CAD and AMI: Research Article

Analyses of Increased Mortality in New and Known Diabetes in Patients with Coronary Disease Enrolled in the NORSTENT Randomized Study

Excess Mortality in New and Known Diabetes

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Abstract

Background
NORSTENT trial randomized 9,013 patients to percutaneous coronary intervention with drug-eluting stents (DES) or bare-metal stents (BMS) with a 5-year follow-up. Among the patients, 5,512 had measured either fasting glucose level or percent glycated hemoglobin (HbA1c) at the index procedure. That cohort constitutes the present study population analyzing mortality and evaluating treatment heterogeneity of randomized stent in diabetic versus nondiabetic subgroups.

Results
The cohort consisted of 4,174 (75.7%) patients without diabetes, 716 (13.0%) with known diabetes, and 622 (11.3%) with no diabetes in history but elevated fasting glucose level >7.0 mmol/L or HbA1c >6.5% and therefore defined as new diabetes. Patients with known diabetes had a significantly increased all-cause (hazard ratio [HR] 1.99, 95% CI 1.51–2.62, $p < 0.001$), cardiac (subhazard ratio [SHR] 2.47, 95% CI 1.55–3.93, $p > 0.001$), and noncardiac (SHR 1.74, 95% CI 1.23–2.44, $p = 0.002$) mortality after adjustment for baseline variables. In the follow-up of 5 years, patients with new diabetes, however, had a marginally increased all-cause (HR 1.40, 95% CI 1.01–1.93, $p = 0.043$) and significantly increased noncardiac mortality (SHR 1.52, 95% CI 1.06–2.20, $p = 0.025$), but no increase in cardiac mortality (SHR 1.06, 95% CI 0.53–2.12), $p = 0.86$) after the same adjustment. The majority of the mortality was cardiac in the first 1–2 years after intervention; thereafter, noncardiac mortality dominated. However, the time period for when noncardiac mortality became the dominating cause varied considerably and significantly between the groups. There was no heterogeneity in mortality in response to randomized stent between diabetics and nondiabetics.

Conclusion

Known diabetes has increased cardiac and noncardiac mortality in contrast to new diabetes which is only associated with increased noncardiac mortality during the 5-year follow-up. Diabetic and nondiabetic patients have the same response to the treatment with BMS or DES.

Keywords

Coronary artery disease; Coronary intervention; Diabetes mellitus; Mortality

Introduction

Diabetes has been found to be a risk factor for death and myocardial infarction in many studies of coronary artery disease [1–6]. The Norwegian Coronary Stent Trial (NORSTENT) randomized 9,013 patients with coronary disease to treatment with drug-eluting stents (DES) or bare-metal stents (BMS) (ClinicalTrials.gov number, NCT00811772) [7]. There was no significant difference between DES and BMS for the main composite end point of death of any cause and nonfatal spontaneous myocardial infarction [7] but a consistent effect of DES on reducing the rate of target lesion revascularization (TLR) [8]. In the main study, 5,512 patients had fasting glucose level or percent glycated hemoglobin (HbA1c) measured and recorded at the index procedure and constitute the population for this study. The aim of this sub-study was to analyze the all-cause, cardiac, and noncardiac mortality in new diabetes and known diabetes compared to nondiabetic patients from that cohort during a median follow-up time of 5 years and to evaluate whether the effect of treatment of DES versus BMS on mortality differs in diabetic versus nondiabetic patients.

Methods

NORSTENT was a multicenter, randomized trial comparing long-term effects of DES versus BMS. The methods and study protocol have previously been reported. Patients were included in the study from September 15, 2008, to February 14, 2011. NORSTENT was an "all-comer" trial with broad inclusion criteria and few exclusion criteria. Clinical follow-up was performed according to the routine practice at each center. There were no per protocol follow-up visits, and follow-up coronary angiography was not routinely performed.

