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Invited commentary

Not all diabetic patients were created equal: How to discriminate risk?

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The debate as to the true risk of patients suffering from diabetes mellitus type 2 has been alive since the original publication by Haffner et al. in which the authors suggested that asymptomatic diabetic patients have the same cardiovascular risk of patients from the general population with prior myocardial infarction [1]. The ATP-III embraced this notion and classified all diabetic patients at the highest risk independent of all other markers of peril [2]. But, is it really true that all diabetic patients were created equal? Or is it appropriate to also risk stratify these patients according to a series of discriminating criteria? The article by Yeboah et al. [3] in a previous issue of the journal suggests that the latter may be a more desirable approach than one based on the simple assumption that risk is equal for all patients affected by a certain disease. Indeed, we have seen prior publications in which 15–25% of diabetic patients harbored no subclinical atherosclerosis, as assessed by coronary artery calcium (CAC) screening, and these patients suffered an event rate as low as patients without diabetes [4–7]. On the other hand, presence of coronary calcium and its progression are harbingers of a poor prognosis in diabetes mellitus [5]. However, is the use of cardiovascular imaging truly worth the cost and risk for the patients to achieve better risk stratification? The notion that risk can be differentiated among diabetic patients is examined in the paper published by Yeboah et al. in this issue of Atherosclerosis [3]. The investigators of two international cohort studies (Multi Ethnic Study of Atherosclerosis – MESA- and Heinz Nixdorf Recall – HNR-study) utilized traditional risk factors as well as C-reactive protein (CRP), CAC score, carotid intima media thickness (cIMT), and ankle brachial index (ABI) to devise a new risk model to estimate risk of incident cardiovascular events in asymptomatic diabetic patients. Of the 1343 patients included in the analyses, 85 (6.3%) suffered an event during a follow-up period of 8.5 years. This is already an indirect proof of the fact that not all diabetic patients are at high-risk according to ATP-III (i.e. >20% at 10 years) since the estimated event rate was merely 7.5% at 10 years [3]. Of note, the new ACC/AHA guidelines on the assessment of cardiovascular risk suggest a risk of 7.5% at 10 years as a cutoff to differentiate low vs high-risk [8]. In the article by Yeboah et al. [3] CAC was the best predictor of events among the non-traditional risk markers taken singly. The investigators then proceeded to select the variables in their combined cohorts that best predicted a hard outcome to develop a new model. Once they identified the following variables: age, sex, systolic blood pressure, duration of diabetes and log CAC score they compared their new model to the two most frequently used risk prediction models for diabetes mellitus, the UKPDS and the Framingham Risk Score. They determined that the new model had incremental predictive value over the previous ones (area under the curve ~0.76 for the new model compared to ~0.69 for the older models). Additionally, the new model demonstrated superior reclassification of risk compared to the older models, allowing approximately 20% of the patients to be reclassified to a higher or lower risk category. The same proportion of ~20% was reclassified if the MESA-HNR score was compared to the score introduced by the very recent ACC/AHA recommendations [8]. When compared to the ATP-III assumption that all diabetic patients are at high-risk the MESA-HNR score allowed reclassification of 74% of the patients. Pending the necessary external validation of the MESA-HNR score, the natural conclusion seems to be that the new method is superior and should be implemented above and beyond all others. Furthermore, the performance of any of the older models improved once CAC was inserted in the model and the new MESA-HNR

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includes CAC. The addition of different demographic and clinical variables improved the ability of CAC to predict events only marginally (AUC for model with CAC alone vs CAC and other variables: 0.74 vs 0.76). This suggests that CAC assessment alone may help refine risk prediction to the same extent as the more complex model presented by the authors. Hence, CAC imaging may be all we need to better capture the heterogeneity of and discriminate risk among diabetic patients. But is it really that easy? The sad reality is that while the ATP-III [2] would have misclassified over 90% of MESA-HRN cohort low-risk diabetic patients as high-risk, it would not have missed any of the high-risk patients. The MESA-HNR score on the contrary ranked as low to intermediate risk 77% of the patients who eventually suffered an event [3]. We are faced again with the same quandary: should we choose a model with high sensitivity and low specificity (ATP-III recommendations), or one with low sensitivity and high specificity (MESA-HNR score)? What is preferable when screening for a disease with high morbidity such as diabetes mellitus? The authors conclude that in the current environment of cost containment and concern with radiation exposure an all-inclusive approach that recommends treating all diabetic patients with statins is preferable. But should we treat all diabetic patients with aspirin, statins, ACE-inhibitors, drugs for aggressive glycemic control and diet when the majority of them may not need them or may not need them for a long time? Are we to be concerned about the cost of CT imaging and risk of radiation exposure and not or more than the cost of treatments and their side effects and the potential risk of unnecessary therapies? "*Primum non nocere*" (first do no harm) is the principle we swore to observe in our profession but the impression of the writers is that often we interpret this notion wrongly: we feel we would hurt our patients by not intervening on a possible risk rather than choosing wisely the individual who needs it most. The "hope" for the potential benefit of our intervention should not induce us to underestimate the risk associated with it. Though data in diabetic patients are scanty, aspirin for primary prevention is associated with an absolute 0.1% risk reduction of cardiovascular events at the cost of 2 cases per 1000 patient-year of major bleeding [9]. Statins may have a more favorable risk-to-benefit profile since their use is associated with a 1–2% absolute risk reduction of cardiovascular events and an incidence of 3.4 cases per 100,000 patient-years of rhabdomyolysis [9]. But is it clear what statins cause as side effect in diabetic patients? Finally, recent data prompted the European Medicines Agency (EMA) to endorse restrictions on the concomitant use of drugs that act on the renin–angiotensin–aldosterone system due to the risk of hyperkalemia, and declining renal function (http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/05/WC500167421.pdf).

The authors of this editorial are convinced that the presence of subclinical atherosclerosis could be a useful marker to identify patients at greater risk and in greater need of intervention "now". However a few aspects need to be elucidated before recommending subclinical atherosclerosis screening. What is the preferable tool for subclinical atherosclerosis assessment? Should it be a tool that assesses functional or morphologic damage of the arterial tree [10]? In light of the multiple factors that may cause an instantaneous perturbation of the arterial function, it is likely that a morphological assessment such as CAC measurement may provide a more accurate assessment of the cumulative risk exposure for the single individual. This might explain why duration of diabetes mellitus (although self reported) but not Ankle Brachial Index (ABI) was identified as a meaningful variable for the MESA-HNR model. What is the best recording site for subclinical atherosclerosis evaluation? How long is the warranty period of a negative result such as "zero" CAC score? Is this approach safe and cost-effective? While fueling the debate on how to stratify risk in diabetic patients, Yeboah and coworkers shed some light on the potential utility of subclinical disease screening for personalized medicine. However, further confirmation is needed before this approach is embraced in daily practice. Until future data become available, we ought to face the "Innocent Prisoner's dilemma": free with suspicion of guilt, or jailed while innocent? Is it better to expose our patients to unnecessary cardiovascular risk (by not treating) or to an unnecessary risk associated with interventions (treat them all)?

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