Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Prevalence of pre-existing dysglycaemia among inpatients with acute coronary syndrome and associations with outcomes ☆

Dinesh C. Mahendran [a], Garry Hamilton [b], Jeremy Weiss [a], Leonid Churilov [c], Jeremy Lew [a], Kaylyn Khoo [a], Que Lam [d], Raymond Robbins [e], Graeme K. Hart [f,g], Douglas Johnson [h,i], David L. Hare [b,i], Omar Farouque [b,i], Jeffrey D. Zajac [a,i], Elif I. Ekinci [a,i,*]

[a] Department of Endocrinology, Austin Health, Melbourne, Victoria, Australia
[b] Department of Cardiology, Austin Health, Melbourne, Victoria, Australia
[c] The Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia
[d] Department of Pathology, Austin Health, Melbourne, Victoria, Australia
[e] Department of Administrative Informatics, Austin Health, Melbourne, Victoria, Australia
[f] Department of Intensive Care, Austin Health, Melbourne, Victoria
[g] Health and Biomedical Informatics Centre, University of Melbourne, Melbourne, Victoria, Australia
[h] Department of General Medicine, Austin Health, Melbourne, Victoria, Australia
[i] Department of Medicine, Austin Health, The University of Melbourne, Melbourne, Victoria, Australia

ARTICLE INFO

Article history:
Received 21 November 2018
Received in revised form
8 March 2019
Accepted 1 July 2019
Available online 4 July 2019

Keywords:
Diabetes
Pre-diabetes
Cardiovascular
Myocardial infarction
Unstable angina
Heart failure

ABSTRACT

Aims: We aimed to confirm the hypothesis that dysglycaemia including in the pre-diabetes range affects a majority of patients admitted with acute coronary syndrome (ACS) and is associated with worse outcomes.

Methods: In this prospective observational cohort study, consecutive inpatients aged ≥ 54 years with ACS were uniformly tested and categorised into diabetes (prior diagnosis/ HbA1c ≥ 6.5%, ≥48 mmol/mol), pre-diabetes (HbA1c 5.7–6.4%, 39–47 mmol/mol) and no diabetes (HbA1c ≤ 5.6%, ≤38 mmol/mol) groups.

Results: Over two years, 847 consecutive inpatients presented with ACS. 313 (37%) inpatients had diabetes, 312 (37%) had pre-diabetes and 222 (25%) had no diabetes. Diabetes, compared with no diabetes, was associated with higher odds of acute pulmonary oedema (APO, odds ratio, OR 2.60, $p < 0.01$), longer length of stay (LOS, incidence rate ratio, IRR 1.18, $p = 0.02$) and, 12-month ACS recurrence (OR 1.86, $p = 0.046$) after adjustment, while no significant associations were identified for pre-diabetes. Analysed as a continuous variable, every 1% (11 mmol/mol) increase in HbA1c was associated with increased odds of APO (OR 1.28, $P = 0.002$) and a longer LOS (IRR 1.05, $P = 0.03$).

Conclusions: The high prevalence of dysglycaemia and association with poorer clinical outcomes justifies routine HbA1c testing to identify individuals who may benefit from

☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

* Corresponding author at: Sir Edward Dunlop Medical Research Foundation Principal Research Fellow in Metabolic Medicine, The University of Melbourne, Department of Medicine, Austin Health, Director of Diabetes Austin Health, Heidelberg, VIC 3081, Australia.
E-mail address: elif.ekinci@unimelb.edu.au (E.I. Ekinci).

https://doi.org/10.1016/j.diabres.2019.07.002

cardioprotective anti-hyperglycaemic agents and, lifestyle modification to prevent progression of pre-diabetes.

1. Introduction

Cardiovascular disease is the primary cause of excess mortality in individuals with diabetes mellitus [1]. Endothelial dysfunction, reduction in nitrous oxide mediated vasodilation, increased inflammatory cytokines and coagulopathy together contribute to unstable fibrous caps in the atherosclerotic lesions of patients with diabetes, resulting in increased risk of clot formation and subsequent cardiovascular events [2].

This increased cardiovascular risk begins prior to the development of diabetes, affecting patients with pre-diabetes. An HbA1c of 5.7% (39 mmol/mol) is associated with 13.3% risk of cardiovascular disease over 10 years [3]. An HbA1c of greater or equal to 5.7% (39 mmol/mol) has also been associated with an increased risk of coronary heart disease in a prospective case-cohort study of individuals without diabetes. In that study, there was an increase in relative risk of coronary heart disease of 2.36 for every 1 percentage increase in HbA1c [4]. In those without diabetes but with insulin resistance and a mean HbA1c of 5.8% (40 mmol/mol), the Insulin Resistance Intervention after Stroke (IRIS) trial in patients who had a stroke demonstrated that pioglitazone reduced the risk of fatal or non-fatal recurrence of stroke or myocardial infarction [5]. The American Diabetes Association guidelines recommend the use of HbA1c as a screening tool for pre-diabetes, defined by an HbA1c of 5.7% to 6.4% (39 to 46 mmol/mol), identifying individuals with a high risk of developing diabetes and, who may be amenable to lifestyle intervention [6]. Diagnosis of pre-diabetes in patients presenting with acute coronary syndrome through routine HbA1c testing may identify a high-risk group of patients who may benefit from lifestyle modification, weight loss and in the future pharmacotherapy.

