Diabetes-related Mortality in Adults with Cystic Fibrosis

Role of Genotype and Sex

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Abstract

Rationale: Diabetes is associated with increased mortality in cystic fibrosis. Aggressive screening and early institution of insulin treatment significantly reduced this risk over the period of 1992–2008.

Objectives: To determine if progressive improvement in cystic fibrosis–related diabetes (CFRD) mortality has continued since 2008, and examine associations with *CFTR* genotypes linked to pancreatic insufficiency and to sex.

Methods: Chart review was performed on 664 patients followed from 2008 to 2012.

Measurements and Main Results: Overall mortality for patients with CFRD was 1.8 per 100 person-years, compared with 0.5 in patients with CF without diabetes ($P = 0.0002$); neither rate changed significantly from mortality reported for 2003–2008. Genotype

impacted both mortality and diabetes risk: adults with severe *CFTR* genotypes experienced greater mortality at every age older than 32 years than those with mild genotypes ($P = 0.002$), and the risk of developing CFRD was also greatly increased in those with severe genotypes (prevalence 60% in adult patients with severe vs. 14% in adults with mild mutations). CFRD had a direct influence on mortality because it was associated with increased risk of death within each genotype category (20 vs. 2%, $P = 0.007$ for mild; 12 vs. 4%, $P = 0.012$ for severe). There was also a sex difference in adults with severe *CFTR* genotypes; both mortality and CFRD prevalence were higher at every age in females than males.

Conclusions: Despite substantial improvement over time, mortality for CFRD patients greater than 30 years remains higher than for patients with CF without diabetes.

Keywords: cystic fibrosis–related diabetes; sex differences; prognosis; survival

Cystic fibrosis–related diabetes (CFRD) is the most common comorbidity in persons with cystic fibrosis (CF). Beginning with a University of Minnesota (UMN) report in 1988 (1), several investigators documented that the additional diagnosis of diabetes was associated with increased mortality, and that women with CFRD were at particularly high risk for early death (2–5).

Those with CFRD, like all patients with CF, almost always die from pulmonary failure rather than from the macrovascular and microvascular disease associated with death in persons with types 1 and 2 diabetes. Diabetes has been directly implicated in the pathophysiology of CF lung function decline, related to both the catabolic effect of insulin insufficiency on nutritional

status and muscle mass (6–10) and the proinflammatory, proinfection impact of chronic hyperglycemia on lung function (11, 12).

In 2009, we published a report in *Diabetes Care* that examined temporal trends in CFRD mortality (13). Using the large UMN CF database, three consecutive time intervals were compared: 1992–1997,

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At a Glance Commentary

Scientific Knowledge on the

Subject: Aggressive diabetes screening and management since the early 1990s has greatly reduced diabetes-associated mortality in persons with cystic fibrosis.

What This Study Adds to the

Field: The most recent data, contained in this report, demonstrate that despite early detection and excellent diabetes control, diabetes is still associated with a greater risk of death. Patients with cystic fibrosis-related diabetes were more likely to have severe *CFTR* genotypes, but both *CFTR* genotype severity and cystic fibrosis-related diabetes were found independently to associate with mortality. Diabetes increased the risk of death in both men and women, but had a more pronounced effect in men, eliminating the protective effect of male gender seen in the nondiabetic cystic fibrosis population.

1998–2002, and 2003–September 15, 2008. Over this span, there was a significant and steady decline in the risk of death associated with CFRD. In the earliest period, 1992–1997, mortality was 13.4 times greater in individuals with CF who had diabetes compared with those without, and this difference was particularly evident in women. During 1998–2002, the mortality rate associated with CFRD declined, especially in men and in youth, but was still 9.0 times greater in individuals with CFRD compared with those without diabetes. By 2003–2008, the situation had dramatically improved. Although mortality was still 3.5 times greater in individuals with CFRD, this difference was only significant in patients older than 30 years, and excess mortality in women relative to men with CFRD had disappeared.