The manual for definitions and classifications of outcomes was provided in the online suppl. Appendix to the main study. All outcomes were adjudicated by an end point committee consisting of clinical and interventional cardiologists and an epidemiologist blinded for the patients' treatment assignment. The median follow-up time was 5 years.

All the patients were prescribed aspirin at a daily dose of 75 mg indefinitely and clopidogrel at a daily dose of 75 mg for 9 months after the procedure regardless of the randomized assignment or the indication for PCI. Drugs for secondary prevention were prescribed according to the current guidelines.

At the index procedure, 5,512 patients had fasting glucose or HbA1c levels measured and constitute the cohort for these analyses. Among them, 716 (13.0%) had known diabetes from the medical history and 622 patients (11.3%) had no known diabetes but had either fasting glucose above 7.0 mmol/L or HbA1c above 6.5% or both and were subsequently diagnosed as new diabetes. In the group with new diabetes, 303 patients (5.5%) had fasting glucose above 7.0 mmol/L and 319 (5.8%) had HbA1c above 6.5%, leaving a total of 4,174 patients without diabetes. The rates of mortality (all-cause, cardiac, and noncardiac) were analyzed in the 3 groups, including a possible interaction effect of randomized stent.

Statistical Analyses

Continuous covariates were tested with the skewness and kurtosis test for normality, and tests between groups were performed with ANOVA or Kruskal-Wallis test accordingly. Categorical variables were tested with Fisher's exact test or χ^2 test in case of excessive permutations.

Multivariable analyses accounting for baseline differences were performed with the Cox proportional hazard regression method for all-cause mortality and competing risk regression for cardiac and noncardiac deaths. The regression models were developed based on directed acyclic graphs (DAGs) created at daggity.net [9, 10] and by evaluating confounding, which was defined as more than 10% change in the exposure variable by an added covariate. Continuous variables were tested for linearity in log hazard by quartile plots and evaluated with fractional polynomials for best fit. The proportional hazard assumptions were evaluated by a test based on Schoenfeld residuals, by log-log survival plots, and by interaction with time and time-split at different points of time. The presence of important heterogeneity in the treatment effect of DES versus BMS on mortality across the cohorts of diabetic patients was assessed by including treatment-subgroup interactions as cross-product terms in the model, requiring $p < 0.01$ for claiming significance due to many comparisons. Missing values were substituted with multiple imputations. Royston-Parmar model for competing risks was employed to visualize the variation in time of the ratio between cardiac and noncardiac mortality. The point in time after the procedure when noncardiac mortality exceeded cardiac mortality was calculated from the model and differences in these points of time between the groups evaluated by bootstrap samples. Robust standard errors were used in the regression models. All analyses were performed in STATA v.14 (Collage Station, TX, USA) with the stpm2cr module in STATA for calculating Royston-Parmar models.

Results

Univariable Analyses

Among the 9,013 patients randomized into the study, 5,512 had fasting blood glucose or HbA1c levels measured at the time of the index procedure and constitute the population analyzed. The distribution of baseline variables between the 3 groups is given in Table 1. Both diabetic groups differed from the nondiabetic patients in practically all baseline variables including indications for the index procedure. Table 2 depicts stent-, lesion-, and procedure-related variables in the cohort of patients with only one treated lesion. Known diabetic patients had a higher percentage of stable coronary disease, fewer cases with STEMI, fewer with visible thrombus, and less use of GPI.

Table 1.

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Baseline characteristics in new diabetes, known diabetes, and no diabetes

Variable	New-onset diabetes (*n*= 622)	Known diabetes (*n*= 716)	No diabetes (*n* = 4,174)	*p*value
Age, mean±SD, years	63.7±10.6	63.5±10.3	62.2±10.8	<0.001
Gender (male), %	74.9	71.9	75.0	0.21
Current smoker, %	34.7	26.8	36.5	<0.001
BMI, kg/m^2	28.2±4.5	29.1±5.0	26.7±3.9	<0.001
Treated hypertension, %	44.1	66.9	37.3	<0.001
Treated hyperlipidemia, %	54.8	72.8	52.0	<0.001
Previous MI, %	11.1	14.3	8.8	<0.001
Previous stroke, %	4.3	5.2	3.4	0.04

