Endocr (2008) 33:225–229
DOI 10.1007/s12020-008-9083-9

ORIGINAL PAPER

Coronary artery disease screening in patients with diabetes

Vincent Savarese · Intekhab Ahmed · Barry J. Goldstein

Received: 3 March 2008 / Accepted: 27 June 2008 / Published online: 26 November 2008

Abstract Coronary artery disease (CAD) is the most common cause of death in patients with diabetes. Many diabetics have asymptomatic CAD, and may benefit from early diagnosis. We review the recent literature to evaluate whether the current evidence supports screening for CAD in asymptomatic diabetics. Currently, no single screening modality has shown sufficient accuracy to determine which patients will have significant CAD. The combination of imaging modalities may show promise in improving the accuracy of screening, and limited data suggest that screening in this population may be associated with improved outcomes. However, based on the current evidence we presently do not recommend screening for CAD in this population.

Keywords Diabetes · CAD · Silent myocardial ischemia · Screening

Introduction

Despite advances in prevention and treatment of cardiovascular events in diabetics in recent years, cardiovascular disease remains the most common cause of death among patients with diabetes mellitus. With treatments for primary and secondary prevention of CV events available such as aspirin, statins, and ACE inhibitors, and interventions for acute coronary syndromes (PCI, CABG), clinicians have numerous tools at their disposal for prevention and treatment of these devastating complications. Diabetes is clearly a very common disease: a recent epidemiologic study estimated lifetime prevalence rates of approximately 33% for men and 39% for women [1]. Additionally, diabetics have a very high risk for cardiovascular complications: it is estimated that up to 80% of diabetics will develop macrovascular disease, and that diabetic patients have a risk of myocardial infarction and stroke two times higher than that of the general population [2]. Furthermore, many patients with diabetes have unrecognized coronary artery disease (CAD), which may progress to what is called silent myocardial ischemia (SMI). Since diabetics are more likely to have autonomic nervous system dysfunction, they may not experience typical anginal pain symptoms that are common indicators of obstructive CAD in non-diabetics. SMI has been reported to be more than twice as common in diabetics than in non-diabetics [3]. SMI is fairly common among diabetics: recent studies estimate that 18–60% of diabetics without typical symptoms of myocardial ischemia have evidence of CAD on perfusion imaging [4–7]. Therefore, because of the large number of asymptomatic patients who are at risk for cardiovascular complications, a great many patients may stand to benefit from early diagnosis of CAD.

Previous ADA guidelines recommended screening asymptomatic diabetic patients with known risk factors for CAD [8]. However, because of shortcomings in noninvasive screening that may lead to false positive results, further invasive testing and potential complications, and the lack of data to show that screening asymptomatic diabetics for CAD improves patient outcomes, widespread screening of asymptomatic diabetics for CAD is currently not recommended by the ADA [9]. Newer noninvasive screening modalities (coronary artery calcium scanning,

V. Savarese · I. Ahmed · B. J. Goldstein (✉)
Department of Medicine, Division of Endocrinology, Diabetes and Metabolic Diseases, Jefferson Medical College, 6th Floor, 211 South 9th Street, Philadelphia, PA 19107, USA
e-mail: Barry_Goldstein@merck.com

ultrasound for carotid intima media thickness) may add to our current ability to evaluate coronary anatomy and the extent of atherosclerosis. While it is not clear that intervention in asymptomatic diabetics improves cardiovascular outcomes, a few investigators recently have suggested that intervention may indeed be of benefit in asymptomatic diabetic patients who are found to have significant CAD [10, 11]. These findings raise several questions. Is there a role for screening for CAD in asymptomatic diabetics? Is there a group of patients who are more likely to benefit from intervention? In reviewing the recent literature on this subject, we will attempt to address these questions.

Prevalence of silent myocardial ischemia

Recent studies have reported a wide range of estimated prevalence for SMI. In the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects (DIAD) study, a large prospective study of 1,123 asymptomatic diabetics, 22% had evidence of SMI on adenosine stress myocardial perfusion imaging [4]. Similarly, Rajagopalan et al. [5] found 18% of 1,427 asymptomatic diabetic patients had high-risk findings on SPECT imaging, although a much higher percentage (58%) had an abnormal SPECT. Other studies have arrived at higher estimates: Zellweger et al. found 39% of patients had perfusion abnormalities on SPECT imaging [5], and Sconamiglio et al. found 60% of asymptomatic patients had evidence of perfusion defects on dypiridamole echocardiography [7]. Given the high lifetime prevalence of diabetes in the population noted above (33% for men, 39% for women [1]), the potential magnitude of this problem and therefore the need for ways of identifying patients who would benefit from screening is great.

