Propranolol and the risk of hospitalized myopathy: Translating chemical genomics findings into population-level hypotheses

Soko Setoguchi, MD, DrPH,[a,d] John M. Higgins, MD,[b,d,e] Helen Mogun, MS,[a] Vamsi K. Mootha, MD,[c] and Jerry Avorn, MD[a] *Boston, MA*

Background A recent large-scale, chemical screening study raised the hypothesis that propranolol may increase the risk of myopathy. We tested this hypothesis in a large population to assess whether (1) propranolol use is associated with an increased risk of myopathy and (2) the concurrent use of propranolol with a statin may further increase risk of myopathy.

Methods New users of propranolol and other β-blockers (BBs) aged ≥65 were identified using data from Medicare and drug benefit programs in 2 states (1994-2005). The primary end point studied was hospitalization for myopathy or rhabdomyolysis. We used stratified Cox proportional hazards regression to estimate the multivariate-adjusted effect of propranolol compared to other BBs and controlled for demographic variables, risk factors for myopathy, other comorbidities, and health service use measures. We also assessed whether co-use of propranolol and statin further increases the risk, by including an interaction term for use of propranolol and statins.

Results We identified 9,304 initiators of propranolol and 130,070 initiators of other BBs and found 30 cases of hospitalized myopathy in 15,477 person-years (PYs) of propranolol use and 523 in 343,132 PYs of other BB use. Comparing propranolol with other BB users, the adjusted hazard ratio was 1.45 (95% CI 1.00-2.11) for myopathy and 1.48 (95% CI 0.82-2.67) for rhabdomyolysis. We could not detect interaction between propranolol and statins due to limited power. Similar results were observed when propranolol users were compared to other antihypertensive drug users.

Conclusions Propranolol may be associated with a 45% increased risk of hospitalized myopathy in the elderly. Our study illustrates how results from in vitro chemical screens can be translated into hypotheses about drug toxicity at the population level. (Am Heart J 2010;159:428-33.)

We recently performed a large-scale, chemical genomic screen of nearly 2,500 drugs in cultured mouse muscle and discovered a molecular and physiologic signature of statin toxicity.[1] The signature of toxicity reported in this cell-based study is consistent with previous reports suggesting that statins may cause myopathy via a mitochondrial mechanism.[2] Surprisingly, we found that treatment of muscle cells with propranolol, but not metoprolol or atenolol, gave rise to a very similar signature of toxicity. Moreover, the study revealed that combination treatment of these cells with a statin and propranolol gave rise to an additive toxicity in a dose-dependent manner. A subsequent study demonstrated increased cellular toxicity for propranolol as compared to other β-blockers (BBs) in a different cell type.[3]

These cell-based studies raise the possibility that propranolol use in humans might be associated with increased risk of in vivo mitochondrial toxicity and possibly clinically significant myopathy. In the current article, we conducted a cohort study using large population-based health care use databases to assess whether (1) propranolol may be associated with an increased risk of myopathy and (2) the concurrent use of propranolol with a statin may further increase the risk of myopathy.

Methods

Data sources and cohort definition

We conducted a cohort study pooling health care use databases from 2 states: (1) Medicare beneficiaries enrolled in

From the [a]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Boston, MA, [b]Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, and [c]Center for Human Genetic Research, Massachusetts General Hospital, Broad Institute of MIT and Harvard, and Department of Systems Biology, Harvard Medical School, Boston, MA.
[d]Cofirst authors.
[e]Current address: Center for Systems Biology and Department of Pathology, Massachusetts General Hospital, and Department of Systems Biology, Harvard Medical School.
Submitted June 9, 2009; accepted December 2, 2009.
Reprint requests: Soko Setoguchi, MD, DrPH, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, 1620 Tremont St, Suite 3030, Boston, MA 02130.
E-mail: ssetoguchi@partners.org
0002-8703/$ - see front matter

doi:10.1016/j.ahj.2009.12.008

Table I. Characteristics of cohort patients with age ≥65 (Medicare and Pharmacy Assistance Program in PA and NJ combined; 1995-2005)

