Racial/Ethnic Differences in Concerns About Current and Future Medications Among Patients With Type 2 Diabetes

Elbert S. Huang, MD, MPH1
Sydney E.S. Brown, AB2
Nidhi Thakur, PhD4
Lisabeth Carlisle, MD3
Edward Foley, MD, MPH4
Bernard Ewigman, MD, MSPh4
David O. Meltzer, MD, PhD5

OBJECTIVE — To evaluate ethnic differences in medication concerns (e.g., side effects and costs) that may contribute to ethnic differences in the adoption of and adherence to type 2 diabetes treatments.

RESEARCH DESIGN AND METHODS — We conducted face-to-face interviews from May 2004 to May 2006 with type 2 diabetic patients ≥ 18 years of age (N = 676; 25% Latino, 34% non-Hispanic Caucasian, and 41% non-Hispanic African American) attending Chicago-area clinics. Primary outcomes of interest were concerns regarding medications and willingness to take additional medications.

RESULTS — Latinos and African Americans had higher A1C levels than Caucasians (7.69 and 7.54% vs. 7.18%, respectively; P < 0.01). Latinos and African Americans were more likely than Caucasians to worry about drug side effects (66 and 49% vs. 39%, respectively) and medication dependency (65 and 52% vs. 39%, respectively; both P < 0.01). Ethnic minorities were also more likely to report reluctance to adding medications to their regimen (Latino 12%, African American 18%, and Caucasian 7%; P < 0.01). In analyses adjusted for demographics, income, education, and diabetes duration, current report of pain/discomfort with pills (odds ratio 2.43 [95% CI 1.39–4.27]), concern regarding disruption of daily routine (1.97 [1.14–3.42]), and African American ethnicity (2.48 [1.32–4.69]) emerged as major predictors of expressed reluctance to adding medications.

CONCLUSIONS — Latinos and African Americans had significantly more concerns regarding the quality-of-life effects of diabetes-related medications than Caucasians. Whether these medication concerns contribute significantly to differences in treatment adoption and disparities in care deserves further exploration.

Type 2 diabetic patients of racial/ethnic minorities experience significantly higher rates of diabetes-related complications than non-Hispanic Caucasians. In population-based studies, non-Hispanic African Americans have rates of renal disease, blindness, amputations, and amputation-related mortality two to four times greater than those of Caucasians (1–3). Similarly, Latinos have higher rates of renal disease and retinopathy than Caucasians (1,2,4,5). African American patients have age-adjusted diabetes mortality rates that are approximately twice those of Caucasians (6). The elimination of such health disparities is a major goal of the U.S. preventive health agenda (7).

CONCLUSIONS — Latinos and African Americans had significantly more concerns regarding the quality-of-life effects of diabetes-related medications than Caucasians. Whether these medication concerns contribute significantly to differences in treatment adoption and disparities in care deserves further exploration.

From the 1Section of General Internal Medicine, Pritzker School of Medicine, University of Chicago, Chicago, Illinois; the 2University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; the 3Ventura Family Practice Residency Program, Ventura, California; the 4Department of Family Medicine, Pritzker School of Medicine, University of Chicago, Chicago, Illinois and the 5Section of Hospital Medicine, Pritzker School of Medicine, University of Chicago, Chicago, Illinois.

CORRESPONDING AUTHOR — Elbert S. Huang, ehuang@medicine.bsd.uchicago.edu.

RESEARCH DESIGN AND METHODS — From May 2004 to May 2006, we conducted face-to-face interviews with diabetic patients aged ≥18.
years attending clinics affiliated with an academic medical center (University of Chicago, Chicago, IL) or physician offices affiliated with a suburban hospital (MacNeal Hospital, Berwyn, IL). Before conducting the study, we knew that patients attending the University of Chicago were predominately African American, whereas patients attending MacNeal Hospital were mainly Latino and Caucasian. To achieve an ethnically diverse study population, we planned for balanced recruitment from the two sites. We identified patients using electronic billing data provided by the clinics. Patients were included if they had an ICD-9 billing code of 250.xx in the past year and were ≥18 years of age. Physicians at each clinic approved which patients we were permitted to contact. We excluded patients with type 1 diabetes, as well as those who had dementia during telephone recruitment. Additional patients were excluded if they scored <17 points on the Mini-Mental State Examination (15) during in-person interviews. Potential subjects were sent study recruitment letters in random order. Letters were followed by a telephone call. We successfully contacted 2,990 patients, 2,398 of whom were determined eligible for the study. A total of 910 patients (38% of eligible subjects) scheduled interviews, and 701 patients (29% of eligible subjects) completed interviews. The average age and sex distributions of subjects who completed interviews did not differ from those of other eligible subjects.

