Fifteen years trends of cardiogenic shock and mortality in patients with diabetes and acute coronary syndromes

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Running Title: Cardiogenic shock and mortality in ACS end diabetes

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ABSTRACT

Purpose - To examine time trends of management and mortality of acute coronary syndrome patients with associated diabetes mellitus.

Methods - We analyzed data from 5 nationwide registries established between 2001 and 2014, including consecutive acute coronary syndrome patients admitted to the Italian Intensive Cardiac Care Units.

Results – Out of 28,225 participants, 8,521 (30.2%) had diabetes: as compared to patients without diabetes, they were older and had significantly higher rates of prior myocardial infarction and comorbidities (all p<0.0001). Prevalence of diabetes and comorbidities increased over time (p for trend <0.0001). Cardiogenic shock rates were higher in patients with diabetes, as compared to those without diabetes (7.8% vs 2.8%, p<0.0001), and decreased significantly over time only in patients without diabetes (p=0.007). Revascularization rates increased over time both in patients with and without diabetes (both p for trend <0.0001), though with persistingly lower rates in patients with diabetes. All-cause in-hospital mortality was higher in patients with diabetes (5.4 vs. 2.5%, respectively, p<0.0001) and decreased more consistently in patients without diabetes (p for trend=0.007 and<0.0001, respectively). At multivariable analysis, diabetes remains an independent predictor of both cardiogenic shock [OR 2.03, 95% C.I. 1.77-2.32, p<.0001] and mortality [OR: 1.95; 95% CI: 1.69–2.26; p < 0.0001].

Conclusions – Despite significant mortality reductions observed over 15 years in acute coronary syndromes, patients with diabetes continue to show 3-fold higher rates of cardiogenic shock and lower revascularization rates as compared to patients without diabetes. These findings may explain the persistingly higher mortality of patients with diabetes and acute coronary syndromes.

Keywords: Acute Coronary Syndrome; Cardiogenic shock; Diabetes; Observational Outcome Study; In-hospital death.

Diabetes mellitus is a major cardiovascular risk factor leading to early death and higher hospitalization and complications rates. Most evidence showing an increased mortality risk associated with diabetes in acute coronary syndromes stems from randomized clinical trials and from registries of non-consecutively enrolled patients[1], thus leaving a relative paucity of data on the actual daily practice. Moreover, it has not been clearly described whether the progressive increase of early revascularization across the spectrum of acute coronary syndromes observed in recent years has reduced the mortality gap between patients with and without diabetes.

Over the last two decades, the Italian Association of Hospital Cardiology (ANMCO) has established a series of prospective registries of consecutive patients with acute coronary syndromes admitted to the Italian network of Intensive Cardiac Care Units (ICCU). Between 2001 and 2014, more than 28,000 patients were enrolled in 5 subsequent Registries, each of them involving a representative sample of the country ICCU network. Over the years, the invasive approach to acute coronary syndromes has steadily increased, with improved outcome in all patient categories, irrespective of age and sex,[2,3] cardiogenic shock status,[4] presence of atrial fibrillation[5] or concomitant vascular disease.[6] The present analysis is aimed to investigate the evolution of patient characteristics, treatment and outcome of patients with diabetes admitted to ICCUs for an acute coronary syndrome.

METHODS

Study design and population

The patients included in the present analysis were enrolled in 5 consecutive nationwide prospective surveys on acute coronary syndromes ICCU admissions coordinated by the ANMCO between 2001 and 2014: Blitz-1 in 2001,[7] IN-ACS Outcome (Italian Network on Acute Coronary Syndromes Outcome) in 2006–2007,[8] Blitz-4 in 2009-2010,[9]

MANTRA (Management of patients with acute coronary syndromes in the real world practice in Italy: an outcome research study focused on the use of ANTithRombotic Agents) in 2009–2010,[10] and EYESHOT (EmploYEd antithrombotic therapies in patients with acute coronary Syndromes Hospitalized in iTalian cardiac care units) in 2013-2014.[11] All studies enrolled across the acute coronary syndromes spectrum, including both ST-Elevation myocardial infarction and Non-ST-Elevation acute coronary syndromes patients. For the present analysis patients were categorized according to diabetes status.

The principles and procedures used for each registry have been described previously.[7-11] The ANMCO Research Centre (Centro Studi ANMCO) was appointed to coordinate the project, to provide support to the committees, local coordinators and participating centres, and to oversee the methodological aspects of the surveys. All databases were set up at the ANMCO Research Centre, according to the requirements defined by the appointed Executive Committee. Informed consent was obtained from all patients. Local Institutional Review Boards approved the protocols.

Definitions

Data on previous medical history and medications ongoing at admission, baseline characteristics, cardiac procedures, use of medications during hospitalization and at hospital discharge, and in-hospital major clinical events, were recorded. The definitions of inclusion criteria and outcome events were consistent throughout the surveys.

The presence of known diabetes was defined by a previous physician's diagnosis reported by the patients, or information from their medical records when available. *De novo* diabetes was defined, according to standard criteria, as absence of a prior diagnosis

of diabetes but a fasting plasma venous glucose ≥126 mg/dL or random plasma venous glucose >200 mg/dL during ICCU stay.

Body mass index (BMI) was calculated by dividing patients' weight in kilograms by their height in meters squared. Patients were considered to have hypertension if their blood pressure was ≥140/90 mmHg or if they were on anti-hypertensive treatment. Venous blood samples were drawn in the morning after an overnight fast. Serum creatinine, glucose, and other biochemical blood measurements were determined using standard laboratory procedures. The glomerular filtration rate (e-GFR) was estimated by the four-variable Modification of Diet in Renal Disease (MDRD) study equation.[12] Presence of chronic kidney disease was defined as an e-GFR value <60 mL/min/1.73 m^2. Conventional trans-thoracic echocardiography or left ventriculography were used to calculate ejection fraction according to international standard criteria. An invasive approach was defined as use of coronary angiography during ICCU stay followed, whenever clinically indicated and technically feasible, by revascularization either by percutaneous coronary intervention or bypass surgery. For the Blitz-4 study, angioplasty and bypass surgery data were not available for patients transferred from Centers without coronary interventional facilities: therefore, revascularization data were not used for this study.