	Propranolol (n = 9304)	Other BBs (n = 130070)	THI (n = 81411)	Angiotensin blockers (n = 110328)	CCBs (n = 70976)	All comparison drugs combined (n = 392785)
Average follow-up (y), time to death (follow-up)	4.7 (3.2)	3.8 (2.9)	4.5 (3.0)	4.2 (3.0)	4.3 (3.1)	4.1 (3.0)
Demographic						
Age	79 (7)	79 (7)	79 (7)	79 (7)	79 (7)	79 (7)
Male	18.7	21.7	16.2	21.4	20.7	20.3
White	91.5	89.9	87.6	88.8	88.7	88.9
Health service use						
No. of physician visits	11 (8)	10 (7)	10 (7)	10 (7)	10 (7)	10 (7)
Prior hospitalization	44.4	57.2	25.3	43.2	47.8	45.0
No. of different drugs taken	11 (6)	12 (6)	9 (5)	10 (6)	11 (6)	11 (6)
Prior nursing home	8.0	12.4	4.8	8.9	10.2	9.4
Comorbidities						
Renal impairment	13.0	19.2	8.9	12.2	15.7	14.5
Hypothyroidism	19.1	20.3	17.7	18.5	18.1	18.9
Hyperthyroidism	5.7	3.1	2.5	2.6	2.8	2.8
Liver disease	7.6	4.1	2.9	3.4	3.5	3.6
Migraines	3.2	1.2	0.9	0.9	1.1	1.0
Prior acute coronary syndrome	13.3	19.0	4.2	9.6	10.1	11.7
Hypertension	77.0	86.8	85.6	84.0	84.7	85.3
Coronary artery disease	49.8	61.3	31.0	45.6	43.5	47.4
Cerebrovascular disease	23.4	27.2	17.1	21.9	23.7	23.0
Heart failure	26.9	36.3	15.0	32.8	27.5	29.3
Diabetes	15.2	19.3	15.7	20.5	16.4	18.4
Chronic pulmonary disease	20.4	26.0	21.6	27.8	31.3	26.5
Cancer	16.2	16.7	14.2	15.4	16.2	15.7
Inflammatory myositis	0.08	0.11	0.09	0.09	0.12	0.10
Rheumatoid arthritis	0.3	0.2	0.2	0.2	0.2	0.2
Depression	14.4	11.8	8.7	10.6	11.3	10.7
Dementia	0.02	0.02	0.02	0.04	0.04	0.03
Anemia	14.8	15.9	10.7	12.8	13.8	13.6
Past drug use						
Antiarrhythmics	39.3	46.9	21.5	33.6	36.9	36.1
Nitrate	25.1	25.5	11.8	18.0	16.2	18.9
CCBs	37.4	43.7	41.7	44.2	0.0	35.5
ACEI/ARB	35.0	47.5	42.0	0.0	46.6	32.9
THI	19.0	23.2	0.0	18.0	24.1	17.1
Statin	18.5	25.5	21.2	19.0	17.0	21.2
Gemfibrozil	0.9	0.9	0.7	0.8	0.8	0.8
Insulin	5.9	7.6	5.1	8.0	6.9	7.1
Digoxin	14.2	14.7	8.0	11.7	11.8	12.0
Loop diuretics	22.4	26.1	12.1	22.8	20.2	21.2
Antiplatelet agents	4.8	7.2	4.2	4.3	4.3	5.3
DMARDs	1.6	1.8	1.7	1.6	1.7	1.7
Antipsychotics	43.3	33.7	30.3	31.0	32.3	32.0
SSRI	15.3	12.1	10.4	10.9	11.0	11.2
Other non-SSRI antidepressants	13.4	9.8	8.6	9.3	9.3	9.3
Warfarin	11.1	12.0	6.9	9.2	8.7	9.6

Covariates were assessed during 1 year before initiation of study drugs. Values represent percentage for binary variables and median (interquartile range) for continuous variables. *ACEI*, Angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *BB*, beta-blocker; *CCB*, calcium-channel blocker; *DMARD*, disease-modifying antirheumatic drug; *SSRI*, selective serotonin reuptake inhibitor; *THI*, thiazide diuretic.

the Pharmaceutical Assistance Contract for the Elderly (PACE) in Pennsylvania from January 1, 1994, to December 31, 2005, and (2) Medicare beneficiaries enrolled in the Pharmaceutical Assistance to the Aged and Disabled (PAAD) or in Medicaid in the state of New Jersey from January 1, 1994, to December 31, 2005. Both drug benefit programs in Pennsylvania and New Jersey provided comprehensive pharmacy coverage with a small or no copayment. Patients were eligible for coverage by PACE or PAAD if their income is above the Medicaid annual income threshold but less than approximately $35,000, thus, including primarily lower middle-class elderly. The linked Medicare/state drug benefit program data provide basic demographic and coded diagnostic and procedural information as well as complete pharmacy dispensing information with high accuracy.[4,5] The Institutional Review Board of the Brigham and Women's Hospital and Massachusetts General Hospital approved this study, and data use agreements were established. All potentially traceable personal identifiers were removed from

the data before analyses to protect patients' privacy. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed to the article as written.