Baseline characteristics in new diabetes, known diabetes, and no diabetes

Variable	New-onset diabetes (*n*= 622)	Known diabetes (*n*= 716)	No diabetes (*n* = 4,174)	*p*value
Previous CABG, %	8.0	12.7	4.7	<0.001
Creatinine, µmol/L	78.7±18.9	82.2±38.0	77.9±25.3	0.13
One-vessel disease, %	59.3	54.1	60.5	<0.001 [§]
Two-vessel disease, %	27.5	26.4	27.9	
Three-vessel disease, %	13.2	19.6	11.5	
HbA1c, %	6.5±1.0	7.6±1.5	5.8±0.32	<0.001
Fasting glucose, mmol/L	7.9±1.8	8.9±3.0	5.6±0.64	<0.001
Indication for index procedure				
Stable coronary disease, %	29.2	36.4	27.3	<0.001 [§]
Unstable angina, %	11.0	14.0	10.9	
NSTEMI, %	29.7	27.5	32.4	
STEMI, %	30.0	22.1	29.5	
CKMB before procedure, mean±SD, IU/L	34±77	21±61	32±114	<0.001
Troponin T before procedure, mean±SD, ng/L	748±1,908	512±1,525	567±1,627	<0.001

Variables tested for equality between groups using ANOVA or Kruskal-Wallis test for continuous variables and χ^2 or Fisher's exact test for categorical variables.

Table Footnotes

- [§]For the whole distribution of diseased vessels/indications for index procedure.

Table 2.

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Baseline stent-, lesion-, and procedure-related variables in new diabetes, known diabetes, and no diabetes*

Variable	New-onset diabetes (*n* = 436)	Known diabetes (*n* = 473)	No diabetes (*n* = 2,826)	*p*value
Stent length, mean±SD, mm	22.3±12.6	20.8±11.1	21.2±11.2	0.10
Stent diameter, mean±SD, mm	3.19±0.48	3.14±0.51	3.16±0.48	0.14
Delivery pressure bars, mean±SD	15.8±2.4	16.1±2.7	16.0±2.6	0.40
Ostial lesion, %	6.9	3.2	5.3	0.034

Baseline stent-, lesion-, and procedure-related variables in new diabetes, known diabetes, and no diabetes*

Variable	New-onset diabetes (*n* = 436)	Known diabetes (*n* = 473)	No diabetes (*n* = 2,826)	*p*value
Visible thrombus, %	31.9	19.9	27.9	<0.001
Visible calcification, %	21.1	22.4	19.0	0.15
Bifurcation lesion, %	17.2	9.9	13.6	0.006
Chronic occlusion, %	3.2	3.6	2.6	0.38
Lesion type, %				
A	6.7	13.3	12.4	0.011§
B1	42.4	44.6	43.0	
B2	26.2	26.2	23.7	
C	24.8	24.8	20.9	
Degree of stenosis, mean±SD, %	89.0±11.9	86.7±12.3	88.4±12.1	0.001
TIMI flow, %				
0	29.6	20.9	24.2	0.03§
1	3.9	3.4	3.9	
2	11.2	10.6	13.0	
3	55.3	65.1	59.0	
Use of GPI, %	23.4	15.6	22.7	0.001

GPI, glycoprotein IIb/IIIa inhibitor.

Table Footnotes

- *Patients with only one treated lesion. Variables tested for equality between groups using ANOVA or Kruskal-Wallis test for continuous variables and χ^2 or Fisher's exact test for categorical variables.
- §For the whole distribution of lesion types and TIMI flows.

During the index procedure, the total number of stented segments did not differ between the groups, with 1.4 ± 0.74 in new diabetes, 1.4 ± 0.79 in known diabetes, and 1.4 ± 0.73 in no-diabetes patients (p = 0.46). The total number of stents used to treat all lesions in the index procedure was practically identical in the groups with 1.6 ± 0.9 in new diabetes, 1.6 ± 0.9 in known diabetes, and 1.6 ± 0.9 in nondiabetic patients (p = 0.94).