The EMPA-REG OUTCOME trial (EMPA-REG) [7], the Canagliflozin Cardiovascular Assessment Study (CANVAS) [8], the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) [9] and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) [10], demonstrated that Sodium Glucose Linked co-Transporter-2 (SGLT-2) inhibitors and Glucagon Like Peptide-1 (GLP-1) receptor analogues were effective in reducing cardiovascular events when used in patients with a long duration of diabetes mellitus and a high prevalence of established macrovascular disease. In the case of empagliflozin and liraglutide, subsequent cardiovascular death rates were reduced. Therefore, for individuals presenting with acute coronary syndrome with a background of diabetes, we now have cardioprotective anti-hyperglycaemic agents which can be used to prevent further cardiovascular events. Routine HbA1c testing of patients presenting with acute coronary syndrome therefore provides an opportunity to optimise therapy in line with recent evidence without the need for prior fasting.

In patients presenting with acute coronary syndrome, HbA1c testing is not affected by stress-induced hyperglycaemia which may result in a false positive result when fasting plasma glucose is used instead [11]. Hyperglycaemia in acute coronary syndrome has been extensively investigated, but previous literature has mainly focused on stress-induced hyperglycaemia being a potential poor prognostic factor. In a large population of consecutive patients admitted with ST-segment elevation myocardial infarction, those with elevated admission glucose and HbA1c but without diabetes had higher one year and total mortality [12]. In a study examining a small number of consecutive admissions with myocardial infarction, admission plasma glucose was associated with 28-day mortality after adjustment for HbA1c [13]. A *meta*-analysis of 15 studies examining the rates of in-hospital mortality and congestive heart failure in patients admitted with myocardial infarction found adverse outcomes in those whose glucose concentrations were over 6.0 mmol/L compared to those whose glucose concentrations less than or equal to 6.0 mmol/L [14]. Another study found a high prevalence of diabetes in patients with acute coronary syndrome and HbA1c testing at admission [15]. Prior literature has failed to explore pre-diabetes and, its association with clinical outcomes in acute coronary syndrome. The relationship between HbA1c and acute pulmonary oedema, an important complication of heart failure after acute coronary syndrome has not previously been studied.

We hypothesised that a high proportion of patients presenting with ACS would have dysglycaemia and that this would be associated with poorer acute and chronic clinical outcomes. In the current study, we therefore aimed to use routine HbA1c measurements, to (i) estimate the prevalence of diabetes and pre-diabetes and (ii) clinical outcomes over 12 months in successive patients presenting with acute coronary syndromes (ACS). Our pre-specified clinical outcomes obtained were (i) in-hospital mortality, (ii) acute pulmonary oedema (APO), (iii) total hospital length of stay (LOS), (iv) 28-day readmission rate, (v) 12-month recurrent ACS and, (vi) 12-month all-cause mortality.

2. Subjects

The study included consecutive hospital inpatients aged $\geq$ 54 years with acute coronary syndrome where unstable angina, non-ST elevation myocardial infarction and ST elevation myocardial infarction was the principal diagnosis.

3. Materials and methods

As part of the Diabetes Discovery Initiative, in this prospective observational cohort study, routine HbA1c testing was performed using an automated order through the Cerner

Millennium IT Health Platform on all inpatients aged ≥ 54 years admitted to Austin Health, a tertiary hospital, between July 2013 and July 2015 provided there was no HbA1c result recorded within the preceding 90 days on the CERNER hospital electronic medical record system. Testing was limited to this age group based on a previous study using HbA1c in screening inpatients for diabetes. This previous study found the highest proportion of new diagnosis of diabetes in those over the age of 54 [16]. All HbA1c results were reported via electronic medical records and were accessible to the patients' treating doctors [17,18].

Ethylenediaminetetraacetic acid (EDTA) whole blood was obtained from patients for analysis. HbA1c was measured by turbidimetric inhibition immunoassay (TINIA) on Cobas Integra 800 (Roche Diagnostics, Mannheim, Germany). This assay was standardised to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference method. The between run coefficient of variation was 2.5% for HbA1c 5.6% (30 mmol/mol) and 1.5% for HbA1c 9.7% (83 mmol/mol).

Hospital admissions where unstable angina, non-ST elevation myocardial infarction and ST elevation myocardial infarction was the principal diagnosis were included using the following ICD-10 codes: I20.0, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9. All included subjects had the accuracy of their diagnosis confirmed manually. Unstable angina was confirmed in patients presenting with angina at rest, new onset of severe exertional angina or sudden intensification of previously stable angina and not meeting the definition of myocardial infarction [19]. The diagnosis of myocardial infarction was confirmed using the third universal definition of myocardial infarction as determined by the Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and the World Heart Federation [20].