In the 2009 manuscript, we postulated that the decline in diabetes-associated pulmonary mortality over this 16-year interval was related to institution of rigorous oral glucose tolerance test (OGTT) screening and early intervention with insulin therapy. We further hypothesized that with more time the gap in survival between adult patients with CF with and without diabetes would

diminish, as a younger generation of patients who had received early and intensive diabetes treatment matured. The current analyses were performed to build on the previous study by adding data from the most recent time period, September 16, 2008–December 31, 2012, to determine if progressive improvement in CFRD mortality has continued, and by examining effects of CF transmembrane conductance regulator (*CFTR*) genotype and sex on CFRD and mortality.

Some of these data were presented in symposium sessions at the annual meetings of the American Thoracic Society (San Diego, CA, May 2014) and the North American Cystic Fibrosis Conference (Atlanta, GA, October 2014); results were not published on either occasion.

Methods

CFRD Diagnosis and Management

Patients with CF are seen at the UMN CF Center at quarterly intervals, and clinical data are recorded in the Minnesota CF Database. Diabetes is diagnosed by standard criteria as previously described (14). Annual OGTT was instituted at UMN in the 1990s for patients with CF aged 6 years and older. Before 2003, the most common insulin regimen for patients with fasting hyperglycemia was a single injection of NPH (neutral protamine Hagedorn) insulin at bedtime and three to four injections of regular insulin (before 2000) or four to six injections of rapid-acting insulin (after 2000) with meals and snacks. Since 2003, basal-bolus insulin therapy has been routinely prescribed, with a single daily injection of basal insulin plus multiple injections of rapid-acting insulin to cover meals, or use of an insulin pump. Patients with diabetes without fasting hyperglycemia were not usually treated with insulin before 2003. Since approximately 2005, they have been routinely prescribed either premeal rapid-acting insulin or a single daily injection of basal insulin. For the last decade, hospitalized patients are treated with insulin if they are hyperglycemic for more than 48 hours; the need for persistent insulin therapy is reevaluated once they are clinically well.

Database Review

Clinical information was reviewed from consenting patients with CF of all ages

followed at the UMN CF Center from September 16, 2008–December 31, 2012. All but two patients seen in the CF clinic during this interval gave informed consent permitting their records to be reviewed for research purposes ($n = 664$; 99.7%). The age-adjusted mortality rate per 100 patient-years was determined for this cohort and compared with earlier, previously reported patient data from 1992–2008.

In addition, because CFRD is most common in adults, mortality rates per person and per 100 patient-years for the current time period were calculated for patients aged 20 years and older, and analyzed by CFRD and genotype status. Further analyses were performed to assess the impact of sex.

Finally, because the risk of diabetes-associated mortality in CF only becomes apparent after age 30 and to compare similarly aged patients, patients with CF with and without diabetes who had severe genotypes were compared at the beginning of two high-risk age decades: 30–39 years ($n = 137$) and 40–49 years ($n = 51$). CFRD patients who survived were also compared with CFRD patients who died during these decades. All patients seen during either of these age decades were included; 29 patients contributed data in both decades. Patients diagnosed with diabetes before or during the decade were included in the CFRD group. Age, outpatient percent-predicted FEV₁ and FVC, body mass index (BMI), HbA_{1c}, and lung transplant status were taken from the measurement closest to the beginning of the decade for each patient; for most patients this was within 2 years. Duration of diabetes, if applicable, and final lung transplant status were determined at the time of death, the end of the age decade (40 or 50 yr), or December 31, 2012, whichever came first.