In the databases, we identified a cohort of subjects aged ≥65 years who were newly started on propranolol or another β-blocker. New use of propranolol was defined as having filled a prescription for propranolol during the study period and not having used the drug during the 12 months before the index use. Patients who used other BBs during the 12 months before the index use of propranolol were considered as new users of propranolol. The same definition was applied to define new users of other BBs. This "new user" design is preferable because including prevalent users can underestimate the true effect of an exposure by missing events that might have occurred soon after the first exposures, as well as by focusing on patients who were less susceptible to a given risk.[6] All patients were required to have at least one filled prescription and use of at least one clinical service during each of 2 consecutive 6-month periods before the index use of any BB, to ensure ongoing eligibility and to assess prior comorbid conditions. The earliest observation included in the analyses was January 1, 1996.

Study exposure

The exposure of interest was use of propranolol. We chose other BB users as a comparison group because the comparison between active users of similar medications can help protect against confounding by indication and other selection biases related to use of preventive medications.[7] Cohort follow-up started at the first prescription of propranolol or other BB during the study period. We did not allow patients to cross over between categories and instead censored them as soon as they stopped taking the exposure medication of interest. We assessed dose response by determining the daily dose of propranolol based on the closest dispensing to the outcome or censoring event, we then categorized the dose into low (≤40 mg) and high (>40 mg), given a median dose of 40 mg/d.

Study end points

Subjects were censored at the earliest of (1) the last use of propranolol or other BBs, (2) death, or (3) end of the study period. The last use of propranolol or other BB was defined as the last date of prescription plus the number of days supplied, plus a 14-day grace period to account for the time lag between filling a prescription and the actual intake of the medication. The primary end point studied was the first incidence of severe myopathy after the initiation of the study drugs, defined as hospitalization in an acute care facility with myopathy-related codes including *International Classification of Diseases, Ninth Edition* (ICD-9) code for rhabdomyolysis (ICD-9 of 710.4, 728.8X, 728.9, 729.1, 791.3, 359.4. 359.8, 359.9) as the primary or secondary diagnosis listed in the discharge summary. The secondary outcome was the first incidence of rhabdomyolysis. A specific ICD-9 code for rhabdomyolysis (728.88) became available only after October 2003. We therefore defined rhabdomyolysis using a previously developed algorithm by Andrade et al[8] up to October 2003. After October 2003, we defined rhabdomyolysis as hospitalization in an acute care facility with rhabdomyolysis (ICD-9 of 728.88) as the primary or secondary diagnosis in the discharge summary. The cases of rhabdomyolysis would be a subset of hospitalized myopathy cases because ICD-9 codes used to defined rhabdomyolysis in the algorithm by Andrade and the new code for rhambdomyolysis (728.88) were part of ICD-9 codes used to define hospitalized myopathy.

Potential confounders

Potential confounders were measured during the 12 months before the exposure to propranolol or other BB, using diagnosis and procedure codes and/or prescription information in the data, including demographic variables; risk factors for myopathy including renal impairment, hypothyroidism, hyperthyroidism, liver disease, other comorbidities; and use of other medications (see Table I for the list of comorbidities and medications).

Analysis

Cox proportional hazards regression was used to estimate the unadjusted, age-sex–adjusted, and multivariate-adjusted effect of propranolol versus other BB on the occurrence of hospitalization for myopathy or rhabdomyolysis. Patients from the 2 states were combined and analyzed in stratified Cox proportional hazards regression, allowing different baseline incidence of the outcomes between the 2 regions. The model was also stratified by calendar year to adjust for any trend or variation in the exposure and outcomes. We also adjusted potential confounders using propensity score methods.[9] The propensity scores were estimated as a probability of receiving propranolol compared to another BB, given all potential covariates that predicted the use of propranolol. To estimate propensity scores, we also included several covariates not included in the final multivariate models: use of other medications and health service. Dose response was assessed by replacing indicator variables with propranolol categories versus the comparison drug.