Mortality Analyses

In the cohort of 5,512 patients with a median follow-up of 5 years, there were a total of 322 deaths with 25,593 patient-years at risk. Death was classified as cardiac in 92 (28.6%) patients and noncardiac in 230 (71.4%) patients (Table 3). Kaplan-Meier estimates of all-cause mortality over time in new diabetes, known diabetes, and no diabetes are depicted in Figure 1. The diabetic groups both had significantly higher mortality than the nondiabetic population.

Table 3.

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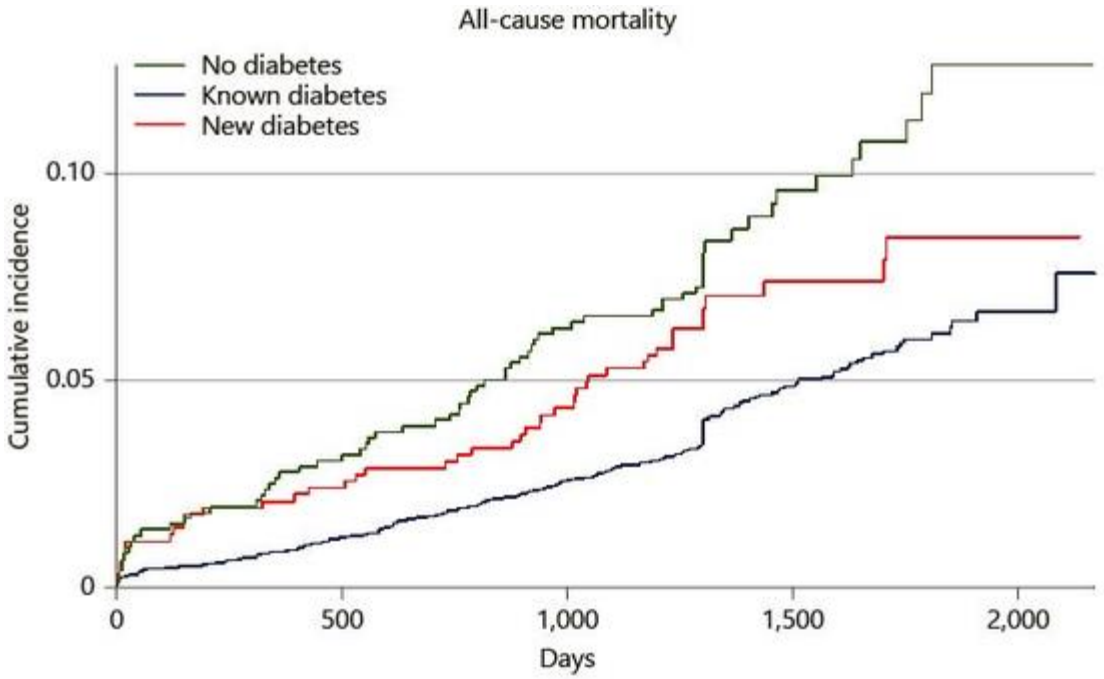
Distribution of death causes				
Death cause	**New diabetes, *n*(%)**	**Known diabetes, *n*(%)**	**No diabetes, *n*(%)**	***p*value**
Cardiac deaths	*n* = 10	*n* = 25	*n* = 57	
Within 28 days after spontaneous MI	7 (70)	10 (40)	22 (38.6)	
Within 28 days after procedure-related MI	0	0	1 (1.8)	
Sudden unexpected	1 (10)	13 (52)	26 (45.6)	
Noncoronary heart disease	2 (20)	2 (8)	8 (14.0)	0.24*
Noncardiac deaths	*n* = 36	*n* = 44	*n* = 150	
Hemorrhagic stroke	2 (5.6)	0	4 (2.7)	
Nonhemorrhagic stroke	0	2 (4.6)	4 (2.7)	
Stroke unspecified	2 (5.6)	1 (2.3)	1 (0.7)	
Other cardiovascular deaths	2 (5.6)	4 (9.1)	6 (4.0)	
Noncardiovascular deaths	24 (66.7)	35 (79.6)	129 (86.0)	
Unknown cause	6 (16.7)	2 (4.6)	6 (4.0)	0.029*
Deaths from all-cause	*n* = 46	*n* = 69	*n* = 207	