For the purposes of this analysis, we focused on the 676 patients who identified themselves as non-Hispanic African American, non-Hispanic Caucasian, or Latino. To determine race/ethnicity, we separately asked patients to identify their race (e.g., African American, Caucasian, Asian, Native American) and to identify themselves as Hispanic, Latino, or Spanish. Interviews took approximately 1 h and were conducted by trained interviewers in English or Spanish. All Spanish interview materials were professionally translated and back translated. The overall survey included an in-depth examination of health state utilities related to diabetes treatments and complications not included in this analysis (16,17).

For the purposes of this analysis, we focused on the responses to questions regarding current and future medications. The concepts included in the section of medication concerns were partially drawn from the existing literature (18,19) and were influenced by our prior qualitative research with older diabetic patients (20). New questions were developed and revised in an iterative fashion by the investigative team with input from pilot testing with patients. This section included statements regarding concerns about current medications such as anxiety about side effects, fear of dependency on medications, need for help taking medications, concerns regarding medication costs, and reports of pain or discomfort related to medication taking. In a similar question format, patients were also asked about the implication of changes to their medication regimen for their daily routine and worries about their health. These statements referred to patients’ perceptions of their overall medication regimen and not to their diabetes-specific medication regimen. Responses to these statements were recorded on a five-point Likert scale ("agree strongly," "agree slightly," "neither agree nor disagree," "disagree slightly," and "disagree strongly").

These questions were accompanied by a series of questions regarding their willingness to adopt future changes in treatment regimens. Patients were specifically asked whether they would be willing to take additional medications if told by their physician that such a change in their treatment regimen would be beneficial. Among patients currently not taking insulin, the same question was asked regarding the potential addition of insulin. Responses were recorded as "Yes," "No," or "Don’t know." These questions were followed by a series of statements regarding potential concerns regarding the meaning and consequence of changes in medications.

We also asked patients a variety of questions regarding their health-related quality of life (12-item Short-Form Health Survey, Version 2 [21]), functional status, current medications, and diabetes-related complications. We examined medical records for additional data on comorbidities (Charlson Comorbidity Index [22]) and current risk factor levels. To assess the reliability of chart abstraction, we performed a 10% re-review. The intraclass correlation coefficients for A1C, systolic blood pressure, and LDL cholesterol were 0.96, 0.81, and 0.91, respectively. The \( \kappa \) statistic for micro- and cardiovascular complications of diabetes was 0.79. These statistics indicate moderate-to-high inter-rater reliability.

Statistical analysis
All analyses were performed using SAS statistical software (Release 8.1; SAS Institute, Cary, NC). The major outcomes of interest were 1) concerns regarding medications and 2) reluctance to add more medications or insulin; the major predictor of interest was race/ethnicity. For statements describing concerns for current and future medications, we dichotomized Likert scale responses by grouping responses of "Agree somewhat" and "Agree strongly" together. For questions regarding willingness to take additional medications, we dichotomized responses into "No" and all other responses. In unadjusted analyses, we compared these proportions using the \( \chi^2 \) test. For adjusted analyses, we used logistic regression. In the adjusted analyses, we accounted for covariates such as age, sex, education, income, and duration of diabetes.

We also examined the interrelationship of concerns regarding medications and reluctance to add more medications or insulin. For these analyses, the main outcome of interest was reluctance to add more medications. As described above, we first performed unadjusted analyses examining the relationship between each of the concerns for medications and reluctance to add more medications. We then constructed a multivariable logistic regression model, first considering variables significantly associated with outcomes in univariate analysis, followed by a search for collinear terms. With this preliminary model, ethnicity was then incorporated and evaluated for its effects as a confounder of medication-concern variables.