To test the hypothesis that concomitant use of statin and propranolol may be associated with a further increase in the risk of myopathy, we assessed the most recent use of statins in patients taking propranolol and other comparison drugs before the previously specified outcomes or censoring events. We then included an interaction term between propranolol and statin use in the fully adjusted Cox model to determine whether there was a synergistic effect for statins and propranolol.

We conducted sensitivity analyses using other comparison groups within the same population. We identified new users of 3 other classes of antihypertensive medications: angiotensin blockers (ABs), calcium-channel blockers (CCBs), and thiazide diuretics (THI). We repeated the same analyses comparing propranolol users to AB users, CCB users, THI users, and all comparison drug users (AB + CCB + THI + other BB users).

Results

Study patients and their characteristics

We identified 9,304 initiators of propranolol and 130,070 initiators of other BBs. Among the 130,070 other BB users, the most frequent BB used was metoprolol (57%) followed by atenolol (27%). We also identified new users of AB (n = 110,328), CCB (n = 70,976), or THI (n = 81,411) for sensitivity analyses. Table I presents the characteristics of the study population aged ≥65 and older measured during the 12-month period before exposure to

Table II. Number of cases, person-years, and incidence rate of hospitalized myopathy and rhabdomyolysis

		Hospitalized myopathy	Rhabdomyolysis
Propranolol (n = 9304)	No. of cases	30	12
	P-Y	15477	16064
	IR	19.4	7.5
Other BBs (n = 130070)	No. of cases	523	227
	P-Y	343132	364969
	IR	15.2	6.2
Other BB, THI, CCB, or ACE/ARBs (n = 360668)	No. of cases	1497	649
	P-Y	1080612	1137135
	IR	13.9	5.7

P-Y, Total person-years; *IR*, incidence rate (per 10000).

the study drugs. Age was similar across the groups, but propranolol users generally had fewer comorbidities compared to other BB users or all other users of comparison drugs. Depression, hyperthyroidism, liver disease, and migraine were slightly more common in propranolol users. Propranolol users were more likely to use antipsychotics, selective serotonin reuptake inhibitor, and nonselective serotonin reuptake inhibitor antidepressants than users of comparison drugs and were less likely than other BB users to have a history of antiplatelet agent use.

Incidence rates of hospitalized myopathy and rhabdomyolysis

We identified 30 cases of hospitalized myopathy in 15,477 person-years of propranolol use and 523 cases in 343,132 person-years of other BB use (Table II), and 12 admissions for rhabdomyolysis in propranolol users and 227 in other BB users. Compared to other BB users or all other comparison drug users (other BB, AB, CCB, and THI combined), the incidence of hospitalization for myopathy and rhabdomyolysis was elevated in propranolol users (crude rate ratio of 1.3:1.7 for hospitalized myopathy and 1.2:1.6 for rhabdomyolysis).

Association between propranolol and myopathy and rhabdomyolysis

After adjusting for potential confounders in the Cox proportional hazards models, we continued to find a significantly increased risk of hospitalized myopathy in propranolol users compared to other BB users or all other comparison drug users (Table III). For rhabdomyolysis, we found a similar degree of increase in the risk, but the 95% CIs were wider due to a smaller numbers of events (hazard ratio [HR] for rhabdomyolysis comparing propranolol users to other BB users was 1.48, 95% CI 0.82-2.67). Because the definition of rhabdomyolysis by Andrade et al[8] had positive predictive value of 75%, it is likely that the misclassification bias brought the estimate toward the null. After October 2003, the specific ICD-9 code for rhabdomyolysis became available. Analysis of the subset of the data with patients at risk for developing rhabdomyolysis after October 2003 found that the HR for rhabdomyolysis comparing propranolol to other BB users was 1.96 (95% CI 0.97-3.97) and the HR comparing propranolol to all other comparison drug users was 2.09 (95% CI 1.04-4.21).

The HR of hospitalized myopathy for high-dose propranolol (HR 1.68, 95% CI 1.01-2.77) was somewhat higher than that for low-dose propranolol (HR 1.26, 95% CI 0.74-2.15), suggesting a possible dose response. Propensity score analyses yielded similar results to the multivariate analyses, with the propensity score-adjusted HR having narrower CIs (Table III). These results were consistent when propranolol users were compared to users of AB, CCB, and THI separately.