Table Footnotes

- Fisher's exact test for the total distribution of cardiac and noncardiac deaths.

Fig. 1.



All-cause mortality is given by a Kaplan-Meier failure estimate. The figure is estimated with no diabetes, new diabetes, and known diabetes as the only covariates. Both new diabetes (p = 0.005) and known diabetes ($p < 0.001$) have a significantly higher all-cause mortality rate than no-diabetes patients, with a nonsignificant difference between the diabetic groups (p = 0.14).

All-Cause Mortality

With markedly different baseline variables, adjustments for the effect of diabetes on outcomes were conducted through the creation of DAGs from all baseline covariates in Table 1. These analyses revealed that total adjustment was achieved by including age and BMI in the mortality analyses. The same covariates were the only ones with a confounding effect above 10% on the coefficients for diabetes.

The Cox model for all-cause mortality is shown in Table 4 for unadjusted model, age adjusted model, and multivariable adjusted model according to the results of DAG. No significant interaction was found between new (p = 0.05) or known diabetes (p = 0.15) and randomized stent, and there was no indication of violation of proportional hazard assumption. In the multivariable model, both new diabetes and, to a larger extent, known diabetes had a significant impact on subsequent all-cause mortality (Table 4). All covariates in Table 2 concerning procedure-related characteristics were tested for confounding in the model, and no covariate affected the coefficients of the diabetic groups more than minimally (maximum 2.9% change in diabetes coefficients).

Table 4.

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HRs for all-cause mortality using Cox proportional hazard regression models

Variable	Unadjusted HR (95% CI) *p*value	Age-adjusted HR (95% CI)	Multivariable-adjusted model HR (95% CI)*
No diabetes	1 (reference)		
New diabetes	1.52 (1.10–2.09)0.011	1.33 (0.97–1.84)0.077	1.40 (1.01–1.93)0.043

HRs for all-cause mortality using Cox proportional hazard regression models

Variable	Unadjusted HR (95% CI) *p*value	Age-adjusted HR (95% CI)	Multivariable-adjusted model HR (95% CI)*
Known diabetes	2.01 (1.53–2.64)<0.001	1.90 (1.45–2.49)<0.001	1.99 (1.51–2.62)<0.001

HR, hazard ratio.

Table Footnotes

- *Multivariable model from directed acyclic graph evaluation of estimation total effect of diabetes on all-cause mortality. The analyses revealed age and BMI as the only covariates necessary to adjust for (all baseline variables assessed).

Cardiac Mortality

A competing risk regression model with noncardiac mortality as the competing risk was used to evaluate the effect of diabetes on cardiac mortality. The DAG and confounders for cardiac mortality were identical to that for all-cause mortality and in the multivariable model age and BMI were adjusted for. In Table 5, unadjusted, age adjusted, and multivariable adjusted models are given. In the multivariable model, the interactions between new and known diabetes and randomized stent were not significant (p = 0.63 and 0.25, respectively), and none of the covariates were significant when interacted with time. In the multivariable model, new diabetes showed no evidence of excess cardiac mortality while known diabetes had a considerable and highly significant excess cardiac mortality (Table 5), and the difference between the effect of known versus new diabetes was significant (subhazard ratio [SHR] 2.32, 95% CI 1.11–4.84, p = 0.025). Covariates from Table 2 were tested for confounding in the model with minimal impact on the diabetes coefficients (maximum modification 4.3%).

Table 5.