Study outcomes

In-hospital all-cause mortality was the primary outcome of the present analysis. The main secondary outcome of interest was cardiogenic shock. In all of the study protocols, cardiogenic shock was defined as systolic blood pressure (BP) of ≤90 mmHg lasting more than 60 min, nonresponsive to water challenge or requiring the administration of inotropic drugs in order to obtain a systolic BP of >90 mmHg, with clinical signs of peripheral

hypoperfusion such as sensorial obnubilation, low urine output (<30 ml/h), cold sweat or cyanosis.[4] All study outcomes were ascertained in the whole cohort and are herein shown separately for patients with and without diabetes.

Statistical analysis

Categorical variables are presented as number and percentages, and continuous variables as means and standard deviations (SD), except for the duration of hospitalization and the length of ICCU stay, which are reported as median and inter-quartile range (IQR). Categorical variables were compared by the χ^2 test, while continuous variables by the *t*-test, if normally distributed, or the Mann-Withney U-test, if not. Temporal trends were tested using the Cochran-Armitage test for binary variables and the Kendall Tau rank correlation coefficient with the Jonckheere-Terpstra test for continuous variables. A multivariable analysis (logistic model) was performed to evaluate the association between diabetes and cardiogenic shock, over time, adjusting for study cohort (year, 2001 as reference), diabetes, and the following variables: gender, prior myocardial infarction, prior heart failure, Killip class at entry >1, acute coronary syndrome presentation (ST elevation vs Non ST elevation), and age, systolic blood pressure, heart rate, and length of hospital stay, as continuous.

Furthermore, a multivariable analysis (logistic regression) was performed to evaluate the association between diabetes and in-hospital all-cause mortality over time, adjusting for study cohort (year, 2001 as reference), gender, age (continuous), (treated) hypertension, smoking, BMI (<25 as reference; ≥25; missing), chronic obstructive pulmonary disease, history of heart failure, prior stroke/transient ischemic attack, prior myocardial infarction, prior revascularization, peripheral vascular disease, eGFR at entry (<60; ≥60 as reference; missing), acute coronary syndrome presentation (STE vs NSTE), and

systolic blood pressure (as continuous). In case of categorical variables, when more than two categories were present, dummy variables were introduced to define a reference group. As sensitivity analysis, the model on in-hospital all-cause mortality was performed separately in patients with ST elevation and Non ST elevation, further adjusting for coronary revascularization in ST elevation patients and coronarography during admission in patients with non ST elevation acute coronary syndrome. The risk estimates are reported as Odds Ratio (OR) and 95% confidence interval (CI). All tests were 2-sided; a p value<0.05 was considered statistically significant. All analyses were conducted with SAS system software version 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

The overall study cohort included 28,225 acute coronary syndrome patients, of which 8,521 (30.2%) had diabetes. Most patients with diabetes had previously known disease (n=7,327; 86.0%). Over the years diabetes prevalence increased from 22.2% in 2001 to 32.3% in 2014 (*P for trend* <0.0001), as shown in **Figure 1**. The identification of diabetes subtypes was not possible by study design, although the vast majority of cases had likely type-2 diabetes. As shown in **Table 1**, patients with diabetes were more often women and significantly older, as compared to those without diabetes. The diagnosis of diabetes was also accompanied by a higher prevalence of comorbidities (particularly chronic obstructive pulmonary disease and impaired kidney function at entry), as well as prior cardiovascular events (myocardial infarction, stroke) and revascularization procedures. Left ventricular ejection fraction was significantly lower in patients with diabetes. As for the acute coronary syndrome presentation, the prevalence of non ST elevation acute coronary syndrome was higher in individuals with *vs.* without diabetes

(59.2 *vs.* 50.6%, *P* <0.0001). The prevalence of chronic kidney disease, as well as clinical history of coronary angioplasty or bypass surgery, increased over time in the whole cohort (**Supplementary table 1**), and in patients with and without diabates.

Treatment strategies

In the overall study cohort, coronary angiography was performed in 78.8% of patients with, as compared to 84.7% of those without diabetes (p<0.0001) (**Supplementary Table 2)**. Percutaneous or surgical coronary revascularization was performed in 57.7% of patients with vs 63.9% of those without diabetes (p<0.0001), with angioplasty representing the majority of the revascularization procedures (92.9% in patients with diabetes vs 95.5%, in patients without diabetes, p<0.0001). Overall, patients with diabetes were more likely to be treated by medical-only therapy as compared to those without diabetes (42.3 *vs.* 36.1%, *P* <0.0001).

As shown in **Table 2**, there was an increase over time in referral to coronary angiography, and a reduction in thrombolytic therapy in ST elevation myocardial infarction, both among patients with and without diabetes. Few differences were found in cardiac specific medications in patients with or witout diabetes (**Supplementary Table 2**).

Cardiogenic shock

Overall, cardiogenic shock rates were 3-fold higher in patients with diabetes (7.8% vs. 2.8%, p<0.0001). Over the years (**Figure 2**), cardiogenic shock rates decreased significantly in patients without diabetes (p for trend=0.007) but remained unchanged in patients with diabetes (p for trend=0.74). At multivariable analysis, diabetes was an independent predictor of cardiogenic shock (OR 2.03, 95% C.I. 1.77-2.32, p<.0001) (**Figure 3A**).