All admission episodes with an HbA1c result within 90 days prior to the admission date or up to 7 days after their admission date were eligible for inclusion in this study. HbA1c results, their interpretation and follow-up plans were automatically inserted into patient discharge summaries. As part of the Diabetes Discovery Initiative, all patients with HbA1c ≥ 8.3% (67 mmol/mol) were automatically reviewed by the endocrinology team to educate, intensify and optimize diabetes treatment, screen for complications and, devise plans for further outpatient management as required [17,18].

Individual inpatient admission episodes were then divided into three groups according to their dysglycaemic status using medical records and their HbA1c result as: (i) 'diabetes' if a previous diagnosis of diabetes had been documented in the medical record, regardless of HbA1c result or if the HbA1c result was ≥ 6.5% (48 mmol/mol) without a previous diagnosis of diabetes; (ii) 'pre-diabetes' if the HbA1c result was between 5.7% and 6.4% (39 and 47 mmol/mol) without a previous diagnosis of diabetes and (iii) 'no diabetes' if the HbA1c result was ≤ 5.6% (38 mmol/mol) without a previous diagnosis of diabetes.

Pre-specified baseline demographic data, principal admission diagnosis, clinical characteristics and biochemical laboratory values were extracted from electronic medical records and hospital databases. Estimated glomerular filtration rate (eGFR) was calculated based on the CKD-EPI formulae using extracted data (age, gender and creatinine levels).

Pre-admission use of beta blockers, Angiotensin Converting Enzyme (ACE) inhibitors or angiotensin II receptor blockers, statins and antiplatelet agents were extracted manually from medical records and verified by a second investigator. Pre-existing risk factors such as hypertension, dyslipidaemia, smoking status and previous myocardial infarction were ascertained from medical records manually based on the noted background medical history of the patient on admission and/or through their pre-existing pharmacotherapy.

Pre-specified outcomes ascertained in the current study were (i) in-hospital mortality, (ii) acute pulmonary oedema (APO), (iii) total hospital length of stay (LOS), (iv) 28-day readmission rate, (v) 12-month recurrent ACS and, (vi) 12-month all-cause mortality. In-hospital mortality was defined as death during the period of inpatient stay. APO was defined as Killip classification 3 pulmonary oedema [21] within 24 h of admission. 28-day readmission rate was defined as an unplanned repeat admission to the same hospital within a 28-day period after the index admission. 12-month recurrent ACS was defined as formally diagnosed unstable angina or myocardial infarction within the 12-month period from index admission date. 12-month all-cause mortality was defined as death from any cause within 12-months from the index admission date. All-cause mortality data was available if the patient had died during any hospital admission or if the hospital had been notified of their death within the 36-month study period. Vital status was confirmed through the patient's general practitioners. Patients where 12-month data could not be assessed were excluded from the 12-month all-cause mortality and 12-month recurrent ACS analyses.

Data were analysed using Stata Version 13IC (StataCorp, College Station, TX, USA). Baseline characteristics were reported as medians and interquartile ranges (continuous characteristics) or counts and percentages (categorical characteristics) and compared across the three groups, using Kruskal-Wallis or chi-squared/Fischer's exact tests respectively. Multivariable analyses were conducted using negative binomial regression for length of stay outcome (presented as a count of days) and logistic regression for binary outcomes. Two analyses were performed: (1) with diabetes status classified categorically as diabetes, pre-diabetes and, no diabetes; and (2) with HbA1c as a continuous marker. A-priori chosen adjustment covariates included age, previous myocardial infarction, sex and smoking status. Standard analyses of collinearity and model fit were performed. A two-sided p-value < 0.05 was considered statistically significant.

This study was approved by Austin Health Research Ethics Committee, who waived the need for informed consent for a planned practice change agreed to by the hospital senior medical staff as part of the Austin Health Diabetes Discovery Initiative.

4. Results

847 consecutive patients were admitted with a primary diagnosis of unstable angina or myocardial infarction. In 16 (1.9%) patients, post-admission 12-month mortality and ACS

recurrence data were unavailable and these individuals were excluded from 12-month outcome analyses.

4.1. Baseline characteristics

The baseline characteristics of patients organised according to diabetes status are shown in Table 1.

Median age was 73 (IQR 64–82). The study population included 279 (33%) females and 568 (67%) males. Of these 183 (22%) individuals were diagnosed with ST- elevation myocardial infarction (STEMI), 537 (63%) patients were diagnosed with Non- ST- elevation myocardial infarction (NSTEMI) and 127 (15%) patients experienced unstable angina (UA). The incidence of each type of ACS did not differ between the no diabetes, pre-diabetes or diabetes groups (p = 0.243).