Genetic Classification

CFTR genotypes were classified as severe or mild by first classifying the mutations reported for each of the component *CFTR* alleles. *CFTR* mutations were classified based on the predicted effect on gene expression (e.g., nonsense mutation, splice junction) or protein function, and using the rate of pancreatic insufficiency among individuals with that genotype in the CFTR2 study (15). Mutations were classified as severe if at least 80% of

individuals who carry that mutation, in *trans* with another known severe *CFTR* mutation, have been shown to have pancreatic insufficiency (16, 17) or if the predicted effect on *CFTR* gene expression is that little to no functional protein would be expressed. Mutations were classified as mild based on conferring pancreatic sufficiency (in *trans* with a known severe *CFTR* mutation) or conferring milder *CFTR* dysfunction. Mutations reported to confer intermediate rates of pancreatic exocrine insufficiency and/or delayed-onset pancreatic insufficiency were classified as intermediate. Eight mutations were not able to be classified based on data in the CFTR1 and CFTR2 databases including one mutation that did not match a known *CFTR* mutation (4095 + 1G>T) and was unable to be confirmed using available source documents; these and the intermediate mutations were labeled “unclassified.” Patients with both *CFTR* alleles having severe mutations (severe/severe) were considered to have a severe genotype, whereas those with at least one mild mutation (severe/mild or mild/unclassified or mild/unknown or mild/mild) were considered to have a mild genotype. Patients with severe/unclassified, severe/unknown, unclassified/unclassified, and unknown mutations were “unclassified.” Table E1 in the online supplement lists the classification of *CFTR* mutations observed in our sample of adult patients with CF, aged 20 and over.

Statistical Methods

Mortality rates per person were estimated by percent and compared by chi-square or Fisher exact test. Mortality rates per 100 patient-years were estimated using Poisson regression models; rates are presented with 95% confidence intervals, or with standard errors for comparison with previously published results (13). Survival curves were estimated by the product-limit (Kaplan-Meier) method and compared by log-rank tests. Comparisons for patients with CF with and without diabetes in the age decades of 30s and 40s were performed for each decade separately, using observations closest to the start of each age decade for each patient; continuous outcomes were compared with two-sample *t* tests, whereas categorical outcomes were compared by chi-square or Fisher exact test. Means $\pm$ standard errors are reported in the text. Computations were done using SAS

Version 9.4 (2012; SAS Institute, Cary, NC); graphs were prepared using R (2014; R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>).

Results

CF Mortality, Total Population (All Ages)

For the current period, overall age-adjusted mortality for patients with CFRD was 1.8 per 100 person-years, compared with 0.5 in patients with CF without diabetes ($P = 0.0002$) (Table 1). This represented a 3.5-fold increase in per-person mortality in those with CFRD (14 vs. 4%; $P = 0.0001$) (Table 2). This was not significantly different than rates we reported for 2003–2008 (13). CF mortality rates by age decade, sex, and CFRD status for the current period and for previously reported periods going back to 1992 are shown in Figure 1 (13).

The increased mortality rate in adult CFRD patients seemed to be age related. Among those aged 30 and older, patients with CF with diabetes had significantly higher age-adjusted mortality than those with no diabetes (4.7 vs. 1.1; $P = 0.003$) (Table 1). Those under age 30 may have had similarly increased mortality rates compared with those without CFRD (1.0 vs. 0.3; $P = 0.064$), but this did not achieve

statistical significance, perhaps because of low death rates in this young age group. Stratifying by sex, there were higher mortality rates among males with CFRD compared with males without diabetes (1.8 vs. 0.1; $P = 0.003$), but a suggested increase in females was not statistically significant (1.8 vs. 1.0; $P = 0.143$). These age and sex differences were similar to those observed during 2003–2008 (Table 1).

Relations among Mortality, CFRD, Genotype, and Sex

Population survival data in adults. Because CFRD rates are strongly dependent on *CFTR* genotype (occurring much less frequently among people with genotypes conferring pancreatic exocrine sufficiency), we examined whether the effect of CFRD on mortality rates in adults could be confounded by *CFTR* genotype severity. Among 462 patients age 20 and older, 314 (68%) had a *CFTR* genotype classified as severe and 72 (16%) had a genotype classified as mild; 76 (16%) individuals had genotypes that were not classified (conferred intermediate rates of pancreatic insufficiency, unknown/no data on pancreatic insufficiency rates, or subjects with missing *CFTR* genotype information), and they were excluded from genotype analyses. See Table E1 for a listing of the specific mutations in each category.