In-hospital mortality

As shown in **Table 3**, patients with diabetes had significantly higher rates of in-hospital all-cause death (5.4% vs 2.5%, *p* <0.0001), and in-hospital complications (22.3% *vs.* 10.8%, *P* <0.0001) as compared to those without diabetes. Notably, patients with diabetes displayed at least 2-fold higher mortality rates as compared to those without DM across all study years, despite a remarkable reduction of overall mortality in both patient subsets after the BLITZ-1 study in 2001. Case fatality of cardiogenic shock was similar in patients with or without diabetes (42.6% vs 43.1%, p=0.86) but, due to higher rates of cardiogenic shock among patients with diabetes, it accounted for 61.1% of overall mortality among patients with diabetes (283 out of 463 deaths), as compared to 48.0% among patients without diabetes (233 out of 485 deaths). Both the total (8 [5-11] *vs.* 7 [5-9] days, *P* <0.0001) and ICCU-specific (4 [3-6] *vs.* 4 [2-5] days, *P* <0.0001) length of stay were longer in patients with *vs.* without diabetes.

At multivariable analysis in the whole acute coronary syndrome population, DM was found to be an independent predictor of in-hospital all-cause mortality (OR 1.95; 95% CI 1.69-2.26; p <0.0001) together with other established predictors (**Figure 3B**). The strong association between diabetes and in-hospital mortality remained even in the sensitivity analysis, stratifying for acute coronary syndrome presentation and further adjusting for coronary revascularization in patients with ST elevation (OR 2.04; 95% CI 1.69-2.45, p<0.0001) and coronary angiography on admission for patients with non ST elevation acute coronary syndrome (OR 1.72; 95% CI 1.35-2.20, p<0.0001).

DISCUSSION

The present analysis provides an update of the epidemiology, management and outcome of patients with diabetes mellitus and acute coronary syndromes, based on a series of contemporary nationwide registries of consecutive ICCU admissions. The main findings are the following: 1. nearly 30% of acute coronary syndrome patients have diabetes (4% as de novo diagnosis), and this rate has been increasing over time; 2. as compared to patients without diabetes, those with diabetes are older, and have a higher prevalence of prior cardiovascular events and comorbidities; 3. After adjustment for prior cardiac events and comorbidities, patients with diabetes have twice the rate of cardiogenic shock, as compared to patients without diabetes, with the same case-fatality; 4. the rates of cardiogenic shock have decreased significantly among patients without diabetes, but not among those with diabetes; 5. the use of revascularization has significantly increased in all patients over the years, but both coronary angiography and angioplasty rates remained lower in patients with diabetes; 6. in-hospital mortality did decrease over time both in patients with and without diabetes, but remained two-fold higher among patients with diabetes; 7. after adjustment for multiple comorbidities and prior coronary revascularization, diabetes remains among the independent predictors of mortality.

This data is consistent with a systematic review and metanalysis of 110 studies, including randomized trials and registries,[1] but provide new epidemiological insight, since they derive from a representative nationwide sample of acute coronary syndrome patients in a period of transition from a predominantly medical to a largely interventional treatment of acute coronary syndromes. According to the present data, the rates of patients with diabetes are much higher in clinical practice than in randomized clinical trials that form the evidence basis of practice guidelines.[13]

Several studies have described how the management of patients with acute coronary syndromes and diabetes has improved with early reperfusion and revascularization.[13,14] However, as shown by a recent metaregression analysis, the incremental mortality risk associated with diabetes among acute coronary syndrome patients has remained constant over a long period of time (1970 to 2011).[1] Our results are in line with this data, also showing a temporal decrease in the overall risk of in-hospital mortality and confirming the independent and strong association between diabetes and mortality across the spectrum of acute coronary syndromes.

The present data may help discriminating the causes for this persistingly higher mortality among acute coronary syndrome patients with diabetes. Patients with diabetes are older, as compared to patients without diabetes, most probably reflecting the epidemiological predominance of maturity-onset type 2 diabetes.[15,16] However, patients with diabetes present more often with prior myocardial infarction and revascularization procedures, reflecting the premature progression of coronary disease caused by the disease. Prevalence of chronic kidney dysfunction has also been found to be 3-fold higher among patients with diabetes, and increasing over time, reflecting more extensive vascular disease. For all these reasons, not surprisingly the rates of coronary revascularization, though increased overtime in the overall population, remained significantly lower in patients with diabetes.

This combination of prior coronary events, particularly myocardial infarction, and also lower revascularization rates in the acute phase, is the most likely explanation of the higher rate of cardiogenic shock among patients with diabetes. Diabetes is largely over-represented in the cardiogenic shock population: whereas in the overall acute coronary syndrome population patients with diabetes increased from 22% in 2001 to 32% in 2014, they increased from 35% to 56% in the cardiogenic shock population, a rate even higher

in clinical practice than that enrolled in the most recent Culprit Shock randomized trial of acute coronary syndrome patients with multivessel coronary disease.[17] Whether this most severe presentation of acute coronary syndromes among patients with diabetes is to be attributed to pre-existing myocardial damage, to worse myocardial metabolism under ischemic conditions,[18,19] or both, remains matter of further investigation. After the acute coronary syndrome event, markers of myocardial dysfunction have been shown to be by far the most important predictors of mortality among patients with diabetes.[20] Over the present study period, the case fatality of cardiogenic shock decreased from 68% in 2001 to 38% in 2014, both in patients with and in those without diabetes. Therefore, at least part of the persistingly higher mortality risk associated with diabetes in the setting of acute myocardial infarction should be attributed to higher rates of cardiogenic shock, which were reduced significantly over time in patients without diabetes, but did not change among those with diabetes. In the present analysis, cardiogenic shock has been found responsible for 61% of mortality in patients with diabetes, as compared to 48% among those without diabetes.