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SHRs for cardiac and noncardiac mortality using competing risk regression models*

Variable	Unadjusted SHR (95% CI) *p*value	Age-adjusted SHR (95% CI)	Multivariable-adjusted model SHR (95% CI)§
Cardiac mortality			
New diabetes	1.18 (0.60–2.31)0.63	1.05 (0.53–2.07)0.89	1.06 (0.53–2.12)0.86
Known diabetes	2.59 (1.62–4.14)<0.001	2.43 (1.52–3.90)<0.001	2.47 (1.55–3.93)<0.001
Noncardiac mortality			
New diabetes	1.64 (1.14–2.36)0.008	1.45 (1.00–2.09)0.050	1.52 (1.06–2.20)0.025
Known diabetes	1.74 (1.25–2.44)0.001	1.64 (1.17–2.29)0.004	1.74 (1.23–2.44)0.002

SHR, subhazard ratio.

Table Footnotes

- *No diabetes was used as reference group (SHR = 1) in all analyses.
- §Multivariable model from directed acyclic graph evaluation. The analyses revealed age and BMI as the only covariates necessary to adjust for (all baseline variables assessed) for both cardiac and noncardiac mortality.

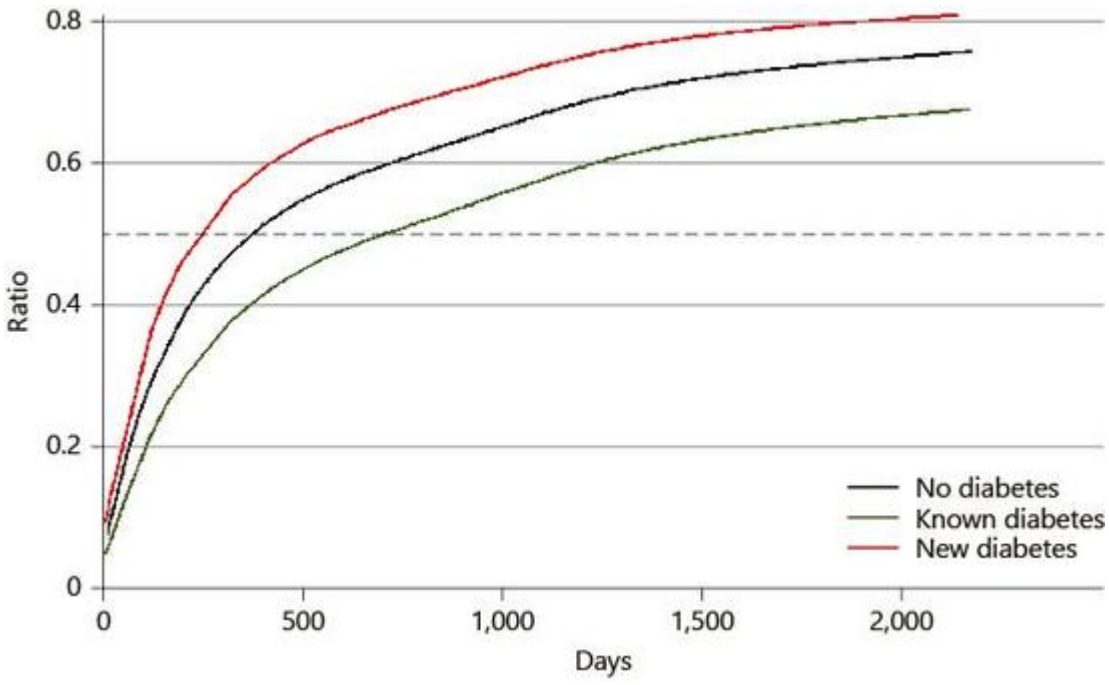
Noncardiac Mortality

A competing risk regression model with cardiac mortality as the competing risk was used to analyze noncardiac mortality with the results given in Table 5. The DAG and confounders indicated the same covariates for optimal adjustment as in all-cause mortality and cardiac mortality. In the multivariable model, the interaction with DES/BMS was borderline significant for known diabetes ($p = 0.01$) and not significant for new diabetes ($p = 0.06$).

