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The Effectiveness of β-Blockers After Myocardial Infarction in Patients With Type 2 Diabetes

Response to McDonald et al.

In the September 2005 issue of *Diabetes Care*, McDonald et al. (1) showed that β-blocker therapy after myocardial infarction (MI) was not associated with reduced mortality or fewer recurrent events in people with type 2 diabetes in routine practice. This contrasted with studies performed before intervention with drugs such as ACE inhibitors and statins were available. These studies showed a significant decrease in mortality and reinfarction post-MI in diabetic subjects (2,3). The authors conclude that the benefits of β-blockers are attenuated in the era of multiple interventions.

I believe that there is another reason for the decreased effectiveness of β-blockers in the modern era. When the older studies were preformed, the majority of β-blockers used were nonselective β-blockers that blocked both the β_1 and the β_2 receptors. Selective β_1 blockers, unless used intravenously at the time of the MI, have never been shown to decrease reinfarction or mortality post-MI (4). In contrast, nonselective β-blockers (propranolol and pindolol) with normal ventricular function, as well as carvedilol with decreased ventricular function, have been shown to decrease cardiac events and mortality post-MI.

Therefore, I believe that the shift in effectiveness of β-blockers post-MI is not due to multiple other interventions but to utilization of β_1-blockers, which—especially at lower doses—have not been shown to decrease mortality or reinfarction. A reanalysis based on the use of β_1 selective and nonselective β-blockers could prove or disprove this theory.

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The Effectiveness of β-Blockers After Myocardial Infarction in Patients With Type 2 Diabetes

Response to Bell

We thank Dr. Bell (1) for his interest in and insightful comments about our study. Dr. Bell proposes that the use of lower doses of cardioselective β-blockers could have reduced the effectiveness of this class of agents after myocardial infarction (MI) in diabetic subjects, a reasonable hypothesis. Another hypothesis is that short-acting cardioselective β-blockers lead to periods of withdrawal and decreased efficacy (2).

As in previous studies (3,4), we assumed a class effect among β-blockers. Unfortunately, we could not differentiate the type of β-blockers that were prescribed, although our sample size would have been precipitously reduced if we had done so. However, atenolol and metoprolol are the most commonly prescribed β-blockers in Canada (5).

Dr. Bell asserts that cardioselective β-blockers have never been shown to reduce mortality post-MI unless used intravenously. However, meta-analyses have demonstrated a 25% reduction in mortality with long-term β-blockade after MI (including cardioselective agents) (6,7); cardioselectivity or membrane-stabilizing activity did not predict mortality. Rather, Yusuf et al. (6) demonstrated decreased effectiveness when trials using agents with intrinsic sympathomimetic activity (ISA) were pooled (odds ratio [OR] for agents with ISA 0.90 [0.77–1.05]; OR without ISA 0.69 [0.61–0.79]). Freemantle et al. (7) also failed to demonstrate a significant effect of cardioselectivity, although the OR for the protective effect of β-blockers with ISA was 1.19 (0.96–1.47). Moreover, older observational studies of β-blockers (as a class) post-MI, conducted in an era when metoprolol and atenolol were frequently prescribed, have found no effect of cardioselectivity (3,4,8). For example, in the Bezafibrate Infarction Prevention (BIP) study, mortality was similar in patients who received propranolol or a cardioselective β-blocker (4), and in the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study, metoprolol was an independent predictor of reduced mortality after MI (relative risk ratio 47%) (8). If Dr. Bell's hypothesis is correct, it seems unlikely that these earlier studies would have shown mortality benefit.

Therefore, we believe that the putative benefits of β-blockade were less in our study because of cointerventions that also reduce mortality. Future studies should include the type of β-blocker as a covariate rather than assuming a class effect, as we and others have done. The answer to this question is clinically

important, and we thank Dr. Bell for his interest in our work.

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Type 1 Diabetes and Autism: Is there a link?

Response to Freeman et al.

In a recent issue of *Diabetes Care*, Freeman et al. (1) discussed a possible link between type 1 diabetes and autism spectrum disorder (ASD). Their data suggested that the prevalence of ASD in nearly 1,000 children with type 1 diabetes may be greater than that in the general population.

We investigated the presence of ASD in 5,178 children diagnosed with type 1 diabetes at age ≤14 years from the Prospective Childhood Diabetes Registry of Finland. Children with type 1 diabetes were born between 1980 and 2000. The data were linked to the nationwide Hospital Discharge Register (HDR) by the end of the year 2003 using the unique personal identity number that is assigned to all residents of Finland. We included autism, Asperger disorder, pervasive developmental disorder–not otherwise specified, Rett's syndrome, and childhood disintegrative disorder in the diagnosis of ASD (2). We also linked the data of mothers of ASD cases to the HDR and reviewed hospital records in order to find out pregnancy and delivery complications related as potential risk factor for subsequent ASD in the child.

Seven cases with type 1 diabetes fulfilled the criteria of ASD, giving a cumulative incidence of 1.35/1,000 (95% CI 0.5–2.8). The cumulative incidence of ASD did not differ from that in the background population. The cumulative incidence of ASD was 1.39/1,000 (1.2–1.57) at age 18 years in northern Finland (3). There was male excess in ASD; five of seven cases were boys. Perinatal risk factors were present in five cases of ASD; some of them had several: asphyxia during delivery was present in two cases, umbilical cord around the neck in three cases, and excess bleeding during delivery in two cases, of which one had asphyxia and one had umbilical cord around neck.

Some studies have suggested that a family history of autoimmune disorders is more common among children with ASD than those healthy control children (4). However, there are many limitations in these studies, especially regarding sample sizes and study designs. A recent appropriately designed case-control study, much larger than those conducted earlier, found no overall association between ASD risk in children and autoimmune disorders in mothers; only psoriasis occurred more frequently (5).

Finland provides free or low-cost health service for all the habitants. Specialized health care like child neurological and psychiatric services are available in central hospitals and university hospitals that can all be found in the HDR. The HDR also covers central institutions for the mentally disabled. The HDR has nationwide coverage of inpatient treatment facilities. However, we were not able to capture cases who were diagnosed and treated as outpatient only; therefore, some mild cases of ASD may have remained unrecognized.

In conclusion, our observations do not support the suggestion about the link between type 1 diabetes and ASD. These findings, however, suggest that a subgroup of children developing autism suffered exposure to adverse prenatal and neonatal asphyxia (6) and unfavorable events in pregnancy, delivery, and the neonatal phase.

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