Prevalence of angiographic CAD in SMI

Of asymptomatic diabetic patients with perfusion abnormalities on noninvasive imaging, how many will have angiographically proven significant coronary artery disease? Two of the above-mentioned studies addressed this question. Rajagopalan et al. [5] reported 61% of 127 asymptomatic diabetics with a high-risk SPECT had severe angiographic coronary disease. Sconamiglio et al. reported 60% of 1,899 asymptomatic patients with diabetes had perfusion defects on dipyridamole stress echocardiography, and of these, 65% had evidence of $\geq$50% stenosis on angiography. Taken together, 39% of their initial sample of asymptomatic subjects had angiographic evidence of significant CAD [7].

Can we identify patients likely to benefit from screening?

Traditional risk factors

A recent review by Cosson et al. points out that several traditional risk factors for CAD have been found in studies to be predictive of SMI: male gender, age, hypertension, dyslipidemia, smoking, and albuminuria. The authors further point out that no single risk factor seems to have sufficient predictive value, and that the total number of risk factors may be of use in this capacity [3]. Sconamiglio et al. evaluated whether the number of risk factors predicts rates of SMI. The investigators stratified 1,899 asymptomatic diabetics into two groups: those with one or fewer risk factors, and those with two or more. Risk factors used were dyslipidemia, hypertension, smoking, family history of premature CAD, and albuminuria. Rates of abnormal stress imaging (59.4% of for those with $\geq$2 RF vs. 60% for those with $\leq$1 RF) as well as rates of significant angiographically proven CAD on angiography (64.6% vs. 65.5%) were almost identical. Interestingly, while the number of risk factors did not predict incidence of SMI, the authors did observe that patients with two or more risk factors were more likely to have unfavorable anatomy (three-vessel disease, diffuse disease, vessel occlusion) [7]. These findings suggest that while traditional risk factors help in identifying which diabetic patients are more likely to develop cardiovascular complications, they do not clearly predict which patients will have subclinical or SMI, and thus may not be of great value in stratifying diabetic patients to be screened for SMI. Furthermore, the finding that more risk factors may predict unfavorable anatomy argues for the importance of identifying CAD in a subclinical stage.

Perfusion imaging

The most common method of evaluating patients for the presence of ischemic heart disease is perfusion imaging. Perfusion imaging has been shown to predict cardiac events in diabetics [12], and has been shown to have comparable sensitivity and specificity in diabetics and nondiabetics alike who undergo stress testing for suspicion of CAD. In a retrospective study by Kang et al. [13], among diabetic patients who had SPECT imaging and later underwent coronary angiography, sensitivity and specificity rates for SPECT were 86 and 56%, respectively, using an angiographic criterion of >50% stenosis, and 90 and 50%, respectively, using 70% as the cutoff. These results were similar to results with nondiabetic patients. However, this was a study of patients undergoing stress testing for suspicion of CAD, and thus may not be representative of a

screening population. In fact, perfusion imaging may be less useful in screening asymptomatic diabetics: in a review by Rutter and Nesto, the authors report poor sensitivity and negative predictive value of noninvasive testing that may lead to many false negative results [14]. Raggi et al. point out that event rates remain high even in patients with low-risk noninvasive imaging [15]. Given the limitations of noninvasive perfusion imaging noted earlier, some investigators have examined alternative screening modalities in the hope of finding additional ways to help identify patients at high risk for CAD. The two most studied imaging modalities are coronary artery calcium (CAC) scanning by cardiac computed tomography and assessment of carotid intima-media thickness (CIMT) by ultrasound.

Coronary artery calcium

Cardiac CT has been used increasingly in recent years as another way to noninvasively assess coronary atherosclerosis. As opposed to perfusion imaging which shows coronary vessel stenosis, CAC scanning is largely used to detect atherosclerotic plaque, not necessarily stenosis. CAC scoring may be useful in identifying diabetic patients with subclinical or SMI by identifying patients with large atherosclerotic burden who might be at increased risk for cardiac events but who may not have hemodynamically critical stenoses, and hence may not be identified by noninvasive stress imaging. CAC is thought to be an accurate marker of atherosclerotic burden and, in fact, several studies have shown an association between CAC scores and cardiac events [16–18].