These conclusions may have important implications for clinical practice. According to the present data, acute care of acute coronary syndromes has provided consistent benefit both in patients without and with diabetes. More effort should be devoted to preventing the first acute coronary syndrome event through aggressive risk factor control,[21] as well as ischemic recurrencies and left ventricle deterioration by a more extensive integration of recent pharmacological advances in antidiabetic therapy.[22]

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Conflicts of interest: none. See enclosed CoI document

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FIGURE LEGENDS

Figure 1 – Nationwide prevalence of diabetes mellitus (DM) in 28,225 patients hospitalized for Acute Coronary Syndrome in the italian Intensive Cardiac Care Units over 2001-2014.

The picture shows the overall study-specific prevalence of diabetes mellitus stratified as to whether the diagnosis was already present prior to hospital admission (*known* diabetes) or it occurred during hospitalization (*de novo* diabetes), as a combination of data from five consecutive nationwide prospective surveys conducted between 2001 and 2014 and comprising 28,225 patients. De novo diabetes evaluated excluding Blitz-1 study (data on glycemia not available).

Figure 2 – Cardiogenic shock rates in patients with or without diabetes mellitus in the 5 ICCU registries.

Bars are percentages of patients with or without diabetes. P-value for comparison within each study: *p=0.0002; **p<0.0001.

Figure 3A – Independent predictors of cardiogenic shock at logistic regression analysis.

The predictors are ordered according to χ^2 value. Per cent predictive information is calculated as the proportion of the individual χ^2 compared to the sum of all χ^2.

[a]Analysed as continuous variable (the reported OR is for 1-year increase in age, 1mmHg increase in blood pressure, 1 beat per minute increase in heart rate).

Figure 3B– Independent predictors of all-cause in-hospital mortality at logistic regression analysis.

The predictors are ordered according to χ^2 value. Per cent predictive information is calculated as the proportion of the individual χ^2 compared to the sum of all χ^2.

[a]Analysed as continuous variable (the reported OR is for 1-year increase in age, 1mmHg increase in blood pressure, 1 beat per minute increase in heart rate).

Clinical significance points

1. Mortality in Acute Coronary Syndromes has improved with early invasive treatment. Whether this is true in patients with diabetes is unclear.
2. Rates of early revascularization have increased both in patients with and in those without diabetes.
3. Cardiogenic shock rates decreased only in patients without diabetes.
4. Mortality decreased more consistently in patients without diabetes.

Table 1 - Main demographic, clinical and biochemical characteristics of 28,225 patients admitted to the ICCUs.

	ALL (N=28,225)	Patients WITH diabetes (N=8,521)	Patients WITHOUT diabetes (N=19,704)	*P*-value
Male, n (%)	19,688 (69.8)	5,429 (63.7)	14,259 (72.4)	<0.0001
Age, years, mean±SD	68±13	71±11	66 ±13	<0.0001
BMI, kg/m^{2} [#], mean±SD	26.9 ±4.2	27.7±4.5	26.5±4.0	<0.0001
Systolic blood pressure, mmHg, mean±SD	137±27	139±28	136±26	<0.0001
Diastolic blood pressure, mmHg, mean±SD	79±15	78±15	80±15	<0.0001
Heart rate, bpm, mean±SD	79±19	83±21	77±18	<0.0001
Diabetes, n, %	8,521 (30.2%)	8,521 (100.0)	-	
- *De novo*[§]	1,194 (4.5%)	1,194 (14.8)	-	
- *Known*	7,327 (25.9%)	7,327 (85.9)	-	
Diabetes medications^, n (%)				
- *Insulin (only)*	-	1,656 (22.6)	-	-
- *Oral hypoglycemic drugs (only)*	-	4,082 (55.7)	-	-
- *Both Insulin and oral hypoglycemic drugs*	-	167 (2.3)	-	-
- *Diet*	-	1,422 (19.4)	-	-
Plasma glucose at CCU admission, mg/dL[*], mean±SD	150±73	216±94	120±27	<0.0001
Current smoking, n (%)	8,917 (31.6)	1,865 (21.9)	7,052 (35.8)	<0.0001
Hypertension on treatment, n (%)	16,307 (57.8)	5,997 (70.4)	10,310 (52.3)	<0.0001
Total cholesterol, mg/dL [**], mean±SD	190±45	180±45	194±44	<0.0001
Lipid-lowering medications, n (%) [***]	5,818 (22.7)	2,443 (31.7)	3,375 (18.8)	<0.0001
Cardiovascular medications, n (%)				
- *ACE-I or ARBs* [***]	10,630 (41.4)	4,036 (52.4)	6,594 (36.7)	<0.0001
- *Betablockers* [***]	5,874 (22.9)	2,166 (28.1)	3,708 (20.6)	<0.0001
- *Antiplatelets or Anticoagulants*°	10,930 (38.8)	4,477 (52.6)	6,453 (32.8)	<0.0001
Creatinine, mg/dL [$], mean±SD	1.1±0.8	1.3±1.0	1.1±0.7	<0.0001
e-GFR$_{MDRD}$, mL/min/1.73 m^{2} [$], mean±SD	76±29	68.3±29	80±28	<0.0001
e-GFR$_{MDRD}$ <60 mL/min/1.73 m^{2}, n (%)	6,365 (26.2)	2,959 (39.2)	3,406 (20.4)	<0.0001

