Potential Implications of Coronary Artery Calcium Testing for Guiding Aspirin Use Among Asymptomatic Individuals With Diabetes

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OBJECTIVE—It is unclear whether coronary artery calcium (CAC) is effective for risk stratifying patients with diabetes in whom treatment decisions are uncertain.

RESEARCH DESIGN AND METHODS—Of 44,052 asymptomatic individuals referred for CAC testing, we studied 2,384 individuals with diabetes. Subjects were followed for a mean of 5.6 ± 2.6 years for the end point of all-cause mortality.

RESULTS—There were 162 deaths (6.8%) in the population. CAC was a strong predictor of mortality across age-groups (age <50, 50–59, ≥60), sex, and risk factor burden (0 vs. ≥1 additional risk factor). In individuals without a clear indication for aspirin per current guidelines, CAC stratified risk, identifying patients above and below the 10% risk threshold of presumed aspirin benefit.

CONCLUSIONS—CAC can help risk stratify individuals with diabetes and may aid in selection of patients who may benefit from therapies such as low-dose aspirin for primary prevention.

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Although diabetes has been considered a coronary heart disease (CHD) risk equivalent (1), not all individuals with diabetes carry equivalent risk. Coronary artery calcium (CAC), a marker of atherosclerosis, has been shown to independently predict cardiovascular events as well as enhance risk stratification in patients with diabetes (2–5). Although recent guidelines recommend consideration of CAC testing for risk assessment in adults with diabetes ≥40 years (6), we sought to evaluate whether CAC effectively stratifies individuals with diabetes across age, sex, and risk factor (RF) burden. This question is particularly important given recent guidelines recommending selected use of aspirin in patients with diabetes based on underlying CHD risk (7).

RESEARCH DESIGN AND METHODS

The study cohort consisted of 44,052 asymptomatic individuals without known CHD referred for CAC screening. There were 2,384 (5.4%) individuals with diabetes by self-report. Details for RF collection have been described previously (8). All subjects underwent CAC scoring at baseline and were followed for a mean of 5.6 ± 2.6 years (median 5 years, range 1 to 13 years) for the primary end point of all-cause mortality verified using the Social Security Death Index. Annualized all-cause mortality rates were estimated by dividing number of deaths by number of person-years at risk.

The population was stratified into the following age-groups: <50, 50–59, and ≥60 years. Additionally, individuals were stratified into high-, intermediate-, and low-risk subgroups (based on age/sex and presence of additional RF) per recent guidelines detailing aspirin use in patients with diabetes as follows: *1*) high risk (10-year cardiovascular disease [CVD] risk >10%: 'aspirin is reasonable'): men ≥50 and women ≥60 with 1 or more RF; *2*) intermediate risk (10-year CVD risk 5–10%: 'aspirin might be considered'): men ≥50 and women ≥60 without RF and men <50 and women <60 with RF; and *3*) low risk (10-year CVD risk <5%: 'aspirin should not be recommended'): men <50 and women <60 without RF (7).

RESULTS

Mean age of the 2,384 study subjects was 58 ± 11 years; 52% were men. A total of 500 participants (21%) were <50 years old, 863 (36%) were age 50–59, and 1,021 (43%) were at least 60 years old. A total of 535 individuals (22%) had CAC = 0, whereas 779 (33%) and 1,070 (45%) had CAC 1–100 and >100, respectively. Overall, there were 162 deaths (6.8%). CAC was a strong predictor of mortality in each age-group (expressed in deaths/1,000 person-years with 95% CI): age <50, CAC 0: 0; CAC 1–100: 7.8 (3.7–16.3); CAC >100: 18.2 (9.1–36.4); age 50–59, CAC 0: 3.2 (1–10.1); CAC 1–100: 7.3 (3.9–13.5); CAC >100: 16.6 (11.1–24.7); and age ≥60, CAC 0: 9.9 (4.4–22); CAC 1–100: 19.2 (12.5–29.5); CAC >100: 33.1 (26.7–41).

Notably, all individuals ≥60 years with ≥1 RF had a mortality rate >10 deaths/1,000 person-years.