Table 1. Age-adjusted Temporal Trends in Mortality Associated with CFRD at the University of Minnesota over Four Time Intervals

	1992–1997 (n = 752)	1998–2002 (n = 702)	2003–9/15/2008 (n = 647)	9/16/2008–2012 (n = 664)
Total population				
CFRD	4.9 (3–8)*	3.5 (2–5)*	1.9 (1–3)*	1.8 (1–3)*
No CFRD	0.5 (0.3–0.9)	0.5 (0.3–0.9)	0.8 (0.6–1.2)	0.5 (0.3–0.9)
Males				
CFRD	4.0 (2–8)*	2.9 (2–5)*	2.0 (1–3)*	1.8 (1–3)*
No CFRD	0.4 (0.2–0.8)	0.2 (0.1–0.6)	0.8 (0.4–1.3)	0.1 (0.01–0.6)
Females				
CFRD	5.6 (3–10)*	3.9 (2–6)*	1.8 (1–3)	1.8 (1–3)
No CFRD	0.7 (0.4–1.3)	1.0 (0.5–1.7)	1.0 (0.5–1.7)	1.0 (0.5–1.9)
Patients <30 yr of age				
CFRD	4.1 (2–7)*	1.9 (1–3)*	0.9 (0.5–1.8)	1.0 (0.5–2.1)
No CFRD	0.4 (0.2–0.8)	0.3 (0.1–0.6)	0.4 (0.2–0.8)	0.3 (0.1–0.8)
Patients ≥30 yr of age				
CFRD	7.0 (3–14)*	8.7 (5–14)*	5.3 (4–8)*	4.7 (3–7)*
No CFRD	1.0 (0.4–2)	1.8 (1–3)	2.4 (1–4)	1.1 (0.5–2.6)

Definition of abbreviation: CFRD = cystic fibrosis–related diabetes.

Values are age-adjusted mortality rate per 100 person-years (95% confidence interval). Rates were compared between CFRD and no-CFRD patients for each characteristic and time period. The results in the first three columns, 1992–9/15/2008, were previously reported (13).

*Significant differences.

Table 2. Current Mortality Rates per Person and per 100 Patient-Years for Adults Aged 20 and Over, by Genotype and CFRD Status

	Patients (n)	Person-Years	Deaths (n)	Mortality Rate per Person (%)	P Value	Mortality Rate per 100 Person-Years (95% CI)	P Value
No CFRD (all)	241	831	9	4	0.0001	1.0 (0.4–2)	0.001
CFRD (all)	221	809	30	14		4.8 (3–8)	
Mild genotype					0.007		0.038
No CFRD	62	220	1	2		0.5 (0.1–3)	
CFRD	10	35	2	20		5.7 (1–22)	
Severe genotype					0.012		0.027
No CFRD	126	442	5	4		1.1 (0.5–3)	
CFRD	188	689	23	12		3.3 (2–5)	

Definition of abbreviation: CI = confidence interval; CFRD = cystic fibrosis–related diabetes.

There were 76 subjects (16% of total population, 23 of whom had CFRD) who had an unclassified *CFTR* genotype and are not included in this analysis.

CFTR genotype severity was found to correlate with mortality in adult patients with CF aged 20 and older during the current period as demonstrated by Kaplan-Meier survival curves (Figure 2A). Patients with severe genotypes experienced higher cumulative mortality at every age over 32 than those with mild genotypes (log-rank test; $P = 0.002$). The estimated survival curve for females with a severe *CFTR* genotype differed significantly from males (log-rank test; $P = 0.041$). There was no sex difference in survival in those with a mild genotype, and thus these are presented as a single group (Figure 2A). For females with a severe genotype, cumulative mortality after age 30 was consistently higher than in those with a mild genotype; for males with a severe genotype, this increase began about 5 years later, about age 35 (Figure 2A).