	ALL (N=28,225)	Patients WITH diabetes (N=8,521)	Patients WITHOUT diabetes (N=19,704)	*P*-value
LVEF, % [$$], mean±SD	50±11	47.1±11.1	51±10	<0.0001
LVEF				<0.0001
≤ 30%, n (%)	1,657 (6.6)	795 (10.3)	862 (4.9)	
31-44%, n (%)	4,826 (19.1)	1,834 (23.7)	2,992 (17.1)	
≥ 45%, n(%)	18,772 (74.3)	5,097 (66.0)	13,675 (78.0)	
COPD, n (%)	2,146 (7.7)	841 (10.0)	1,305 (6.7)	<0.0001
CKD, n (%)	2,383 (8.4)	1,250 (14.7)	1,133 (5.8)	<0.0001
PVD, n (%)	2,982 (10.6)	1,410 (16.6)	1,572 (8.0)	<0.0001
Family history of CVD[$$$], n (%)	4,087 (27.1)	1,024 (24.2)	3,063 (28.3)	<0.0001
Prior CABG, n (%)	1,716 (6.1)	842 (9.9)	874 (4.4)	<0.0001
Prior PCI, n (%)	3,824 (13.6)	1,518 (17.8)	2,306 (11.7)	<0.0001
Prior MI, n (%)	4,804 (17.0)	1,949 (22.9)	2,855 (14.5)	<0.0001
Prior Stroke/TIA, n (%)	1,649 (5.8)	736 (8.6)	913 (4.6)	<0.0001
ACS etiology, n (%)				<0.0001
(NSTE-ACS), n (%)	15,015 (53.2)	5,045 (59.2)	9970 (50.6)	
(STEMI), n (%)	13,210 (46.80)	3,476 (40.8)	9,734 (49.4)	

[#] available for 27163 patients. [§]*De novo* diabetes was defined as absence of a prior diagnosis of diabetes but a fasting or random plasma venous glucose >200 mg/dL; evaluated among 26266 patients, 8087 with diabetes mellitus (Blitz-1 excluded because glycemia not available). ^Data available in 7,327 patients with history of diabetes. [*] available for 24196 patients. [**] available for 10896 patients. [***] available for 25689 patients. ° available for 28197 patients. [$] available for 24290 patients. [$$] at entry/during hospital stay; available for 25255 patients. [$$$] available for 15069 patients.

ACE-I=angiotensin-converting-enzyme inhibitors; ARB=angiotensin receptor blocker; BMI=body mass index; CABG=coronary artery bypass; CCU=coronary care unit; COPD=chronic obstructive pulmonary disease; CKD=chronic kidney disease; CVD; e-GFR_{MDRD}=glomerular filtration rate estimated according to the Modification of Diet in Renal Disease (MDRD) study equation; ICCU=intensive cardiac care unit; LVEF=left ventricular ejection fraction; MI=myocardial infarction; NSTE-ACS= Non-ST-Segment Elevation acute coronary syndrome; PCI=percutaneous coronary intervention; PVD=peripheral vascular disease; SD=standard deviation; STEMI=ST-Elevation Myocardial Infarction; TIA=transient ischemic attack.

Table 2. Treatment stratified by study in patients with or without diabetes.

STEMI *treatment in patients* *WITH* *diabetes*	**ALL (N=3,476)**	**BLITZ-1 (N=293)**	**IN-ACS OUTCOME (N=608)**	**BLITZ-4 (N=1,589)**	**MANTRA (N=719)**	**EYESHOT (N=267)**	***P* trend**
Coronary angiography %	2,928 (84.2)	115 (39.3)	494 (81.3)	1,447 (91.1)	618 (86.0)	254 (95.1)	<0.0001
Medical only, %	918 (26.4)	132 (45.1)	180 (29.6)	363 (22.8)	200 (27.8)	43 (16.1)	
Primary PCI, %	1,942 (55.9)	24 (8.2)	282 (46.4)	1035 (65.1)	397 (55.2)	204 (76.4)	<0.0001
Thrombolysis, %	616 (17.7)	137 (46.7)	146 (24.0)	191 (12.1)	122 (17.0)	20 (7.5)	<0.0001
PCI#	1,241 (65.8)	54 (18.4)	421 (69.2)	-	539 (75.0)	227 (85.0)	<0.0001
CABG#	46 (2.4)	3 (1.0)	19 (3.1)		20 (2.8)	4 (1.5)	0.87
STEMI *treatment in patients* *WITHOUT* *diabetes*	**ALL (N=9734)**	**BLITZ-1 (N=1,081)**	**IN-ACS OUTCOME (N=1,673)**	**BLITZ-4 (N=4,067)**	**MANTRA (N=2,139)**	**EYESHOT (N=774)**	***P* trend**
Coronary Angiography, %	8539 (87.7)	526 (48.7)	1,460 (87.3)	3,886 (95.5)	1,924 (90.0)	743 (96.0)	<0.0001
Medical only, %	1915 (19.7)	400 (37.0)	393 (23.5)	638 (15.7)	377 (17.6)	107 (13.8)	
Primary PCI, %	5,976 (61.4)	166 (15.4)	837 (50.0)	2,941 (72.3)	1,424 (66.6)	608 (78.6)	<0.0001
Thrombolysis, %	1,843 (18.9)	515 (47.6)	443 (26.5)	488 (12.0)	338 (15.8)	59 (7.6)	<0.0001
PCI*	4025 (71.0)	345 (31.9)	1,271 (76.0)	-	1,735 (81.1)	674 (87.1)	<0.0001
CABG*	91 (1.6)	11 (1.0)	37 (2.2)		35 (1.6)	8 (1.0)	0.67
NSTE-ACS *treatment, in patients* *WITH* *Diabetes*	**ALL (*N*=5045)**	**BLITZ-1 (*N*=141)**	**IN-ACS OUTCOME (*N*=1,116)**	**BLITZ-4 (*N*=2,055)**	**MANTRA (*N*=1,182)**	**EYESHOT (N=551)**	***P* trend**
Coronary angiography, %	3,789 (75.1)	50 (35.5)	808 (72.4)	1,626 (79.1)	877 (74.2)	428 (77.7)	<0.0001
PCI, %°	1,376 (46.0)	20 (14.2)	507 (45.4)	-	580 (49.1)	269 (48.8)	<0.0001
CABG, % °	173 (5.8)	3 (2.1)	78 (7.0)	-	76 (6.4)	16 (2.9)	009
NSTE-ACS *treatment, in patients* *WITHOUT* *Diabetes*	**ALL (N=9,970)**	**BLITZ-1 (N=444)**	**IN-ACS OUTCOME (N=2,497)**	**BLITZ-4 (N=3,731)**	**MANTRA (N=2,354)**	**EYESHOT (N=944)**	***P* trend**
Coronary angiography, %	8,147 (81.7)	200 (45.1)	1,945 (77.9)	3,299 (88.4)	1,891 (80.3)	812 (86.0)	<0.0001
PCI, %**	3,236 (51.9)	70 (15.8)	1,264 (50.6)	-	1,351 (57.4)	551 (58.4)	<0.0001
CABG, %**	286 (4.6)	10 (2.3)	131 (5.3)	-	122 (5.2)	23 (2.4)	0.29