The interaction between known diabetes and randomized stent implied an increase in the noncardiac mortality with the use of BMS which was regarded as a biologically improbable result and thus considered spurious. Interaction of new diabetes with time was significant ($p = 0.015$), but the time varying SHR/year was close to one (0.9999), and thus, the interaction deemed to be of no practical importance. It was therefore not included in the analyses. The other covariates showed no indication of variation in time. The multivariable model showed a significant increase in noncardiac mortality both in new (SHR 1.52, 95% CI 1.06–2.20, $p = 0.025$) and known diabetes (SHR 1.74, 95% CI 1.23–2.44, $p = 0.002$).

In Figure 2, the ratios of cumulative incidence functions for noncardiac mortality to all-cause mortality are given for the 3 groups calculated from a Royston-Parmer model with age and BMI as additional covariates. The ratio for cardiac mortality from this figure is one minus the ratio for noncardiac mortality. From 500 bootstrap populations, the mean and 95% CI for the number of days taken for noncardiac mortality to exceed cardiac mortality was calculated for the 3 groups. For no diabetes, it lasted 497 days (95% CI 483–511 days), for new diabetes 255 days (95% CI 239–270 days), and known diabetes 834 days (95% CI 798–871 days). The differences in time between the groups were highly significant ($p < 0.01$, Kruskal-Wallis test).

Fig. 2.



Ratio of cumulative incidence functions of noncardiac to all-cause mortality from the Royston-Parmar model containing age and BMI as covariates in addition to new and known diabetes. Prediction done at median age and BMI above 25% percentile. Reference line at 0.5 indicating equal contribution of noncardiac and cardiac mortality, and cardiac mortality equals one minus the ratio given in the figure.

Discussion

The 2 main observations from this study are increased mortality in diabetic patients and no interaction between stent type and diabetes. Numerous studies in different clinical settings have shown diabetes as a risk factor for increased mortality [1–6, 11, 12], which our study corroborates (Fig. 1; Table 4). However, by being able to divide diabetes in new and known and mortality in cardiac and noncardiac, a more complex pattern was revealed (Table 5). Increased mortality was demonstrated in both groups; however, only known diabetes but not new diabetes had significantly increased cardiac mortality.

At admission for index procedure, 716 patients had known diabetes and 622 patients had no history of diabetes but fulfilled the usual criteria for diabetes by fasting glucose or HbA1c levels. Strictly speaking, the latter group is not necessarily new onset diabetes as the exact time for the debut of diabetes is unknown. However, the group is definitely newly diagnosed diabetes, and we hypothesized that this group on average would have had diabetes for a shorter period of time than patients with known history of diabetes and probably also at the time a lighter affection of the diabetic state as judged by lower values of HbA1c and fasting glucose level (Table 1). By comparing these groups, early changes in mortality rates of diabetic patients could possibly be detected. Data from such analyses are sparse and have previously been called for [13]. In Figure 2, the ratio of noncardiac to all-cause mortality is depicted for the 3 groups, and cardiac mortality is one minus the given ratio in the figure. Cardiac mortality dominates in the first year which is reasonable to expect in a population with coronary disease severe enough to warrant invasive examination and treatment. However, already after about 1-year noncardiac mortality is the more frequent cause of death. This fact has implications for cardiac interventional studies and is a strong argument for including causes of death in such studies. Not in the least because it is a substantial and highly significant difference in time for when the shift of mainly cardiac to mainly noncardiac mortality happens in different subgroups. These observations with short-term domination of cardiac mortality seem to be at odds to what were reported by Wang et al. [14] but may be due to different populations compared as they reported on insulin-treated type 2 diabetes.