Several investigators have examined the association between CAC and stress perfusion imaging. Ramakrishna et al. studied CAC and perfusion imaging in 835 patients in a retrospective study of patients who had undergone EBCT and SPECT within 3 months; 14% of their sample had diabetes. The authors report increasing proportion of high-risk perfusion imaging among patients with higher CAC scores: 18% of patients with severe CAC had high-risk SPECT compared to 4% of patients with normal CAC. They also report a weak but significant correlation between CAC and SPECT, and that each was independently predictive of mortality and combined death, MI, and late revascularization. Furthermore, they report a higher mortality rate in patients with the combination of high-risk SPECT and severe CAC (>400 AU). It should be noted, however, that this was not a screening population, and as such may not be truly representative of asymptomatic diabetic patients [19]. In a sample more representative of a screening population, Anand et al. evaluated CAC and SPECT perfusion imaging in 510 asymptomatic diabetics without known CAD. They performed perfusion scintigraphy in 127 patients who had CAC scores >100 AU (at least moderate atherosclerosis), as well as 53 patients with CAC <100 AU (at most mild atherosclerosis). The authors report increasing rates of perfusion abnormalities in patients with higher CAC scores: 18.4% in patients with mild CAC (10–100 AU), 22.9% for moderate CAC (101–400 AU), 48.3% for severe CAC (401–1000 AU), and 71.4% for extensive CAC (>1000 AU). They noted moderate-to-large perfusion defects in 31.5% of patients with CAC >100 AU, compared to 18.4% with CAC <100 AU [18]. These studies illustrate the point that coronary calcium scoring and stress imaging may give complementary information regarding risk stratification for SMI. However, we are unaware of any studies to date demonstrating an association between CAC, perfusion imaging abnormalities, and angiographic CAD in asymptomatic diabetic patients. Further studies are required to establish the sensitivity and specificity of utilizing a combination of CAC scanning and noninvasive stress imaging as an effective screening tool, but the combination of testing modalities may show promise.

Carotid intima-media thickness

The assessment of CIMT by ultrasound is an attractive method of noninvasively evaluating for the presence of atherosclerosis. Benefits of this method of screening are the relatively low cost of ultrasound and the noninvasive nature of the procedure and subsequently little risk of adverse events. Numerous studies have shown a relationship between CIMT and CV events [15]. In a review of recent literature on CIMT and coronary atherosclerosis, Bots et al. point out that clinical studies have shown only a modest relationship between CIMT and CAD, indicating variability between the two vascular beds [20]. No studies to our knowledge have examined a relationship between CIMT and SMI.

Is there any relationship between screening and outcomes?

As discussed earlier, SMI is prevalent among diabetics, and there is debate over the best way to identify the patients who would be most likely to benefit from early intervention. But is there evidence that intervention is beneficial to diabetic patients with documented silent myocardial ischemia? Until recently there has been little research to suggest that revascularization provided benefit to asymptomatic patients with diabetes. Because of their high risk of developing cardiovascular complications, diabetes is considered to be a CVD risk equivalent by the NHLBI Adult Treatment Panel III (ATP III) [21]. Based on evidence

from recent clinical trials [22–26], the ADA and AHA recommend aggressive treatment of hypertension, dyslipidemia, and hypercoagulability in diabetic patients, including those with and without established CVD [2]. Therefore, the knowledge that a patient has subclinical CAD may not change management in terms of medical therapy. It could be argued that knowing the CAD status of a diabetic patient may prompt more aggressive risk factor modification, but whether this is true has not been studied. Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are commonly used methods of revascularization in patients with CAD, and have been shown to improve outcomes in patients with acute coronary syndromes. However, until recently there has been little to suggest a benefit in patients with subclinical CAD in diabetics. Recent research has yielded mixed results regarding outcomes related to revascularization in asymptomatic diabetics. A recent large randomized trial comparing optimal medical therapy alone to optimal medical therapy plus PCI showed no benefit to PCI over a median follow-up of 4.6 years; 33% of the sample was diabetic [27]. Another recent study suggests that SMI in diabetics may be partly reversible. The DIAD study investigators performed repeat adenosine-stress myocardial perfusion imaging 3 years after initial perfusion imaging in 358 of the initial 522 participants (164 subjects did not have repeat imaging). They report that among 71 patients who initially had evidence of inducible ischemia, 79% showed resolution on retesting 3 years later [28]. On the other hand, however, two recent studies suggest that intervention in diabetics with SMI may indeed have a benefit in terms of cardiovascular events. In a retrospective, non-randomized study by Sorajja et al., investigators examined the benefit of PCI and CABG compared with medical therapy among 826 asymptomatic diabetics with abnormal SPECT imaging. The authors report a significant survival benefit from revascularization among patients with high-risk SPECT. The benefit appeared to be restricted to patients who underwent CABG: among the groups who underwent CABG, PCI, or medical therapy alone, the 5-year survival rates were 85, 72, and 67%, respectively [10]. In a small prospective, randomized study, Faglia et al. assigned 141 asymptomatic diabetics to either screening with exercise EKG test and dipyridamole stress echocardiography, or no screening. Patients with abnormality on either screening test underwent coronary angiography. Of 14 patients who underwent angiography, 4 underwent CABG and 4 underwent PCI. The patients were then followed for average 54 months and event rates were compared. Cardiovascular events were significantly fewer in the screening arm than in the nonscreening arm, with incidence rates of 1.4% per year in the screening group versus 5.6% in the control group [11]. These findings represent a relatively small pool of data suggesting a benefit from screening and/or intervention, and clearly further studies are needed to confirm these findings.