In the study population, 313 (37%, 95%CI 34%-40%) patients had diabetes (pre-existing or HbA1c $\geq$ 6.5%, $\geq$48 mmol/mol), 312 (37%, 95%CI 34%-40%) had pre-diabetes (HbA1c 5.7%- 6.4%, 39 to 47 mmol/mol) and 222 (25%, 95%CI 23%-29%) had no diabetes (HbA1c < 5.6%, <38 mmol/mol). Of the patients with diabetes, 32 (4%) patients had a HbA1c of $\geq$ 6.5% (48 mmol/mol) without a prior history of diabetes and therefore a potential new diagnosis of diabetes (requiring confirmation with repeat testing). The median HbA1c in patients with diabetes was 7%, IQR 6.5–8.1% (53 mmol/mol, IQR 48–65 mmol/mol) in patients with pre-diabetes was 5.9%, IQR 5.8–6.1% (41 mmol/mol, IQR 40–43 mmol/mol), and, among patients with no diabetes was 5.5%, IQR 5.3–5.5% (37 mmol/mol, IQR 34–37 mmol/mol).

As seen in Table 1, the cardiovascular risk factors of hypertension and dyslipidaemia as well as cardioprotective medication use of aspirin, P2Y12 inhibition, ACE inhibition, beta blockade and statin use were more prevalent in the diabetes group.

With regard to clinical events, 49 of 313 (15.7%) patients with diabetes, 25 of 312 (8.0%) patients with pre-diabetes and 15 of 222 (6.8%) patients with no diabetes developed APO within the first twenty-four hours as a result of their myocardial infarction. 15 patients with diabetes (4.8%), 11 patients with pre-diabetes (3.5%) and 9 patients with no diabetes (4%) died in hospital. 43 patients with diabetes (13.7%), 25 patients with pre-diabetes (8%) and 17 patients with no diabetes (7.7%) had a recurrence of ACS within 12-months. 53 patients with diabetes (16.9%), 32 patients with pre-diabetes (10.3%) and 24 patients without diabetes (10.8%) died within 12-months.

4.2. Multivariable analyses

The multivariable regression analysing categorical diabetes status and clinical outcomes is demonstrated in Table 2. After adjusting for age, sex, smoking status and previous myocardial infarction, the patients with diabetes demonstrated higher adjusted odds of APO compared to the patients with no diabetes with an odds ratio of 2.60 (95% CI 1.39–4.84, p < 0.01), as illustrated in Fig. 1. No significant difference in in-hospital mortality was identified between the no diabetes group and the diabetes group. The diabetes group had a longer expected length of stay than patients with no diabetes, with an incidence rate ratio 1.18 (95% CI 1.02–1.35, p = 0.02). This group did not have a higher 28-day readmission rate but did have, greater odds of ACS recurrence within 1 year with an odds ratio 1.86 (95% CI 1.01–3.41, p = 0.046), as illustrated in Fig. 2.

Compared to the no diabetes group, in the pre-diabetes group, no significant differences in in-hospital mortality, acute pulmonary oedema, total length of stay, 28-day readmission rate, 12-month recurrent ACS or 12-month all-cause

Table 1 – Baseline Characteristics.

	Diabetes	Pre-diabetes	No diabetes	P-value
Number (n)	313	312	222	
Age (years)	73 (65–81)	75 (62–80)	70 (62–80)	0.0045
Male (%)	209 (66.8)	205 (65.7)	154 (69.3)	0.680
Smokers (%)	42 (13.4)	60 (19.2)	39 (17.6)	0.060
HbA1c (mmol/mol)	53.0 (47.5–65.0)	41.0 (39.9–43.2)	36.6 (34.4–36.6)	0.0001
HbA1c (%)	7.0 (6.5–8.1)	5.9 (5.8–6.1)	5.5 (5.3–5.5)	0.0001
Hemoglobin (g/L)	130 (115–142)	138 (125–150)	140 (130–150)	0.0001
CKD-EPI eGFR (ml/min/1.73 m^2)	62 (40–81)	66 (46–81)	74 (56–87)	0.0001
Hypertension (%)	226 (72.2)	211 (67.6)	132 (59.5)	0.000
Dyslipidaemia (%)	230 (73.5)	166 (53.2)	101 (45.5)	0.000
Previous Myocardial infarction (%)	86 (27.5)	65 (20.8)	42 (18.9)	0.054
Aspirin use (%)	175 (55.9)	142 (45.5)	92 (41.4)	0.002
P2Y12 Inhibitor use (%)	59 (18.8)	37 (11.9)	14 (6.3)	0.000
ACE inhibition (%)	215 (68.7)	157 (50.3)	90 (40.5)	0.000
Beta Blockade (%)	131 (41.9)	94 (30.1)	59 (26.6)	0.000
Statin use (%)	213 (68.1)	147 (47.1)	79 (35.5)	0.000
Charlson's index score	6 (4–7)	5 (4–6)	5 (4–6)	0.0001

Categorical variables are reported as counts with percentages (%). Continuous variables are reported as medians with interquartile ranges (IQR). Abbreviations: CKD-EPI = Chronic kidney disease-epidemiology collaboration equation; eGFR = estimated glomerular filtration rate; Charlson's index score = Charlson's comorbidity index score (excluding diabetes component). Continuous explanatory variables were analysed with the use of Kruskal-Wallis test. Categorical explanatory variables were reported as percentages and analyzed with $\chi 2$ tests or Fisher's exact test as appropriate.