#Data available on 1,887 patients. *Data available on 5,667 patients. °Data available on 2,990 patients. **Data available on 6,239 patients.
ACS: Acute coronary syndrome; PCI: percutaneous coronary intervention; CABG: coronary artery bypass.

Table 3 – In-hospital outcomes in patients with and without diabetes, stratified by study.

	ALL (*N*=28,225)			BLITZ-1 (*N*=1,959)		IN-ACS OUTCOME (*N*=5,894)		BLITZ-4 (*N*=11,442)		MANTRA (*N*=6,394)		EYESHOT (*N*=2536)	
Outcomes	**D (*n*=8521)**	**No-D (*n*=19704)**	***P*-value**	**D (*n*=434)**	**No-D (*n*=1,525)**	**D (*n*=1,724)**	**No-D (*n*=4,170)**	**D (*n*=3,644)**	**No-D (*n*=7,798)**	**D (*n*=1,901)**	**No-D (*n*=4,493)**	**D (*n*=818)**	**No-D (*n*=1,718)**
All-cause death (n, %)	463 (5.43)	485 (2.46)	<0.0001	49 (11.3)	95 (6.2)**	79 (4.6)	87 (2.1)*	200 (5.5)	153 (2.0)*	98 (5.2)	111 (2.5*)	37 (4.5)	39 (2.3)**
Cardiogenic shock (n, %)	665 (7.80)	541 (2.75)	<0.0001	46 (10.6)	85 (5.7)**	99 (5.7)	87 (2.1)*	332 (9.1)	212 (2.7)*	121 (6.4)	105 (2.3)*	67 (8.2)	52 (3.1)*
Complicated hospital course* (n, %)	1,901 (22.3)	2,134 (10.8)	<0.0001	149 (34.3)	301 (19.7)*	287 (16.7)	392 (9.4)*	908 (24.9)	859 (11.0)*	363 (19.1)	409 (9.1)*	194 (23.7)	173 (10.1)*
Length of hospital stay (days) Median [IQR]	8 [5-11]	7 [5-9]	<0.0001	10 [8-14]	9 [7-12]**	7 [5-10]	7 [5-9]*	7 [5-10]	7 [5-9]*	7 [6-10]	7 [5-9]*	8 [6-11]	7 [5-9]*
Length of ICCU stay (days)# Median [IQR]	4 [3-6]	4 [2-5]	<0.0001	4 [3-6]	4 [3-5]*	3 [2-5]	3 [2-4]*	5 [3-7]	4 [3-6]*	3 [2-5]	3 [2-5]*	4 [2-6]	3 [2-5]*

* p<0.0001
** p<0.001
#available for 28,222 patients

*Including at least one of the followings: heart failure, pulmonary oedema, cardiogenic shock, re-infarction (in ICCU), stroke/, major bleeding, mechanical or disventilatory complications.

D=diabetes; No-D=no diabetes; ICCU=Intensive coronary care unit
low molecular weight heparin; UFH, un-fractioned heparin; GPI, glycoprotein inhibitors;