Concurrent use of statins and lack of synergistic effect

Concurrent use of any statin was assessed at the time of initiating propranolol, the time of the last prescription before the outcome, or at a censoring event. The co-use of statins was relatively infrequent, for example, the use of statin at the time of last dispensing was 17% (n = 1,557) for propranolol users, 30% (n = 39,171) for other BB users, 25% (n = 19,600) for angiotensin-converting enzyme inhibitor/angiotensin receptor blocker users, 21% (n = 15,251) for CCB users and 23% (n = 27,657) for THI users. We did not find any evidence of a synergistic effect between the use of propranolol and statins in causing myopathy. Among 30 myopathy hospitalizations for the propranolol users, only 6 were exposed to statin at the same time. We therefore did not pursue further analyses assessing additive interactions. Concurrent use with any statin was also assessed at the time of initiating the study drug, but we also did not find any significant interaction between propranolol and statin use in this setting.

Discussion

Using very large population-based databases of typical elderly patients, we found that propranolol might be associated with a 45% increase in the risk of severe myopathy. We also found a statistically nonsignificant 48% increase in the risk of rhabdomyolysis in propranolol users. These results were consistent using multiple comparison groups. These results are compatible with the hypothesis raised by an integrated high-throughput chemical biology and gene expression study.[1] Although there have been a few case reports associating propranolol and myopathy including myotonia[10] and proximal myopathy,[11] to our knowledge, this is the first study to suggest that propranolol may be associated with hospitalization for myopathy at the population level.

Table III. Cox analyses (propranolol vs other BB)

	Hospitalized myopathy			Rhabdomyolysis		
Adjustment	**HR**	**95% CI**		**HR**	**95% CI**	
Unadjusted (crude)*	1.27	0.88	1.84	1.20	0.67	2.15
Unadjusted (Cox)*	1.43	0.99	2.08	1.50	0.84	2.69
Sex, age, and race adjusted (Cox)†	1.44	1.00	2.09	1.52	0.85	2.73
Fully adjusted (Cox)‡	1.45	1.00	2.11	1.48	0.82	2.67
Propensity score adjusted (Cox)	1.42	0.99	2.05	1.53	0.86	2.71
Cox analyses (propranolol vs all other comparison drug users)						
Unadjusted (crude)*	1.40	0.98	2.01	1.31	0.74	2.32
Unadjusted (Cox)*	1.51	1.05	2.17	1.56	0.88	2.77
Sex, age, and race adjusted (Cox)†	1.52	1.06	2.18	1.57	0.89	2.79
Fully adjusted (Cox)‡	1.47	1.02	2.11	1.54	0.87	2.74
Propensity score adjusted (Cox)	1.42	0.98	2.04	1.52	0.86	2.7

* Cox proportional hazards model stratified by calendar year of exposure and state with study time as a time-scale.
† Cox proportional hazards model stratified by calendar year of exposure and state with study time as a time-scale and age, sex, and race in the model.
‡ Cox proportional hazard model stratified by calendar year of exposure and state with study time as a time-scale and age, sex, and adjusted for demographic information (age, race, gender), comorbidities (history of acute coronary syndrome, other coronary artery disease, cerebrovascular disease, peripheral vascular disease, hypertension, chronic kidney disease, chronic airway disease, diabetes, cancer, depression/anxiety, hypothyroidism, hyperthyroidism, liver disease, anemia, depression, inflammatory myositis), and health service use measures (prior nursing home, number of prior hospitalization, number of physician's visits, and number of medications).

One of the promises of modern biomedical research is to inform best practices for patient management with the insights emerging from high-throughput chemical and genomic studies that are now possible. Many previous attempts to extrapolate isolated molecular studies or isolated genomic or proteomic analyses to human populations have failed because these limited experimental systems do not always reflect the true complex dynamics of the organism.[12] We note that the experimental findings motivating this current study are based on an integrated analysis of multiple experimental data sources including studies of cell viability, gene expression, and cell physiology.[1] Some compounds may show a false-positive correlation based on the analysis of any single source of data, but a correlation based on the integration of several different experimental datasets as in this analysis is much more likely to yield a robust prediction. The precise molecular mechanism of the toxicity of propranolol in muscle is still unclear and requires future investigation.