Table 2 – Multivariable analyses.

	n	Diabetes vs no diabetes OR/IRR* (95% CI)	p- value	Pre-diabetes vs no diabetes OR/IRR* (95% CI)	p-value	OR/IRR* (95% CI) per 11 mmol/mol (1%) increase in HbA1c	p-value
Length of stay (IRR)	847	**1.18 (1.02–1.35)**	**0.02**	1.07 (0.93–1.23)	0.35	**1.05 (1.01–1.10)**	**0.03**
28-day readmission (OR)	847	1.31 (0.73–2.37)	0.37	1.12 (0.61–2.04)	0.71	0.99 (0.82–1.19)	0.90
In-hospital mortality (OR)	847	1.09 (0.46–2.59)	0.85	0.76 (0.31–1.86)	0.55	1.21 (0.96–1.53)	0.11
Acute Pulmonary Oedema (OR)	847	**2.60 (1.39–4.84)**	**<0.01**	1.11 (0.57–2.19)	0.76	**1.28 (1.09–1.49)**	**<0.01**
12-month Recurrent ACS (OR)	831	**1.86 (1.01–3.41)**	**0.046**	0.93 (0.48–1.81)	0.83	1.06 (0.88–1.28)	0.52
12-month mortality (OR)	831	1.34 (0.75–2.37)	0.32	0.81 (0.45–1.47)	0.49	1.13 (0.95–1.35)	0.17

Bold values indicate statistically significant results.
* OR = Odds ratio, IRR = Incidence rate ratio.

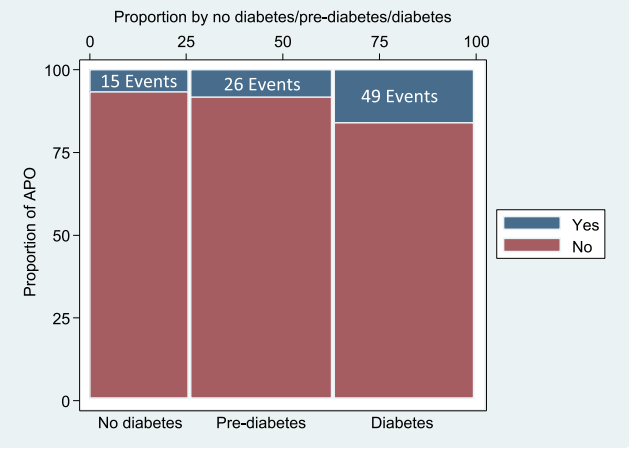

Fig. 1 – Spine plot of acute pulmonary oedema in the first twenty-four hours after admission among patients in the no diabetes, pre-diabetes and diabetes groups. Diabetes vs. no diabetes odds ratio 2.60 (P ≤ 0.01). Pre-diabetes vs. no diabetes odds ratio 1.11 (P = 0.76).

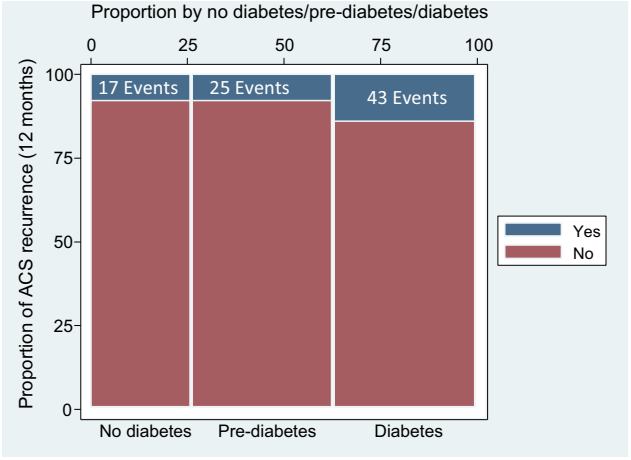

Fig. 2 – Spine plot of 12-month acute coronary syndrome recurrence after index admission among patients in the no diabetes, pre-diabetes and diabetes groups. Diabetes vs. no diabetes odds ratio 1.86 (P = 0.046). Pre-diabetes vs. no diabetes odds ratio 0.93 (P = 0.83).

mortality were identified. No significant differences in 12-month all-cause mortality between the groups was identified.

When analysing HbA1c as a continuous variable, including HbA1c within the no diabetes and pre-diabetes ranges, although there was no significant difference in in-hospital mortality, we did demonstrate higher adjusted odds of APO with an odds ratio of 1.28 (95% CI 1.09–1.49, $p < 0.01$) and, a longer length of stay with incidence rate ratio 1.05 (95% CI 1.01–1.10, $p = 0.03$) for each 1% (11 mmol/mol) increase in HbA1c. There were no significant differences in the remaining clinical outcomes of 28-day readmission, 12-month recurrence of ACS or 12-month all-cause mortality. The association between HbA1c and measured clinical outcomes is displayed in further detail in table 2.