The study protocol was approved by the University of Chicago and MacNeal Hospital Institutional Review Boards and found to be in compliance with human subject protection and Health Insurance Portability and Accountability Act (HIPAA) regulations.

RESULTS — We interviewed 676 patients who identified themselves as Caucasian (34%), African American (41%), or Latino (25%) (Table 1). Latino patients were significantly younger (mean age 55 years vs. 65 years for African Americans and Caucasians; \( P < 0.01 \)), more likely to have been born outside the U.S. (64% vs. 1 and 7%, respectively; \( P < 0.01 \)), and less likely to have completed high school (50% vs. 73 and 84%, respectively; \( P <
Half of the interviews with Latinos were conducted in Spanish. The overall study population was well insured with over half of the patients having some form of private insurance and 90% of patients having a prescription drug plan.

There was no significant difference in the mean duration of diabetes across ethnic groups (9–10 years). However, there were differences in the prevalence of co-morbid conditions or complications across ethnic groups. Latinos had less self-reported hypertension than African Americans and Caucasians, but there was no difference in prevalence of hypercholesterolemia. African Americans had higher rates of self-reported diabetes complications such as eye disease, heart disease, and stroke, whereas Latinos had the lowest rates. For overall health status, Latinos had higher mean physical component summary scores than the other ethnic groups but lower mental component summary scores.

Mean A1C levels were higher for African Americans (7.54%) and Latinos (7.69%) than for Caucasians (7.18%) (P < 0.01); consistent with these differences, lower proportions of African Americans (41%) and Latinos (47%) had A1C levels <7% than of Caucasians (55%) (P < 0.01). With regard to cholesterol control, Latinos also had the highest mean LDL cholesterol levels (102 vs. 95 mg/dl) and the lowest proportion of patients with LDL cholesterol levels <100.
mg/dl (56 vs. 63%) of the three racial/ethnic groups (P < 0.01). The picture was reversed in the case of blood pressure control in that Latinos had the lowest mean systolic blood pressure levels (126 mg/dl) of the three groups, whereas African Americans had the highest (136 mg/dl) (P < 0.01).

Consistent with our findings related to risk factor levels, Latinos had the lowest use of medications among the three racial/ethnic groups: the lowest mean number of both total medications and diabetes-related medications (three vs. four medications for African Americans and Caucasians; P < 0.01). In terms of intensity of glucose control regimen, Latinos also had the lowest percentage of insulin use (18%), whereas African Americans had the highest use of insulin (27%) (P < 0.01). Similarly, Latinos had the lowest percentage of aspirin prophylaxis use (24 vs. 47% for Caucasians) and cholesterol-lowering drug use (51 vs. 68% for Caucasians; both P < 0.01). Frequently used nondiabetes medications included multivitamins, proton-pump inhibitors, calcium supplementation, and thyroid replacement therapy.

In direct questions regarding concerns for medications, both African Americans and Latinos had significantly more concerns about various elements of medication-taking than Caucasians (Table 2). They were more likely to say that they worried about side effects (African Americans 49% and Latinos 66% vs. Caucasians 39%), development of dependency on medications (52% and 65% vs. 39%, respectively), and the potential harms of generic substitutes (35 and 26% vs. 39%, respectively), and the potential harms of generic substitutes (35 and 26% vs. 39%, respectively). Concerns in this domain were attenuated by adjustment for clinical covariates. Latino-Caucasian differences in medication concerns were attenuated by adjustment for clinical covariates but remained significant (Table 3). For example, the association between race/ethnicity and side effect concerns were attenuated by adjustment for clinical covariates but remained significant (Table 3). For example, the association between race/ethnicity and side effect concerns became less pronounced in adjusted analysis (for Latinos, unadjusted odds ratio (OR) 3.00 [95% CI 1.98–4.55] → adjusted OR 2.92 [1.83–4.64]). With regard to the implications of future changes to medication regimens, African Americans and Latinos were more likely to report that changes in their medication regimen would represent a disruption in their daily routine and would raise concerns about their health.