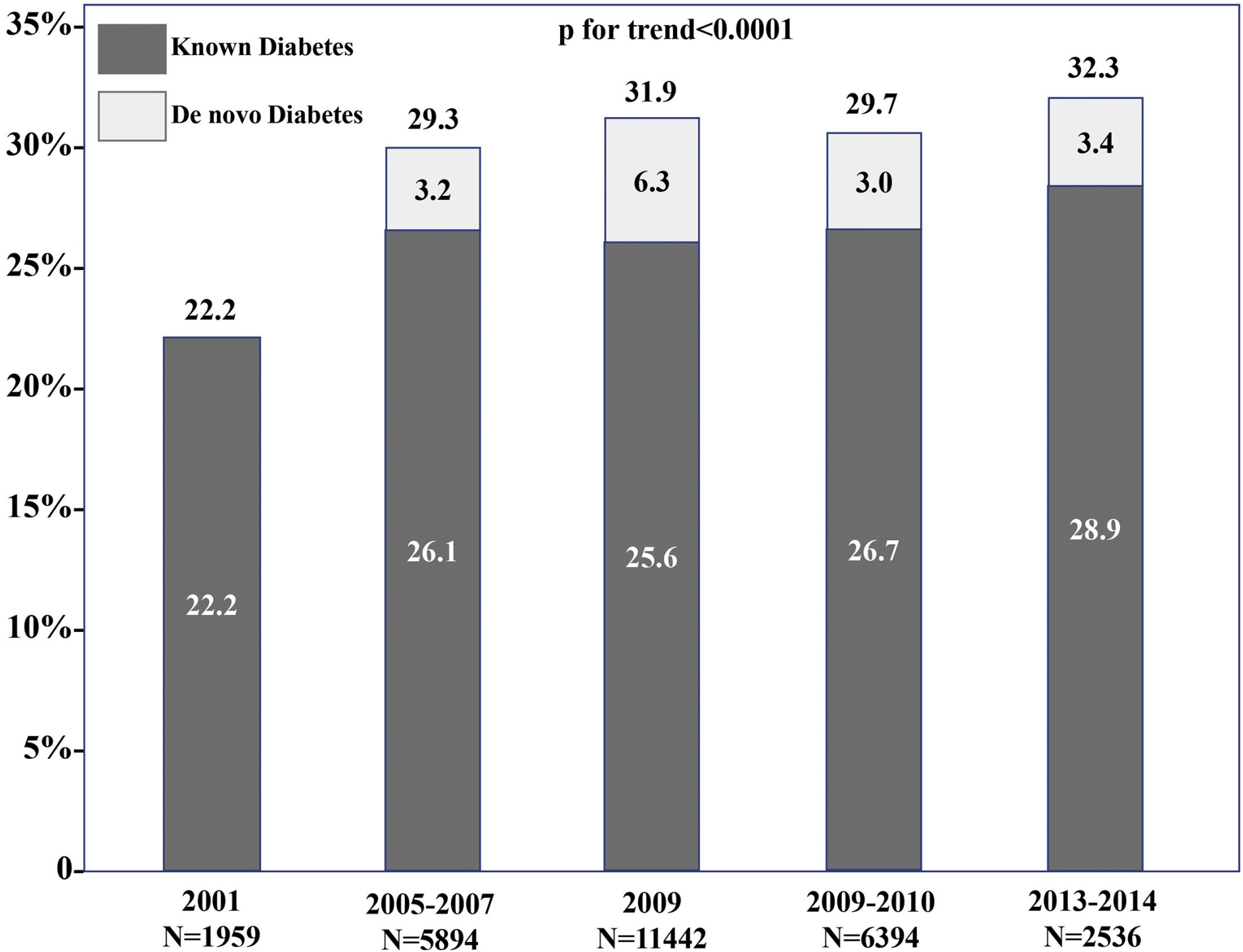


Figure 1

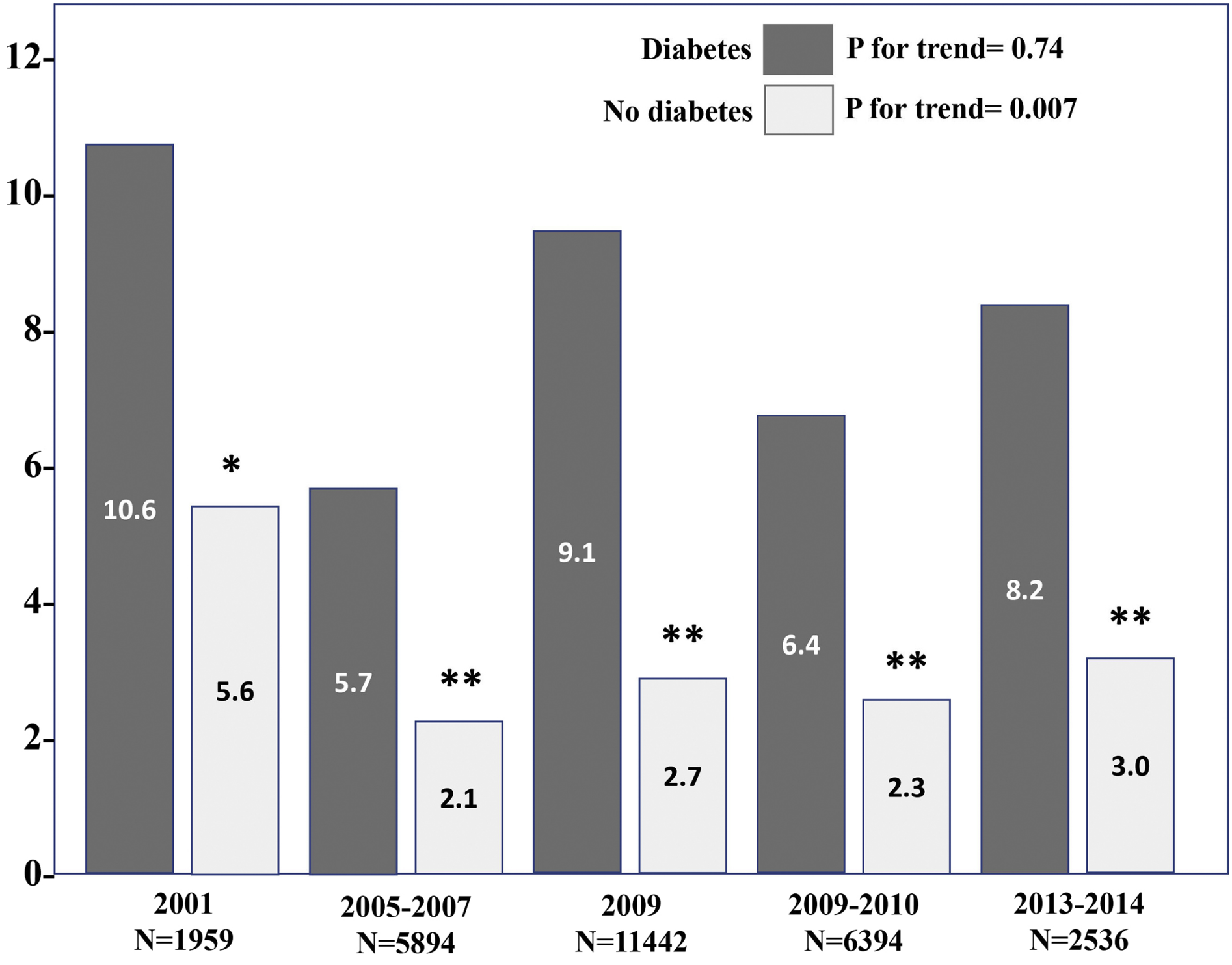
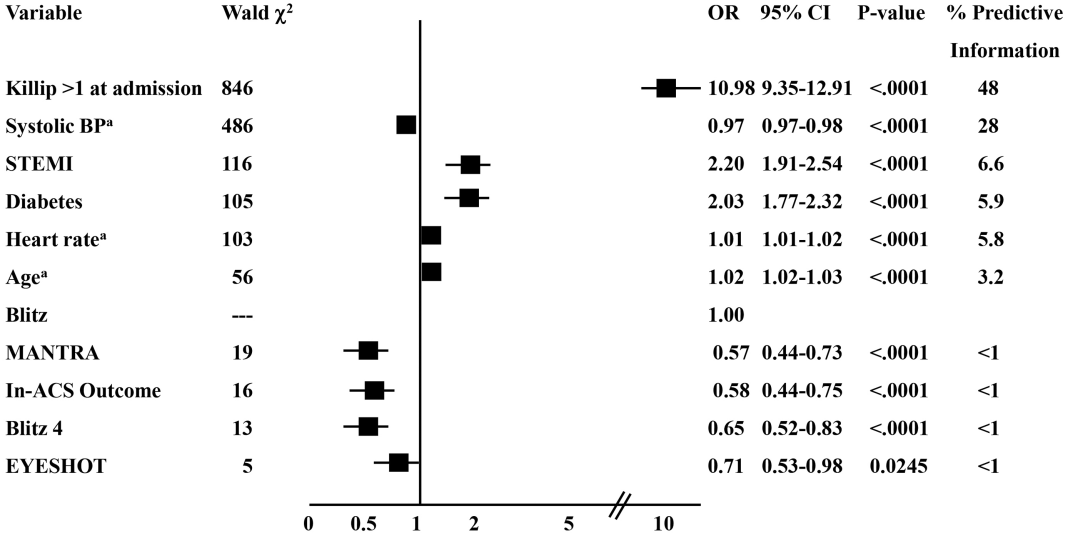