CFRD prevalence in adults. Figure 2B shows Kaplan-Meier estimates of CFRD age prevalence for adult patients with CF age 20 and older during the current period. These curves follow a pattern that is quite similar to the survival curves shown in Figure 2A. Almost half (48%) of adult patients with CF age 20 and older had CFRD, consistent with what we have previously reported for the UMN CF population. However, as seen in Figure 2B, the age prevalence of CFRD differed significantly by genotype and sex.

In the adult population, the overall observed prevalence of CFRD in those with severe *CFTR* genotypes was greater than in those with mild genotypes (60% vs. 14%; $P < 0.0001$). Among those with severe genotypes, the proportion of adult females with CFRD was higher at every age than the proportion of males (log-rank test;

$P = 0.0008$) (Figure 2B). Although severe genotype was equally prevalent in adult males and females (81.4% vs. 81.3%; $P = 0.972$), 66% of females with a severe genotype developed CFRD compared with 54% of males with a severe genotype ($P = 0.024$). Thus, a severe genotype increased the risk of CFRD by a factor of about four in males and five in females.

Prevalence of diabetes increased dramatically with age. For example, during their fifth decade (age 40–49 yr), the observed prevalence of diabetes during the years 2008–2012 was 83% in women with severe genotypes (19 of 23 women) and 64% in men with severe genotypes (18 of 28 men). In the same age group, among those with a mild genotype the prevalence of CFRD was much lower, albeit higher than would be expected in the general population of lean similarly-aged adults (20%; 3 of 15 individuals). There was no difference in CFRD prevalence between males and females with mild genotypes, although the number of cases was small ($P = 0.501$).

Mortality rates within genotype category. Severe *CFTR* genotype was associated with both decreased survival and increased prevalence of diabetes, and thus there may be an indirect relation between CFRD and risk of death. To explore the question of whether diabetes is directly related to mortality, we examined the correlation between mortality rates and CFRD within each genotype category among the 462 adult patients with CF aged 20 and older during the current period. Across genotypes, CFRD was associated with significantly increased risk of death (14 vs. 4%; $P = 0.0001$), and this was true when considering each genotype category separately: 20 versus 2%, $P = 0.007$,

a 10-fold increase for mild; 12 versus 4%, $P = 0.012$, a threefold increase for severe (Table 2). Thus, CFRD associated with mortality rates independently of *CFTR* genotype severity.

Comparison of Severe-Genotype Patients with CF with and without CFRD in High-Risk Age Decades 30–39 and 40–49 Years

To examine associations with the higher mortality seen in CFRD patients age 30 and older, we compared severe-genotype patients with CF with and without diabetes in the age decades 30–39 ($n = 137$) and 40–49 ($n = 51$) years, using measurements from the beginning of each decade so that patients would be compared at approximately the same age (Table 3). This comparison was restricted to the severe-genotype patients because while those with a mild genotype made up about half of the non-CFRD group, less than 7% of CFRD patients in these age decades had a mild genotype. At the beginning of each decade there was no difference in BMI or FEV₁ between patients with CF with and without diabetes, although in 40 year olds, those with diabetes had a lower FVC (74 ± 3 vs. 87 ± 4 ; $P = 0.029$) and were more likely to have had a lung transplant by the end of the decade than patients without diabetes (24% vs. 0%; $P = 0.046$). The transplant data may be difficult to interpret because almost all patients with CF who have had a transplant at UMN have diabetes; if they do not have it before transplant they develop it afterward when they are treated with glucocorticoids and calcineurin inhibitors.