When we directly queried patients about their willingness to adopt more medications, we found significant differences across racial/ethnic groups. More African Americans (18%) and Latinos (12%) than Caucasians would be opposed to the addition of more medications if recommended by their physician (7%) (P < 0.01), although the majority of patients in all groups would accept such changes in their medications. When asked about the possibility of adding insulin (among those not using insulin), the proportion of patients opposed to such a change was larger than the proportion opposed to the general addition of more medications. As observed with the prior question, larger proportions of African Americans (26%) and Latinos (22%) than Caucasians (17%) were opposed to the addition of insulin to their regimens (P = 0.09), although this difference did not reach statistical significance.

The majority of these unadjusted racial/ethnic differences in medication concerns were attenuated by adjustment for socioeconomic, demographic, and clinical covariates but remained significant (Table 3). For example, the association between race/ethnicity and side effect concerns became less pronounced in adjusted analysis (for Latinos, unadjusted odds ratio (OR) 3.00 [95% CI 1.98–4.55] → adjusted OR 2.92 [1.83–4.64]). With regard to responses to questions regarding the addition of more medications, African Americans remained significantly more likely to express a reluctance to add new medications than Caucasians (unadjusted OR 3.05 [1.66–5.61] → adjusted OR 2.53 [1.35–4.72]) even after adjustment for socioeconomic, demographic, and clinical covariates. Latino-Caucasian dif-
ferences in opinion were borderline in significance in unadjusted analysis (1.95 [0.97–3.93]) and became clearly non-significant (1.48 [0.69–3.15]) when accounting for covariates.

In our comprehensive analysis of predictors of a reluctance to add medications, we found that concerns about growing dependent on medications, report of unpleasant or painful experience with medications, anticipated disruption of daily routine, concerns regarding health if faced with medication changes, and concerns over switches from brand-name to generic drugs were all significantly associated with a reluctance to add more medications (all \( P < 0.01 \)). The patient’s physical health status, current number of medications, and current number of diabetes-related medications were not significantly associated with a reluctance to add more medications. Higher mental health status was associated with a lower likelihood of opposing additional medications (\( P < 0.01 \)). After identification and exclusion of collinear variables, the final model of a reluctance to add more medications included report of unpleasant or painful experience with medications (OR 2.43 [95% CI 1.39–4.27]; \( P < 0.01 \)) and anticipated disruption of daily routine (1.97 [1.14–3.42]; \( P = 0.02 \)). African American race remained a significant predictor of reluctance to add more medications even within the fully adjusted model (2.48 [1.32–4.69]; \( P < 0.01 \)).

CONCLUSIONS — Our study provides valuable insights into how concerns regarding quality of life with medications and the willingness to adopt more medications vary across type 2 diabetic patients of various racial/ethnic groups. Over one-half of racial/ethnic minority patients in our sample expressed concerns regarding side effects of medications and the development of possible dependency on medications, in comparison with over one-third of Caucasian respondents. Similarly, approximately one-half of minority patients would be concerned about their health as a result of changes in medication regimens in comparison with 22% of Caucasian patients. Latinos and African Americans were also more likely to voice reluctance to adding medications. In adjusted analyses, this was only found to be significant for African Americans. Patients who expressed a concern regarding the use of medications were more likely to express reluctance to adding medications.

Our findings have implications for the field of health disparities in diabetes care. The basic finding of ethnic differences in concerns regarding life with medications suggests that the everyday experiences of living with diabetes treatments are, on average, experienced differently by ethnic groups. These differences in medication concerns may contribute to differences in perceived quality of life related to diabetes (23). Ethnic differences in perception will require additional study to determine their origins and to clarify their implications for long-term treatment adoption and disparities in care.

It is important to note that many of the concerns and attitudes related to medications were shared among all patients. Patients of ethnic minorities were more likely to express concerns regarding current and future medications, but many Caucasian patients also shared these concerns. Concerns regarding the physical and logistical burdens of managing multiple medications were quite prevalent throughout the population and are clearly important to acknowledge with patients before intensifying or altering medication regimens. We found that the experience of pain or discomfort with the use of current oral medications was an independent predictor of reluctance to add more medications. It should be noted that the majority of patients within each racial/ethnic subgroup were willing to take additional medication, including insulin, if advised to do so by their health care providers. These results are important reminders that it is important for providers to approach patients as individuals and elicit concerns about current and future medications from patients irrespective of race/ethnicity. It may be possible to acknowledge medication concerns while also intensifying diabetes care through a shared decision-making approach to treatment decisions (24).