Tables 1 and 2 indicate considerable baseline differences between the groups of interest, giving support to use multivariable models for comparisons. Typically, the values of the covariates for new diabetes are between those of no diabetes and known diabetes. Using DAGs or evaluating confounding yielded identical results concerning the adjustment of the effects of the diabetic groups. The models revealed a significant increase in noncardiac mortality both in new and known diabetes compared to nondiabetic patients, but no increase in cardiac mortality in new diabetic patients as opposed to a rather large increase in cardiac mortality in known diabetic patients. However, the confidence interval for new diabetes was somewhat wide and a type II error cannot be completely ruled out.

It is intriguing that the augmented risk of mortality for noncardiac reasons is present “at the beginning” of the diabetic state, while increased cardiac mortality seems to need time of presence of the diabetic state for developing. When causes of death are broken down further, the numbers become too small for making inferences (Table 3). Increased risk of cancer in diabetes has been reported before [15–17] as well as noncancer noncardiovascular death [12]. The mechanisms for the relation between cancer deaths and diabetes are debated [15], but the early occurrence as in our data could perhaps indicate a common genetic disposition or multifaceted exposure for the development of diabetes and cancer. Increased cardiac mortality,

however, seems to be dependent on the presence of the diabetic state for some time to develop and could be due to accelerating the atherosclerotic process as we suggested more than 30 years ago [11]. The increased all-cause and cardiac mortality in known diabetes was still present even after adjusting for variables describing the lesion treated. This comparison was done in the cohort with just one lesion treated to be able to know exactly what was "adjusted for." We interpret this observation as differences in lesion characteristics, and treatments cannot explain the subsequent increased cardiac mortality in known diabetes.

There was a significant difference in the distribution of indications for treatment between the groups, with less STEMI and more stable coronary disease in known diabetes. This observation may also be interpreted as less tendency to thrombotic lesions and increased propensity to atherosclerotic lesions in known diabetes. In concert with this is the observation of less-frequent visible thrombus in lesions in patients with known diabetes. However, the indication for treatment was not a significant predictor for mortality when entered into the multivariable models nor a confounder of the coefficients for the diabetic groups.

We found no interaction between stent type and diabetes on all-cause, cardiac, or noncardiac mortality. Previously we have also reported a lack of interaction between stent type and diabetes concerning TLR [8]. Thus, in our experience, diabetes is not an important factor in the evaluation of when to use DES or BMS, whether the decision is based on mortality or TLR. Although diabetes is reported as a risk factor for mortality and TLR [18–20], no studies to our knowledge has reported a significant interaction between stent type and diabetes.

There are several limitations to the study. First, it is a post hoc subgroup analysis with the inherent consequence of being solely hypothesis generating. A number of comparisons are made, and individual *p*values must be viewed with caution. As in some other large studies [12, 21], we do not have data on type of diabetes, but in a cohort like ours recruited based on presence of coronary disease with mean age above 60 years, the vast majority of patients would have type 2 diabetes. In addition, we do not have the exact duration of diabetes in the 2 groups, but consider it a reasonable assumption that patients with "new diabetes" on the average would have had diabetes in a shorter period of time than patients with known diabetes. Furthermore, no data on the impact of glycemic control during follow-up is available. It should also be underlined that our population is not a normal population but one with coronary artery disease severe enough to warrant intervention.

In conclusion, both new and known diabetes have an increased noncardiac mortality. This propensity seems to be present at the time of the appearance of the diagnosis. On the other hand, known diabetes but not new diabetes has increased cardiac mortality during the 5-year follow-up, maybe indicating that cardiac mortality is dependent on a time-consuming process like accelerating atherosclerosis induced by the diabetic state to occur. We did not observe any meaningful heterogeneity in the response to type of stent used and subsequent mortality between diabetic and nondiabetic patients.

Statement of Ethics

The trial was approved by the Norwegian Regional Committee for Medical and Health Research Ethics-Region North (reference number REKNORD 40/2008). All the patients provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have contributed significantly to the analyses and interpretation of the data as well as well as approval of the final version of the article.

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iThe corrections made in this section will be reviewed by journal production editor.

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