Conclusion

In conclusion, deciding whether to screen for CAD in diabetics without symptoms or a known history of CAD is quite challenging. Traditional risk factors (dyslipidemia, hypertension, smoking, albuminuria, age, gender), though predictive of future CV events, may not reliably identify patients likely to have SMI. Noninvasive imaging methodologies individually seem to lack diagnostic accuracy. And intensive medical therapy in most patients with diabetes in recent years has made the benefit of revascularization unclear. For these reasons screening for CAD in asymptomatic diabetics is not generally recommended. The benefit of combined noninvasive imaging modalities may be a promising future direction to help identify patients who may benefit from screening, but further studies are needed to illustrate their diagnostic accuracy. Finally, further studies are needed to establish whether or not revascularization is of benefit in diabetics with SMI.

References

1. K.M. Narayan, J.P. Boyle, T.J. Thompson, S.W. Sorensen, D.F. Williamson, Lifetime risk for diabetes mellitus in the United States. JAMA **290**, 1884–1890 (2003)
2. J.B. Buse, H.N. Ginsberg, G.L. Bakris, N.G. Clark, F. Costa, R. Eckel, V. Fonseca, H.C. Gerstein, S. Grundy, R.W. Nesto, M.P. Pignone, J. Plutzky, D. Porte, R. Redberg, K.F. Stitzel, N.J. Stone, Primary prevention of cardiovascular diseases in people with diabetes mellitus. A scientific statement from the American Heart Association and the American Diabetes Association. Circulation **115**, 114–126 (2007)
3. E. Cosson, J.R. Attali, P. Valensi, Markers for silent myocardial ischemia in diabetes. Are they helpful? Diabetes Metab. **31**, 205–213 (2005)
4. F.J. Wackers, L.H. Young, S.E. Inzucchi, D.A. Chyun, J.A. Davey, E.J. Barrett, R. Taillefer, S.D. Wittlin, G.V. Heller, N. Filipchuk, S. Engel, R.E. Ratner, A.E. Iskandrian; Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care **27**, 1954–1961 (2004)
5. N. Rajagopalan, T.D. Miller, D.O. Hodge, R.L. Frye, R.J. Gibbons, Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. J. Am. Coll. Cardiol. **45**, 43–49 (2005)
6. M.J. Zellweger, R. Hachamovitch, X. Kang, S.W. Hayes, J.D. Friedman, G. Germano, M.E. Pfisterer, D.S. Berman, Prognostic relevance of symptoms versus objective evidence of coronary artery disease in diabetic patients. Eur. Heart J. **25**, 543–550 (2004)