There are some limitations to this study. Our recruitment rate was low, which is likely related to our attempt to recruit patients irrespective of frequency of prior visits to a physician. We speculate that nonrespondents were less frequent attendees of clinic and potentially less adherent to medical therapies than respondents. If that is the case, our findings likely underestimate the level of concern about life with medications among patients with diabetes. A related limitation

### Table 3—Adjusted analyses of concerns about medications by race/ethnicity, adjusted comparisons in adults with type 2 diabetes from Chicago-area clinics, 2004–2006*

| Statements reflecting medication concerns (likelihood of responding affirmatively) | African American vs. Caucasian | Latino vs. Caucasian |
|---|---|---|
| I worry about side effects from my medications. | 1.32 (0.91–1.92) | 2.92 (1.83–4.64) |
| I worry about becoming dependent on my medications. | 1.57 (1.09–2.28) | 2.90 (1.83–4.58) |
| I worry about the expense of my medications or glucose-monitoring supplies. | 0.93 (0.64–1.34) | 1.84 (1.16–2.93) |
| If my doctor asked me to change my medication regimen, it would disrupt my daily routine. | 1.24 (0.75–2.05) | 1.78 (1.01–3.12) |
| If my doctor asked me to change my medication regimen, it would make me worry more about my health. | 2.29 (1.52–3.45) | 3.98 (2.46–6.44) |
| I worry about switching from name brand to generic drugs. | 3.29 (2.06–5.26) | 2.12 (1.21–3.73) |

Willingness to take more medications or insulin (likelihood of responding “No”)

| If your doctor told you that you would benefit from taking more medications, would you be willing to take more? | 2.53 (1.35–4.72) | 1.48 (0.69–3.15) |
| If your doctor told you that you would benefit from taking insulin, would you be willing to take insulin? | 1.59 (0.94–2.70) | 1.15 (0.60–2.21) |

Data are OR (95% CI). *Each logistic regression model adjusted for sex, education (>high school graduate), income (<$10,000 USD/year), and duration of diabetes.
of our study is that the views of the patients whom we surveyed may not be representative of all patients with diabetes. The surveyed patients all had physicians that granted us permission to recruit them; the majority of subjects had health insurance and prescription drug coverage. In addition, our Spanish-speaking Latino patients all saw physicians who spoke Spanish. Given known disparities in insurance coverage and access to providers, it is likely that the degree of health disparities in this sample and the extent of racial/ethnic differences in responses to questions might be less pronounced than in a population-based study. Nonetheless, we still found important disparities in risk factor control and important differences in medication concerns. It is also important to recognize that the ethnic group assignment in our sample reflects the specific ethnic mix of Chicago neighborhoods that composed our clinical sites. The makeup of the same ethnic group categories may differ in other parts of the city, state, and country. Our study findings also reflect the views of patients before the publication of reports regarding the potential risks associated with very intensive glucose control. Current concerns about quality of life with diabetes-related medications may be even more widespread than we have found.

Our study provides insights into how reported concerns regarding diabetes-related medications vary across racial/ethnic groups. However, it remains unclear whether these concerns and perceptions regarding medications are at the root of observed disparities in diabetes care and outcomes (25). Longitudinal studies that help to test the association between medication concerns with intermediate outcomes after adjusting for diabetes severity will be valuable to addressing this critical question in diabetes health disparities research.

Acknowledgments — This study was supported by a National Institute of Aging Career Development Award to E.S.H. (K23-AG021963), a National Institute of Diabetes and Digestive and Kidney Diseases Diabetes Research and Training Center Grant to S.E.S.B., E.S.H., and D.O.M. (P60 DK20595), a Centers for Disease Control and Prevention Potential Extramural Project Grant to E.S.H., S.E.S.B., N.T., E.F., B.E., and D.O.M. (U36-CU319276), and the Chicago Center of Excellence in Health Promotion Economics Grant to E.S.H. and D.O.M. (P30-CDC00147). No potential conflicts of interest relevant to this article were reported.