We also compared characteristics of CFRD patients who survived with those who died in the decades 30–39 and 40–49 years

Figure 1. University of Minnesota mortality rates per 100 patient-years for cystic fibrosis (CF) patients with and without diabetes (DM) by sex and age decade over four time periods: 1992–1997; 1998–2002; 2003–September 15, 2008; and September 16, 2008–2012. Patients with CF with DM are shown with *solid lines*, and patients with CF without DM are shown with *dashed lines*. Females are shown in *red* and males in *blue*. The bottom three panels were previously published in *Diabetes Care* (13).

(see Table E2). Diabetes was well controlled in both survivors and those who died with average HbA_{1c} levels of about 6.4%. Duration of diabetes was the same between each group in each decade. As might be expected, lung function was worse in those who died. In both decades, mortality in patients with CFRD was not associated with genotype (although almost all patients with diabetes had a severe genotype) or rate of lung transplantation.

Discussion

After decades of dramatically improving survival associated with careful screening

and early insulin treatment of CFRD, no further progress was seen in this most recent analysis. Although substantially better than earlier time periods, the mortality rate for patients with CF with diabetes was unchanged from that observed at UMN in 2003–2008, and for patients older than 30 years, remained significantly greater than that of patients with CF without diabetes. Patients with severe *CFTR* genotypes had both worse survival and greatly increased risk of developing diabetes, so mutation severity likely has an indirect impact on the relation between CFRD and mortality. There also seems to be a direct impact of CFRD on survival, with greater risk of death in patients with CFRD versus those

without diabetes in both the mild and severe *CFTR* genotype groups. Diabetes increased the risk of death in both men and women, but had a more pronounced effect in men, essentially erasing the protective effect of male sex seen in the CF population without diabetes so that men and women with diabetes had an equal mortality rate.

CFRD is a clinically insidious disease that usually is only detected by screening. Until the last several years, routine systematic screening was not common in the United States, and patients may have had undiagnosed diabetes for years. Even after diagnosis, it was not common practice to treat early diabetes (diabetes without fasting hyperglycemia) until the Cystic

Figure 2. (A) Kaplan-Meier estimates of survival curves for adult cystic fibrosis patients age 20 and older during the current period, divided into three groups: all with mild genotype, males with severe genotype, and females with severe genotype. Vertical dashes indicate patients still alive at last visit (censored), and the number of patients under observation at each age decade is shown at the bottom. (B) Kaplan-Meier estimates of cystic fibrosis–related diabetes (CFRD) prevalence by age for adult cystic fibrosis patients age 20 and older during the current period, divided into three groups: all with mild genotype, males with severe genotype, and females with severe genotype. Vertical dashes indicate patients without CFRD at last visit (censored).

Fibrosis Related Diabetes Therapy Study established in 2009 that insulin therapy could reverse chronic weight loss in this population (18). Both insulin insufficiency and hyperglycemia have a negative impact on CF lung disease and nutritional status (19). With modern basal-bolus insulin therapy, hyperglycemia is often relatively easy to control in patients with CFRD because, much like patients with type 1 diabetes in the honeymoon stage of the disease, they still produce significant amounts of endogenous insulin. Thus, in recent years there has been hope that early institution of insulin replacement could end diabetes-related pulmonary decline by reversing insulin insufficiency and reducing hyperglycemia. Until the current analysis, UMN saw progressive improvement in CFRD mortality, highlighting the clinical importance of this

approach (13). However, there have not been additional survival gains since 2008.

The cause of this persistent negative impact of diabetes on survival in CF is not clear. HbA_{1c} was equally good in CFRD patients who died and those who survived, and duration of diabetes was no different. Lung function was worse at the ages of about 30 and 40 years in CFRD patients who subsequently died, but it is not surprising that sicker patients would have greater mortality, and the specific role of diabetes is unclear. It is likely, however, that even well-controlled diabetes adds an additional inflammatory burden that together with CF-related pulmonary inflammation creates greater risk of death for these patients.

