk for patients with manifest DM was, however, not observed in patients with pre-DM during the first year after ACS, and we believe this highlights that a direct effect of hyperglycaemia on clinical outcome may not be present, rather the deleterious hyperglycaemic effects may arise after a prolonged and accumulated exposure to dysglycemia.

Limitations

Manifest DM was one of several enrichment criteria employed to enter the PLATO trial if presenting with a non-STEACS [11, 12]. It is likely that the current population exhibited a larger proportion of patients with diagnosed DM than other ACS populations, and consequently proportionally smaller subgroups of patients with pre-DM and no DM. Although follow up was up to one year, the detrimental effect of DM was not observed within the first year of diagnosis in the current study, however this study was not designed to answer these important questions.

Conclusions

Abnormal glucose metabolism is common in patients with ACS and 9% of the PLATO study patients had undiagnosed diabetes. Although the overall event rate during the first year after ACS is high, we only observed patients with definite DM to have a further increased CV risk, indicating that pre-DM is not immediately associated with worse CV outcomes over the first year after ACS. Nonetheless, this finding does not diminish the need for close follow-up of patients with pre-DM in order to detect DM early, as recommended by international guidelines.

Compliance with ethical standards

References

1. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M (1998) Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229–234. https://doi.org/10.1056/NEJM199807233390404

2. Barr EL, Zimmet PZ, Welborn TA, Jolley D, Magliano DJ, Dunstan DW, Cameron AJ, Dwyer T, Taylor HR, Tonkin AM, Wong TY, McNeil J, Shaw JE (2007) Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation 116:151–157. https://doi.org/10.1161/CIRCULATIONAHA.106.685628

3. Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL, ESCCfP Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, De Backer G, Sirnes PA, Ezquerra EA, Avogaro A, Badimon L, Baranova E, Baumgartner H, Betteridge J, Ceriello A, Fagard R, Funck-Brentano C, Gulba DC, Hasdai D, Hoes AW, Kjekshus JK, Knuuti J, Kolh P, Lev E, Mueller C, Neyses L, Nilsson PM, Perk J, Ponikowski P, Reiner Z, Sattar N, Schachinger V, Scheen A, Schirmer H, Stromberg A, Sudzhaeva S, Tamargo JL, Viigimaa M, Vlachopoulos C, Xuereb RG (2013) ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 34:3035–3087. https://doi.org/10.1093/eurheartj/eht108

4. Conaway DG, O'Keefe JH, Reid KJ, Spertus J (2005) Frequency of undiagnosed diabetes mellitus in patients with acute coronary syndrome. Am J Cardiol 96:363–365. https://doi.org/10.1016/j.amjcard.2005.03.076

5. Giraldez RR, Clare RM, Lopes RD, Dalby AJ, Prabhakaran D, Brogan GX Jr, Giugliano RP, James SK, Tanguay JF, Pollack CV Jr, Harrington RA, Braunwald E, Newby LK (2013) Prevalence and clinical outcomes of undiagnosed diabetes mellitus and pre-diabetes among patients with high-risk non-ST-segment elevation acute coronary syndrome. Am Heart J 165:918–925 e2. https://doi.org/10.1016/j.ahj.2013.01.005

6. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendic S, Ryden L, Malmberg K (2002) Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet 359:2140–2144. https://doi.org/10.1016/S0140-6736(02)09089-X

7. Timmer JR, Hoekstra M, Nijsten MW, van der Horst IC, Ottervanger JP, Slingerland RJ, Dambrink JH, Bilo HJ, Zijlstra F, van 't Hof AW (2011) Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment-elevation myocardial infarction treated with percutaneous coronary intervention. Circulation 124:704–711. https://doi.org/10.1161/CIRCULATIONAHA.110.985911

8. James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontny F, Maya J, Nicolau JC, Spinar J, Storey RF, Stevens SR, Wallentin L, Plato Study Group (2010) Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 31:3006–3016. https://doi.org/10.1093/eurheartj/ehq325

9. Sinnaeve PR, Steg PG, Fox KA, Van de Werf F, Montalescot G, Granger CB, Knobel E, Anderson FA, Dabbous OH, Avezum A, Grace I (2009) Association of elevated fasting glucose with increased short-term and 6-month mortality in ST-segment elevation and non-ST-segment elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. Arch Intern Med 169:402–409. https://doi.org/10.1001/archinternmed.2008.572

10. Farhan S, Clare RM, Jarai R, Giugliano RP, Lokhnygina Y, Harrington RA, Kristin Newby L, Huber K (2017) Fasting glucose, NT-proBNP, treatment with eptifibatide, and outcomes in non-ST-segment elevation acute coronary syndromes: an analysis from EARLY ACS. Int J Cardiol 232:264–270. https://doi.org/10.1016/j.ijcard.2017.01.007

11. James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, Skene A, Steg PG, Storey RF, Harrington R, Becker R, Wallentin L (2009) Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J 157:599–605. https://doi.org/10.1016/j.ahj.2009.01.003

12. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Plato I, Freij A, Thorsen M (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361:1045–1057. https://doi.org/10.1056/NEJMoa0904327

13. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Writing Group on the Joint ESC Accf AHAWHF Task Force for the Universal Definition of Myocardial Infarction, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, ESC Committee for Practice Guidelines (2012) Third universal definition of myocardial infarction. Eur Heart J 33:2551–2567. https://doi.org/10.1093/eurheartj/ehs184

14. Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M (2012) Prediabetes: a high-risk state for diabetes development. Lancet 379:2279–2290. https://doi.org/10.1016/S0140-6736(12)60283-9

15. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, ESC Scientific Document Group (2016) 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 37:267–315. https://doi.org/10.1093/eurheartj/ehv320