5. Conclusions

The most important finding in the current study was that both diabetes and a higher HbA1c regardless of dysglycaemic status, was associated with increased odds of APO while the presence of diabetes was associated with a higher 12-month ACS recurrence. The present study demonstrated the feasibility of utilising automated clinical information systems to accurately investigate the burden of diabetes, pre-diabetes and their associations with in-hospital and post-hospital outcomes in successive admissions over a two-year period in patients with acute coronary syndrome.

5.1. *Prevalence of dysglycaemia*

In the current study, we demonstrated that a majority of inpatients admitted with acute coronary syndrome had dysglycaemia with approximately half having pre-diabetes. Education regarding risk of progression to diabetes and lifestyle measures that may help prevent this progression to diabetes in this group will be advantageous [6].

A study of 8795 patients with non- ST elevation acute coronary syndrome, using fasting plasma glucose levels, demonstrated that diabetes was prevalent in 43% (including 12% with a new diagnosis) and pre-diabetes was prevalent in 11% of patients [22]. The use of HbA1c in our study diagnosed more patients with pre-diabetes than the previous study with fasting plasma glucose levels. HbA1c may be a better tool in predicting cardiovascular risk given it is more strongly associ-

ated with cardiovascular risk and death when compared with fasting glucose [23]. Early recognition of this at-risk population is important and allows early and more aggressive medical management for secondary prevention [24].

5.2. *In-hospital mortality*

We did not demonstrate a higher risk of in-hospital mortality in patients with diabetes compared to older studies [25,26] which may be due to more aggressive management including higher rate of aspirin use for primary prevention of acute coronary syndrome, efficacy of percutaneous interventions including drug-eluting stents and, use of more potent PGY12 inhibitors.

5.3. *Acute pulmonary oedema*

Our study demonstrated higher odds of APO in patients with diabetes as opposed to patients without diabetes despite significantly higher beta blockade and angiotensin converting enzyme inhibition. HbA1c analysed as a continuous variable also correlated with higher odds of APO including in the non-diabetes and pre-diabetes range and reinforced the correlation between dysglycaemia and APO. A previous study demonstrated that patients with diabetes presented in APO more frequently than those without diabetes (11 vs. 4%) despite similar infarct size and left ventricular ejection fractions [25]. It was hypothesised that the left ventricle in patients with diabetes tolerated infarction poorly due to pre-existing multi-vessel disease. The older study noted a lower incidence of APO as compared to the present study despite it being conducted in the pre-angiotensin converting enzyme inhibition era which revolutionised cardiac remodelling and heart failure management. As we looked at inpatients aged 54 or more, this difference may be explained by age differences. The current study's median age of 73 was greater than the older study's median age of 59.1, which had excluded those over 75 [25].

Heart failure with preserved ejection fraction is an important mechanism explaining the decreased cardiac reserve in patients with diabetes. In the Prevalence and Clinical Course of Diastolic Dysfunction and Diastolic Heart failure study (DIAST-CHF), prevalence and severity of diastolic dysfunction increased significantly with worsening glucose metabolism [27].

During the current study period, SGLT-2 inhibitors were not available. Our study indicates an area of need for these agents which have been associated with reduced rates of hospitalisation for heart failure and death from cardiovascular causes as seen in the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 inhibitors (CVD-REAL study) [28].

5.4. *Length of stay*

The length of stay was longer among patients with diabetes (median 4 days) as compared to those without diabetes or those with pre-diabetes (both a median of 3 days). When analysed as a continuous variable, a higher HbA1c was also predictive of increase length of stay. Factors including increased severity of myocardial infarction in those with diabetes (as also reflected in the higher incidences of APO) and increased time required for diabetes optimisation may explain this.

5.5. *28-day readmission rate and 12-month acute coronary syndrome recurrence*

There were no significant differences in readmission rate between the pre-diabetes or diabetes group and the no diabetes group. Patients with diabetes had higher odds of ACS recurrence compared to patients without diabetes. Platelet dysfunction may explain this. The platelets in people with diabetes have proven to be hyper-reactive with intensified adhesion, activation and aggregation [29–32]. Strict lipid and blood pressure targets as demonstrated in the Steno-2 follow-up study [33] showed decreased mortality with ongoing intensive management [34]. Increased use of newer adenosine diphosphate receptor antagonists (P2Y12 inhibitors) such as Ticagrelor and Prasugrel which have been proven to decrease risk of recurrent cardiovascular events in patients with diabetes when compared to clopidogrel [35,36] are also important.

5.6. *12-month all-cause mortality*

Patients with pre diabetes or diabetes did not have worse odds of 12-month all-cause mortality after initial ACS, compared to patients without diabetes. This may be explained by advances in percutaneous intervention and modern medical management after ACS in mitigating plaque instability and platelet dysfunction in diabetes, in contrast to older studies [37].

5.7. *Lack of differences in outcomes between the pre-diabetes and normal groups*

The median HbA1c of the no diabetes group was 37 mmol/-mol (5.5%) which was higher when compared to a healthy population without acute coronary syndrome, [38]. As a result, the absolute difference in HbA1c between the pre-diabetes group and no diabetes group was less and, may have resulted in a lack of difference in clinical outcomes between the groups.