The in vitro study by Wagner et al[1] noted at least an additive, and possibly synergistic, effect of propranolol and statins in causing muscle toxicity. In the present population-level study, we were not able to detect a synergistic effect because small numbers of dually exposed patients limited the power of these data to elucidate this relationship. Alternatively, an additive effect of the combination of statin and propranolol on mitochondrial toxicity may not necessarily translate into a synergistic effect of these drugs at the population level. Limited by the small number of cases in the the propranolol users, we were unable to pursue further analyses testing interactions.

The present study has a few limitations. First, we used ICD-9 diagnosis codes or a previously validated algorithm to define hospitalization for myopathy or rhabdomyolysis. These codes and validated algorithm may not have been sufficiently specific. However, such misclassification is likely to be nondifferential and therefore may have led to underestimation of the true risk. Second, our population-based database does not have precise clinical information on all risk factors for myopathy such as body mass index or history of muscle injuries, including creatine kinase elevations. Although we adjusted for liver dysfunction in our study, the condition is likely to be undercoded in the claims data and therefore likely to lead to residual confounding. However, by selecting users of classes of drugs that have similar indications as a comparison group, we may have been able to minimize the potential confounding. Finally, propranolol can be used for treatment of hyperthyroidism, which is also associated with myopathy. To address this potential confounding, we assessed diagnoses for hyperthyroidism and adjusted for the condition in the analyses. We also conducted analyses excluding patients who had diagnosis for hyperthyroidism, which yielded similar hazard estimates (HR was 1.55 with 95% CI of 0.86-2.81 for rhabdomyolysis and 1.45 with 95% CI of 0.98-2.13 for hospitalized myopathy comparing propranolol to other BB initiators). However, residual confounding by misclassification of hyperthyroidism cannot be ruled out. Nonetheless, the degree of residual confounding is expected to be small due to the low prevalence of the condition and relatively small imbalance of the condition in our population.

Our data indicate that propranolol use may pose a 45% greater risk of severe hospitalized myopathy compared to other BBs or other antihypertensive medications. These findings need to be confirmed in other populations. More generally, this study illustrates the potential value of translating findings from chemical and genomic screening studies into testable hypotheses about drug efficacy and toxicity in human populations.

Acknowledgements

We thank Shawn Murphy and Henry Chueh and the Partners Health Care Research Patient Data Registry group for facilitating use of their database.

Dr Setoguchi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

Financial support: Divisional fund; American Diabetes Association/Smith Family Foundation.

References

1. Wagner BK, Kitami T, Gilbert TJ, et al. Large-scale chemical dissection of mitochondrial function. Nat Biotechnol 2008;26:343-51.
2. Dirks AJ, Jones KM. Statin-induced apoptosis and skeletal myopathy. Am J Physiol Cell Physiol 2006;291:C1208-12.
3. Cheong HI, Johnson J, Cormier M, et al. In vitro cytotoxicity of eight beta-blockers in human corneal epithelial and retinal pigment epithelial cell lines: comparison with epidermal keratinocytes and dermal fibroblasts. Toxicol In Vitro 2008;22:1070-6.
4. Stergachis AS. Record linkage studies for postmarketing drug surveillance: data quality and validity considerations. Drug Intell Clin Pharm 1988;22:157-61.
5. McKenzie DA, Semradek J, McFarland BH, et al. The validity of Medicaid pharmacy claims for estimating drug use among elderly nursing home residents: the Oregon experience. J Clin Epidemiol 2000;53:1248-57.
6. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915-20.
7. Glynn RJ, Schneeweiss S, Wang PS, et al. Selective prescribing led to overestimation of the benefits of lipid-lowering drugs. J Clin Epidemiol 2006;59:819-28.
8. Andrade SE, Graham DJ, Staffa JA, et al. Health plan administrative databases can efficiently identify serious myopathy and rhabdomyolysis. J Clin Epidemiol 2005;58:171-4.
9. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med 1997;127(8 Pt 2):757-63.
10. Blessing W, Walsh JC. Myotonia precipitated by propranolol therapy. Lancet 1977;1:73-4.
11. Forfar JC, Brown GJ, Cull RE. Proximal myopathy during beta-blockade. Br Med J 1979;2:1331-2.
12. Sobie EA, Guatimosim S, Song LS, et al. The challenge of molecular medicine: complexity versus Occam's razor. J Clin Invest 2003;111:801-3.