JACC VOL. 68, NO. 12, 2016
SEPTEMBER 20, 2016:1368–74

most feminine (versus masculine) patients have a higher burden of risk factors, with nearly twice the prevalence of diabetes and prior cardiovascular disease (CVD) and a higher likelihood of hypertension and smoking. This pattern (which can extend to unmeasured/unknown variables) might be expected if feminine characteristics were protective for ACS, as only those feminine patients with an extreme risk factor burden would be at risk for the index ACS event. Without accounting for all shared risk factors for the index and recurrent event, residual bias (i.e., positively associating femininity with the recurrent event) will be present. Although regression analyses can be adjusted for CVD risk factors, residual bias remains a concern because of omission of some risk factors (e.g., diabetes), model misspecification, and perhaps most insidiously, unknown risk factors that cause both ACS and its recurrence.

The hypothesis that gender effects might be separable from sex effects is an intriguing and creative one, but perhaps early explorations of this idea should focus on population samples since recurrence risk studies that condition on having a first event are notoriously unreliable with regards to causal inference. For this reason (and many others), we recommend caution before advising post-ACS patients to adopt more masculine attributes.

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http://dx.doi.org/10.1016/j.jacc.2016.03.612

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REPLY: Sex Versus Gender in Recurrent Events Following Acute Coronary Syndrome

A "Femininity Paradox?"

Drs. Paulus and Kent bring up the concept of index event bias (IEB) in potentially explaining the association between gender and recurrent acute coronary syndrome (ACS). In our study the possible effect of IEB is unlikely given that a feminine gender was also associated with risk factors for ACS (1). Therefore, the effect of gender was in the same direction both for the index and the recurrent event.

We found that gender characteristics traditionally ascribed to women, such as home responsibilities and caring attributes, were related to a higher risk of recurrent ACS. We constructed a novel gender score to assess this association (1). The message to draw from our study is not that patients should adopt a more masculine gender but that patient and provider should recognize that roles and traits traditionally ascribed to women are associated with outcome independent of sex. For example, a person with demanding household responsibilities including caring for children may be less likely to adhere to treatment or may have difficulty managing disease and thus be at higher risk of a recurrent event.

Preventing recurrent events is of tantamount importance given that an acute event often represents the first opportunity for risk reduction. The possibility of IEB should not be a deterrent as the association between gender, risk factors, and recurrent events is not a paradox.

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http://dx.doi.org/10.1016/j.jacc.2016.06.046

Please note: Dr. Pilote has reported that she has no relationships relevant to the contents of this paper to disclose.

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Trading Lower HbA_{1c} for Increased Adverse Events

A Zero Sum Game?

The review by Waldrop et al. (1) may not have addressed all of the evidence summarized in a systematic review of 43 clinical trials and 12 observational studies (2) for increased cardiac failure with dipeptidyl peptidase-4 inhibitors (DPP-4Is). Glitazones also increase cardiac failure (3). Practitioners may be unaware that DPP-4I trials have failed to show

improvements in any clinical outcomes. Side effects increase linearly with increasing dose, but with inhibitors, efficacy plateaus above the medium effective dose (ED50; the mean dose in the population that causes half maximal lowering of blood glucose concentration). Sitagliptin is prescribed at 50 to 100 mg (ED50: approximately 15 mg). Similarly, gliclazide is prescribed at 30 to 160 mg daily (ED50: approximately 20 mg) and pioglitazone at 15 to 45 mg (ED50: approximately 15 mg). Metformin, the only oral hypoglycemic which improves outcomes, is used below its ED50, approximately 2 g daily.

More intensive blood glucose lowering can increase cardiovascular events and total mortality (4). The lower glucoses may impair myocardial function or lower plasma oncotic pressure and contribute to pulmonary edema. Increased insulin can cause renal sodium retention (5).

Sulfonylureas, glitazones, and insulin have failed to reduce cardiovascular events, possibly partly because they cause weight gain, which, long-term, increases blood glucose, lipids, and blood pressure. The sodium-glucose-linked transporter 2 inhibitor (SGLT2-I) empagliflozin reduces weight (as does metformin), cardiac failure, and total mortality. Risk benefit in cardiac failure dictates that SGLT2-Is supplant gliptins. Favorable outcomes rather than glucose measurements should dictate management in type 2 diabetes mellitus.

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http://dx.doi.org/10.1016/j.jacc.2016.06.045

Please note: Dr. Warren is Director of Consultancy, Medicines Assessment Ltd. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REPLY: Trading Lower HbA_{1c} for Increased Adverse Events

A Zero Sum Game?

We appreciate the comments from Dr. Dimmitt and colleagues in response to our paper (1). They claim that DPP4 inhibitors (DPP4i) may not provide a sufficient balance between safety and efficacy. They liken DPP4i's to other glycemia-lowering agents that may increase cardiovascular (CV) events and appear to suggest that the weight gain seen with these agents may contribute to adverse CV events. Furthermore, they seem to be strong proponents of SGLT-2i therapy in lieu of DPP4i and suggest that CV event reduction rather than glycemia lowering should dictate choice of therapy in diabetes.

We do not agree with Dr. Dimmitt and colleagues for several reasons. Although DPP4i do not appear to lower CV outcomes, 2 out of the 3 DPP4i trials were designed as noninferiority studies to meet a regulatory requirement and were not powered for efficacy (1). The average duration of follow-up of <3 years in these studies, is not sufficient duration for a glycemia-lowering strategy to demonstrate an effect on CV events (2). These agents do not increase blood pressure or increase weight in contrast to antidiabetes agents. There is no indication that side effects with DPP4i are any higher at the highest doses used in clinical practice (3). As such, DPP4i are extremely well tolerated agents and arguably the best investigated class of any anti-diabetic agent. Dimmitt and colleagues claim that metformin is the only agent that improves CV outcomes, despite the fact that the benefit from metformin in the United Kingdom Prospective Diabetes Study (UKPDS) was derived from a post hoc analysis of a small number of patients (<350 patients in the metformin arm) (4).

Although reduction of CV events is clearly an important goal of treatment in type 2 diabetes, the pernicious attrition of quality of life by microvascular complications cannot be ignored and remains a significant goal of glycemia-lowering drugs. Although SGLT-2i may indeed emerge as a frontline consideration in high-risk patients with diabetes, the data from Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG outcome) trial would need to be confirmed in other studies (5).