References
1. Carter JS, Pugh JA, Monterrosa A: Non-insulin-dependent diabetes mellitus in minorities in the United States. Ann Intern Med 125:221–232, 1996
2. Lanting LC, Joung IM, Mackenbach JP, Lamberts SW, Bootsma AH: Ethnic differences in mortality, end-stage complications, and quality of care among diabetic patients: a review. Diabetes Care 28:2280–2288, 2005
3. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE: Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 23:934–942, 2000
4. Emanuele N, Sacks J, Klein R, Anderson R, Duckworth W, Abraira C, the Veterans Affairs Diabetes Trial Group: Ethnicity, race, and baseline retinopathy correlates in the Veterans Affairs Diabetes Trial. Diabetes Care 28:1954–1958, 2005
5. Harris MI, Klein R, Cowie CC, Rowland M, Byrd-Holt DD: Is the risk of diabetic retinopathy greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites with type 2 diabetes? A U.S. population study. Diabetes Care 21:1230–1235, 1998
6. National Center for Health Statistics: Age-adjusted death rates for diabetics, by race and sex: United States, 1970–2006. MMWR Recomm Rep 57:855, 2008
7. Department of Health and Human Services: Healthy People 2010: Understanding and Improving Health. Washington, DC, U.S. Govt. Printing Office, 2000
8. American Diabetes Association: Standards of medical care for patients with diabetes mellitus. Diabetes Care 25(Suppl. 1):S33–S49, 2002
9. Steinbrook R: Patients with multiple chronic conditions: how many medications are enough? The N Engl J Med 338:1541–1542, 1998
10. Murray MD, Kroenke K: Polypharmacy and medical adherence. J Gen Intern Med 16:137–139, 2001
11. Grant RW, Pirraglia PA, Meigs JB, Singer DE: Trends in complexity of diabetes care in the United States from 1991 to 2000. Arch Intern Med 164:1134–1139, 2004
12. Saydah SH, Fradkin JE, Cowie CC: Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 291:335–342, 2004
13. Heisler M, Faul JD, Hayward RA, Lang KM, Blaum C, Weir D: Mechanisms for racial and ethnic disparities in glycemic control in middle-aged and older Americans in the health and retirement study. Arch Intern Med 167:1853–1860, 2007
14. Vijan S, Hayward RA, Ronis DL, Hofer TP: The burden of diabetes therapy: implications for the design of effective patient-centered treatment regimens. J Gen Intern Med 20:479–482, 2005
15. Folstein MF, Folstein SE, McHugh PR: “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198, 1975
16. Neumann PJ, Goldie SJ, Weinstein MC: Preference-based measures in economic evaluation in healthcare. Annu Rev Public Health 21:587–611, 2000
17. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC: The role of cost-effectiveness analysis in health and medicine. J Am Med Assoc 276:1172–1177, 1996
18. Boyer JG, Erp JA: The development of an instrument for assessing the quality of life of people with diabetes. Diabetes-39. Med Care 35:440–453, 1997
19. Fitzgerald JT, Davis WK, Connell CM, Hess GF, Funnell MM, Hiss RG: Development and validation of the Diabetes Care Profile. Eval Health Prof 19:208–230, 1996
20. Huang ES, Gorawara-Bhat R, Chin MH: Self-reported goals of older patients with type 2 diabetes mellitus. J Am Geriatr Soc 53:306–311, 2005
21. Ware JE, Kosinski M, Keller SD: SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales. Boston, Massachusetts, The Health Institute, New England Medical Center, 1995
22. Charlson ME, Pompei P, Alex K, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383, 1987
23. Huang ES, Brown SE, Ewigman BG, Foley EC, Melzer DO: Patient perceptions of quality of life with diabetes-related complications and treatments. Diabetes Care 30:2478–2483, 2007
24. Montori VM, Gafni A, Charles C: A shared treatment decision-making approach between patients with chronic conditions and their clinicians: the case of diabetes. Health Expect 9:25–36, 2006
25. Jackevicius CA, Li P, Tu JV: Prevalence, predictors, and outcomes of primary non-adherence after acute myocardial infarction. Circulation 117:1028–1036, 2008