5.8. *Strengths and limitations*

This is the first prospective observational study examining both acute and 12-month outcomes in a consecutive inpatient population presenting with ACS that is fully stratified by HbA1c and clearly defining pre-diabetes in addition to diabetes. We demonstrated that routine, automated measurement of HbA1c in a tertiary hospital is feasible [17]. In fact, this has become embedded into routine clinical care at our centre [18]. A previous study demonstrating increased risk with increasing HbA1c in patients without diabetes studied outpatients with use of now dated therapies [4]. Another study in those who had acute coronary syndrome without ST elevation myocardial infarction used fasting glucose to diagnose pre-diabetes which could be compromised by false positives in the context of acute illness [22]. In the current

study, selection bias was reduced by the consecutive nature of patient selection without exclusion. Our study therefore accurately reflected a patient population presenting with acute coronary syndrome and is translatable to real-world practice.

A limitation of our study is its relatively short duration of follow-up (12 months). This limited the number of events recorded and, may have resulted in smaller differences in clinical outcomes between the dysglycaemic and normal groups resulting in a failure to reach statistical significance. The limited duration of follow-up did make the measured HbA1c data more relevant as HbA1c may change over time especially with subsequent outpatient diabetes care. We did not have weight or body mass index which may be important confounding factors in observed clinical outcomes. Another limitation of our study is that it excluded younger patients, under the age of 54 for reasons mentioned prior [16].

5.9. *Summary and conclusions*

In summary, the present study accurately assessed the high burden of dysglycaemia in a study population presenting with acute coronary syndrome. In our study, 37% of patients had diabetes. Patients with diabetes had an increased length of stay and had higher odds of APO, and ACS recurrence. As a result of uniform HbA1c testing, 4% of patients had a potential new diagnosis of diabetes. Our study also showed the burden of pre-diabetes in patients presenting with ACS was approximately the same as diabetes at 37%, an area not studied adequately prior. When we examined HbA1c as a continuous variable, we showed that higher levels of HbA1c, even in the pre-diabetes and in the normal range, was associated with a longer LOS and increased risk of APO. HbA1c is therefore an important prognostic test, stratifying risk in those presenting with ACS. In the face of recent evidence of improved cardiovascular and heart failure outcomes, SGLT-2 inhibitors and GLP-1 agonists are prime candidates in improving clinical outcomes associated with this group with its high prevalence of diabetes mellitus. The high prevalence of pre-diabetes identified in this group also provides an ideal opportunity to identify individuals who may benefit from education regarding lifestyle change in order to prevent progression to overt diabetes mellitus.

Author contributions

D.Mahendran was involved in literature review and synthesis, data, acquisition, detailed data analysis, critical discussion, drafting and revision of the manuscript. G.Hamilton and J. Weiss was involved in critical discussion, data collection, detailed data analysis and assisted revision of the manuscript. L.Churilov conducted statistical analysis, analysis and provided input into the manuscript. J.Lew and K.Khoo were involved in critical discussion, drafting and revision of the manuscript. Q.Lam was involved in critical discussion and data acquisition. R. Robbins was involved in data acquisition and analysis. G K.Hart was involved in project conception and analysis of the manuscript. D.Johnson, D L.Hare and, O.Farouque were involved in critical discussion, drafting and revision of the manuscript. J. Zajac was involved in project conception, analysis of the manuscript and supervision of the project. E. I Ekinci was involved in project conception, experimental design, analysis of the manuscript, supervision of the project.

Statements of assistance

None.

Guarantor's name

Dr. Elif I Ekinci.

Funding/financial support

None.

Prior publication of study

None.

Declaration of Competing Interest

Author declares that there is no conflicts of interest.

Acknowledgements

The authors are grateful to Peter Davey (Department of Administrative informatics, Austin Health) and Harvey Sutcliffe (Pathology IT Services, Austin Health) for assistance with data retrieval and information technology support. Dr Ekinci was supported by a Viertel Clinical Investigatorship, RACP – JDRF Fellowship and Sir Edward Weary Dunlop Medical Research Foundation and Diabetes Australia Research Program research grants.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.07.002.

REFERENCES

[1] Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. 2011 Mar 3; 2011(364):pp. 829-841.
[2] Eckel RH, Wassef M, Chait A, Sobel B, Barrett E, King G, et al. Prevention conference VI: diabetes and cardiovascular disease. Circulation 2002;105(18):e138–43.
[3] Ackermann RT, Cheng YJ, Williamson DF, Gregg EW. Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A1c: National health and nutrition examination survey 2005–2006. Am J Prev Med 2011;40 (1):11–7.
[4] Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic control and coronary heart disease risk in