Among the nearly 2,000 *CFTR* mutations reported in the CF Mutation Database, at least 127 disrupt *CFTR*

biosynthesis or function and thereby cause CF (15). Among the CF disease-causing *CFTR* mutations, there is variation in the severity of the resulting *CFTR* dysfunction, which is associated with the severity of exocrine pancreatic insufficiency (20, 21). We chose to classify *CFTR* mutations by the risk of pancreatic exocrine insufficiency because long-term pancreatic sufficiency and the milder *CFTR* mutations associated with it confer a reduced risk of CFRD (16, 22). In addition, milder *CFTR* mutations are found more frequently among long-term survivors with CF (23). Therefore, we believed that *CFTR* genotype severity needed to be included in the analyses of CFRD and mortality. Both *CFTR* genotype severity and CFRD were found independently to associate with mortality in this study. It should be

Table 3. Comparison between Severe-Genotype Patients with CF with and without CFRD during Age Decades of 30–39 and 40–49 for the Period of September 16, 2008 to December 31, 2012

	Age 30–39 yr			Age 40–49 yr		
	CFRD	No CFRD	P Value	CFRD	No CFRD	P Value
Sample size, n	91	46		37	14	
Body mass index, kg/m ²	22.6 ± 0.4	23.5 ± 0.6	0.209	22.8 ± 0.6	23.3 ± 0.9	0.596
% predicted FEV ₁	63 ± 2	66 ± 3	0.851	56 ± 4	63 ± 6	0.328
% predicted FVC	80 ± 2	83 ± 3	0.499	74 ± 3	87 ± 4	0.029
Transplant at start, %	7	2	0.267	16	0	0.165
Transplant by study end, %	14	8	0.349	24	0	0.046

Definition of abbreviation: CFRD = cystic fibrosis–related diabetes.

Age, body mass index, outpatient percent-predicted FEV₁ and FVC, and lung transplant status are from the observations closest to the start of each age decade. Transplant at study end refers to lung transplant status at the time of death, final follow-up visit, the end of the age decade (40 or 50 yr) or December 31, 2012, whichever came first. Data are expressed as rate (95% confidence interval), mean ± standard error, or percent; P values compare CFRD with no CFRD within each decade.

emphasized that the association of *CFTR* genotype classification with mortality applies to the groups of *CFTR* genotypes as classified, and should not be extrapolated to any individual genotypes or to individuals carrying particular genotypes.

Where do we go from here to reduce CFRD-associated mortality? With OGTT screening and currently available diabetes therapies now maximized, it is unlikely that we can further improve diabetes metabolic control in this population. However, there might be a CF-specific approach to this problem on the horizon. Recent data suggest there may be an intrinsic defect in β -cell function in CF. *CFTR* is expressed in human and mouse pancreatic α and β cells, and *CFTR*

conductance has been measured in mouse β cells (24, 25). Whether *CFTR* plays a role in insulin secretion is unknown. New classes of drugs have been developed to “correct” or “potentiate” *CFTR* function. A small pilot project provided the first evidence in humans that potentiation of *CFTR* may increase insulin secretion (26), providing a potential novel mechanism for preventing or treating diabetes. Further study is necessary to confirm this relation and to determine if these new drugs will have a long-term impact on diabetes-associated mortality.

In conclusion, despite extensive efforts over the last decade to maximize diabetes management and achieve tight metabolic control, the mortality rate for patients with

CFRD older than 30 years remains higher than that of patients with CF without diabetes, and after several years of dramatically improving survival statistics, now seems to be “stuck” at about 1.8 per 100 person-years. Although this highlights the need to remain vigilant about detecting and aggressively treating diabetes, it is clear that new approaches to tackling this problem are needed if diabetes-associated mortality is to be further reduced. It will be interesting to see if new therapies that correct the basic CF chloride channel defect will impact the consequences of diabetes in this population. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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