Table 1 presents mortality rates by CAC score according to estimated 10-year CVD

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Table 1—*All-cause mortality rates by CAC score according to estimated 10-year CVD risk per the recent aspirin use guidelines* (based on age, sex, and presence of RFs)*

Predicted 10-year CVD risk per guidelines	Number of individuals (%)	Number of deaths (%)	Mortality rate/1,000 person-years at risk	95% CI for rate
Low risk (<5%) "aspirin not recommended"	89			
CAC = 0	38 (42.7)	0	0	—
CAC 1–100	35 (39.3)	1 (2.9)	5.75	0.81–40.83
CAC >100	16 (18)	3 (18.8)	39.42	12.72–122.24
Intermediate risk (5–10%) "aspirin to be considered"	979			
CAC = 0	288 (29.4)	3 (1)	2.29	0.74–7.09
CAC 1–100	370 (37.8)	10 (2.7)	6.24	3.36–11.59
CAC >100	321 (32.8)	27 (8.4)	20.37	13.97–29.71
High risk (>10%) "aspirin reasonable"	1,316			
CAC = 0	209 (15.9)	6 (2.9)	6.59	2.96–14.67
CAC 1–100	374 (28.4)	26 (7)	16.32	11.11–23.97
CAC >100	733 (55.7)	86 (11.7)	28.60	23.15–35.33

*Risk classification according to recent guidelines for aspirin use in patients with diabetes (7): *1*) high risk (10-year CVD risk >10%: 'aspirin is reasonable'): men ≥50 and women ≥60 with 1 or more RF; *2*) intermediate risk (10-year CVD risk 5–10%: 'aspirin might be considered'): men ≥50 and women ≥60 without RF and men <50 and women <60 with RF; and *3*) low risk (10-year CVD risk <5%: 'aspirin should not be recommended'): men <50 and women <60 without RF.

risk category using criteria from the recent aspirin use guidelines. It is noteworthy that within the low and intermediate risk groups, we observed that individuals with CAC >100 had a mortality rate of >10 deaths/1,000 person-years, consistent with a recommendation for aspirin therapy. Additionally, absence of CAC among high-risk individuals translated into a low risk of 6.59 deaths/1,000 person-years.

CONCLUSIONS—We have shown that CAC measurements may help risk stratify patients with diabetes across age-group, sex, and RF burden. Most individuals with diabetes <60 years of age have a low near-term risk of <5 deaths/1,000 person-years when CAC = 0. Additionally, we have shown that most individuals with CAC >100 have a mortality rate of >10 deaths/1,000 person-years. We have also demonstrated that individuals with diabetes ≥60 years have a mortality rate of >10 deaths/1,000 person-years, regardless of CAC score, when at least one other RF is present.

Although diabetes is defined by some guidelines as a CHD risk equivalent, the use of aspirin for primary prevention among individuals with diabetes remains controversial. Given the conflicting data, a consensus group recently provided updated recommendations concluding that patients with diabetes with a 10-year CVD risk >10% should receive low-dose aspirin for primary prevention (7), further emphasizing the importance of enhanced risk stratification among individuals with diabetes.

CAC has the potential to identify individuals who are at higher risk and thus might benefit from aspirin (based on a 10-year CVD risk >10%) and who may not otherwise be identified by age and RF-based risk estimates. Additionally, among individuals identified as high risk by age and RF (10-year CVD risk >10% and thus recommended for aspirin), 16% had CAC = 0, which translated into a mortality rate of <10 deaths/1,000 person-years; this suggests that even among individuals classified as high risk by age and RF, absence of CAC can identify individuals with a 10-year CVD risk <10%, whose risk of bleeding from aspirin may outweigh potential benefit.

The main limitation of our data is the use of all-cause mortality in place of CVD event rates. Although most deaths in patients with diabetes are cardiovascular in origin, many CVD events do not result in death. This would predominantly lead to event rate underestimation. Self-reported RF is an additional limitation. Although the absence of continuous risk variables may represent an additional limitation, the use of categorical RF data has been validated as a method of risk stratification (9).

In conclusion, CAC has the ability to help risk stratify individuals with diabetes across age-group, sex, and RF burden and may help identify individuals who may benefit from more aggressive therapy, such as low-dose aspirin, for primary prevention. Our study also points to individuals with diabetes who likely will not benefit from CAC testing, namely those ≥60 years with additional RF, because their 10-year CVD risk is >10%. Although our study is informative, definitive recommendations must come from clinical outcomes trials where treatment decisions are driven by CAC-based risk stratification.

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