persons with and without diabetes: the atherosclerosis risk in communities study. Arch Intern Med 2005;165(16):1910–6.
[5] Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med. 2016;2016 (374):1321–31.
[6] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care. 2014 Jan 1; 37 (Supplement 1):pp. S81-S90.
[7] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373 (22):2117–28.
[8] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017.
[9] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;2016(375):311–22.
[10] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375 (19):1834–44.
[11] d'Emden MC, Shaw JE, Colman PG, Colagiuri S, Twigg SM, Jones GR, et al. The role of HbA. Med J Australia 2012 Aug 20;197(4):220–1.
[12] Timmer JR, Hoekstra M, Nijsten MW, van der Horst IC, Ottervanger JP, Slingerland RJ, Dambrink JH, Bilo HJ, Zijlstra F, van't Hof AW. Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment–elevation myocardial infarction treated with percutaneous coronary intervention. Circulation 2011;1. CIRCULATIONAHA-110.
[13] Hadjadj S, Coisne D, Mauco G, Ragot S, Duengler F, Sosner P, et al. Prognostic value of admission plasma glucose and HbA1c in acute myocardial infarction. Diabet Med 2004;21 (4):305–10.
[14] Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000;355(9206):773–8.
[15] Oldroyd J, O'Neil A, Hare DL. Can patients presenting with acute coronary syndrome be screened for diabetes using glycosylated haemoglobin? Med J Australia 2015;203 (10):401–11.
[16] Simpson AJ, Krowka R, Kerrigan JL, Southcott EK, Wilson JD, Potter JM, et al. Opportunistic pathology-based screening for diabetes. BMJ Open 2013;3(9):e003411.
[17] Nanayakkara N, Nguyen H, Churilov L, Kong A, Pang N, Hart GK, et al. Inpatient HbA1c testing: a prospective observational study. BMJ Open Diab Res Care 2015;3(1): e000113.
[18] Yong PH, Weinberg L, Torkamani N, Churilov L, Robbins RJ, Ma R, et al. The presence of diabetes and higher HbA1c are independently associated with adverse outcomes after surgery. Diabetes Care 2018;41(6):1172–9.
[19] Braunwald E, Jones RH, Mark DB, Brown J, Brown L, Cheitlin MD, et al. Diagnosing and managing unstable angina. agency for health care policy and research. Circulation 1994;90 (1):613–22.
[20] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33(20):2551–67.
[21] Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit: a two year experience with 250 patients. Am J Cardiol 1967;20(4):457–64.
[22] Giraldez RR, Clare RM, Lopes RD, Dalby AJ, Prabhakaran D, Brogan GX, et al. Prevalence and clinical outcomes of undiagnosed diabetes mellitus and prediabetes among patients with high-risk non–ST-segment elevation acute coronary syndrome. Am Heart J 2013;165(6):918–25.
[23] Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;2010(362):800–11.
[24] Dunstan D, Zimmet P, Welborn T, de Courten M, Cameron A, Sicree R, et al. The rising prevalence of diabetes and impaired glucose tolerance: the Australian diabetes, obesity and lifestyle study. Diabetes Care 2002;25:829–34.
[25] Granger CB, Califf RM, Young S, Candela R, Samara J, Worley S, et al. Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agents. J Am Coll Cardiol 1993;21(4):920–5.
[26] Donahoe SM, Stewart GC, McCabe CH, Mohanavelu S, Murphy SA, Cannon CP, et al. Diabetes and mortality following acute coronary syndromes. JAMA 2007;298 (7):765–75.
[27] Stahrenberg R, Edelmann F, Mende M, Kockskämper A, Düngen HD, Scherer M, et al. Association of glucose metabolism with diastolic function along the diabetic continuum. Diabetologia 2010;53(7):1331–40.
[28] Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, Norhammar A, Birkeland KI, Jørgensen M, Thuresson M, Arya N. Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study. Circulation 2017;18. CIRCULATIONAHA-117.
[29] Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J 2013;34(31):2436–43.
[30] Stratmann B, Tschoepe D. Pathobiology and cell interactions of platelets in diabetes. Diabetes Vasc Dis Res 2005;2(1):16–23.
[31] Ferroni P, Basili S, Falco A, Davì G. Platelet activation in type 2 diabetes mellitus. J Thromb Haemost 2004;2(8):1282–91.
[32] Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramírez C, Sabaté M, Jimenez-Quevedo P, et al. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. Diabetes 2005;54(8):2430–5.
[33] Pedersen O, Gæde P. Intensified multifactorial intervention and cardiovascular outcome in type 2 diabetes: the steno-2 study. Metabolism 2003;31(52):19–23.
[34] Gæde P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358(6):580–91.
[35] Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357 (20):2001–15.
[36] James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontny F, Maya J, Nicolau JC, Spinar J, Storey RF, Stevens SR. 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 2010;31(24):3006–16.
[37] Miettinen H, Lehto S, Salomaa V, Mähönen M, Niemelä M, Haffner SM, Pyörälä K, Tuomilehto J. FINMONICA myocardial infarction register study group. Impact of diabetes on mortality after the first myocardial infarction. Diabetes Care 1998;21(1):69–75.
[38] Borg R, Kuenen JC, Carstensen B, Zheng H, Nathan DM, Heine RJ, Borch-Johnsen K, Witte DR. ADAG study group. real-life glycaemic profiles in non-diabetic individuals with low fasting glucose and normal HbA1c: the A1C-derived average glucose (ADAG) study. Diabetologia 2010;53(8):1608–11.