Figure 2

A



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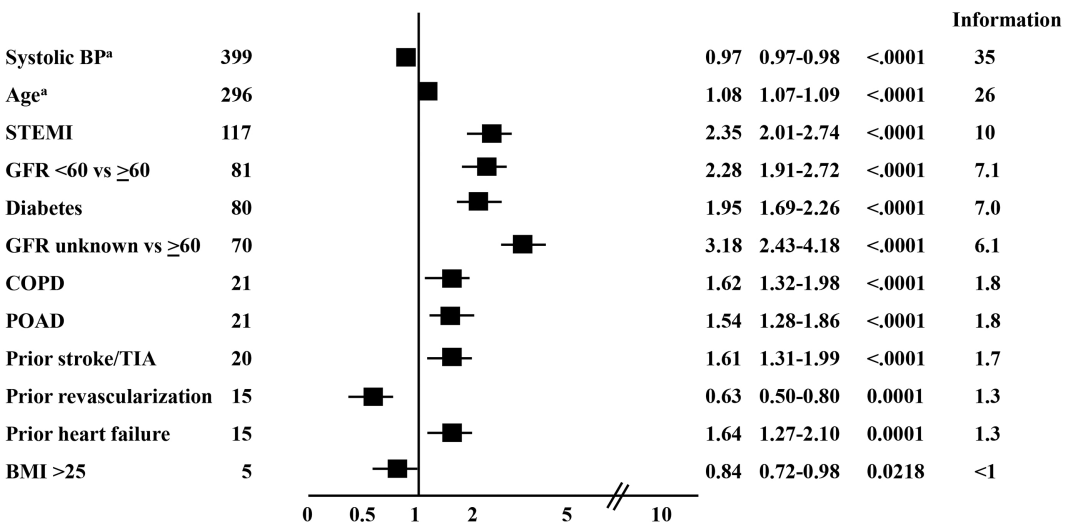

Figure 3

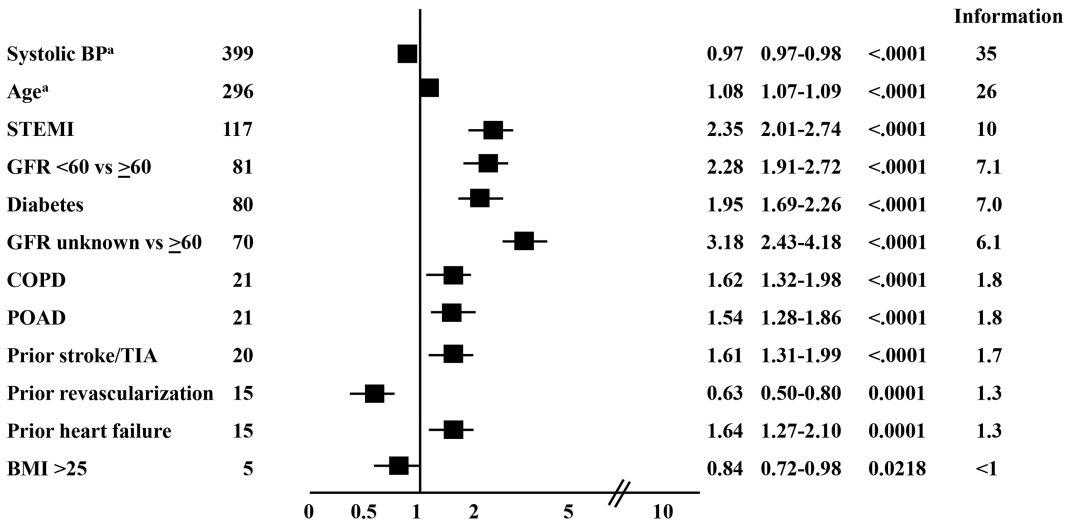

Figure 4.