7. R. Scognamiglio, C. Negut, A. Ramondo, A. Tiengo, A. Avogaro, Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. J. Am. Coll. Cardiol. **47**, 65–71 (2006)
8. American Diabetes Association. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10–11 February 1998, Miami, Florida. Diabetes Care **21**, 1551–1559 (1998)
9. J.J. Bax, L.H. Young, R.L. Frye, R.O. Bonow, H.O. Steinberg, E.J. Barrett, Screening for coronary artery disease in patients with diabetes. Diabetes Care **30**, 2729–2736 (2007)
10. P. Sorajja, P. Chareonthaitawee, N. Rajagopalan, T.D. Miller, R.L. Frye, D.O. Hodge, R.J. Gibbons, Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging treated with coronary artery bypass grafting. Circulation **112**(suppl I), I-311–I-316 (2005)
11. E. Faglia, M. Manuela, Q. Antonella, G. Michela, C. Vincenzo, C. Maurizio, M. Roberto, M. Alberto, Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: an open-label randomized pilot study. Am. Heart J. **149**, 283.e1–283.e6 (2005)
12. S. Giri, L.J. Shaw, D.R. Murthy, M.I. Travin, D.D. Miller, R. Hachamovitch, S. Borges-Neto, D.S. Berman, D.D. Waters, G.V. Heller, Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. Circulation **105**, 32–40 (2002)
13. X. Kang, D.S. Berman, H. Lewin, R. Miranda, J. Erel, J.D. Friedman, A.M. Amanullah, Comparative ability of myocardial perfusion single-photon emission computed tomography to detect coronary artery disease in patients with and without diabetes mellitus. Am. Heart J. **137**, 949–957 (1999)
14. M.K. Rutter, R.W. Nesto, The changing costs and benefits of screening for asymptomatic coronary heart disease in patients with diabetes. Nat. Clin. Pract. Endocrinol. Metab. **3**, 26–35 (2007)
15. P. Raggi, A. Bellasi, C. Ratti, Ischemia imaging and plaque imaging in diabetes. Diabetes Care **28**, 2787–2794 (2005)
16. W. Qu, T.T. Le, S.P. Azen, M. Xiang, N.D. Wong, T.M. Doherty, R.C. Detrano, Value of coronary artery calcium scanning by computed tomography for predicting coronary heart disease in diabetic subjects. Diabetes Care **26**, 905–910 (2003)
17. P. Raggi, L.J. Shaw, D.S. Berman, T.Q. Callister, Value of coronary artery calcium screening in subjects with and without diabetes. J. Am. Coll. Cardiol. **43**, 1663–1669 (2004)
18. D.V. Anand, E. Lim, D. Hopkins, R. Corder, L.J. Shaw, P. Sharp, D. Lipkin, A. Lahiri, Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. Eur. Heart J. **27**, 713–721 (2006)
19. G. Ramakrishna, T.D. Miller, J.F. Breen, P.A. Araoz, D.O. Hodge, R.J. Gibbons, Relationship and prognostic value of coronary artery calcification by electron beam computed tomography to stress-induced ischemia by single photon emission computed tomography. Am. Heart J. **153**, 807–814 (2007)
20. M.L. Bots, D. Baldassarre, A. Simon, E. de Groot, D.H. O'Leary, W. Riley, J.J. Kastelein, D.E. Grobbee, Carotid intima-media thickness and coronary atherosclerosis: weak or strong relations? Eur. Heart J. **28**, 398–406 (2007)
21. S.M. Grundy, J.I. Cleeman, C.N. Merz, H.B. Brewer Jr., L.T. Clark, D.B. Hunninghake, R.C. Pasternak, S.C. Smith Jr., N.J. Stone; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines [published correction appears in Circulation **110**, 763 (2004)]. Circulation **110**, 227–239 (2004)
22. R. Collins, J. Armitage, S. Parish, P. Sleigh, R. Peto; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. Lancet **361**, 2005–2016 (2003)
23. F. Turnbull, B. Neal, C. Algert, J. Chalmers, N. Chapman, J. Cutler, M. Woodward, S. MacMahon; Blood Pressure Lowering Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch. Intern. Med. **165**, 1410–1419 (2005)
24. L. Hansson, A. Zanchetti, S.G. Carruthers, B. Dahlof, D. Elmfeldt, S. Julius, J. Menard, K.H. Rahn, H. Wedel, S. Westerling; HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet **351**, 1755–1762 (1998)
25. R.O. Estacio, B.W. Jeffers, N. Gifford, R.W. Schrier, Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care **23**(suppl 2), B54–B64 (2000)
26. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study report 14. JAMA **268**, 1292–1300 (1992)
27. W.E. Boden, R.A. O'Rourke, K.K. Teo, P.M. Hartigan, D.J. Maron, W.J. Kostuk, M. Knudtson, M. Dada, P. Casperson, C.L. Harris, B.R. Chaitman, L. Shaw, G. Gosselin, S. Nawaz, L.M. Title, G. Gau, A.S. Blaustein, D.C. Booth, E.R. Bates, J.A. Spertus, D.S. Berman, G.B. Mancini, W.S. Weintraub; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary artery disease. N. Engl. J. Med. **356**, 1503–1516 (2007)
28. F.J. Wackers, D.A. Chyun, L.H. Young, G.V. Heller, A.E. Iskandrian, J.A. Davey, E.J. Barrett, R. Taillefer, S.D. Wittlin, N. Filipchuk, R.E. Ratner, S.E. Inzucchi, for the Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) Study. Diabetes Care **30**, 2892–2898 (2007)