Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Jackevicius CA, Tu JV, Demers V, et al. Cardiovascular outcomes after a change in prescription policy for clopidogrel. N Engl J Med 2008;359:1802-10.

Statistical Appendix

I. *Time Series Statistical Analysis: Detailed Methods and Results*

A. *Autocorrelation Structure:*

Methods:

Autoregressive integrated moving average (ARIMA) interrupted time-series analyses were used to model the monthly composite outcome and mortality rates to assess the effect of the drug policy change on the outcomes. The following procedures were employed. Preintervention ARIMA models of serial dependence were identified. First, we checked for stationarity of the time series using the augmented Dickey-Fuller test (ADF). We conducted an autocorrelation check for the presence of white noise. From examining the autocorrelation (ACF) and partial autocorrelation, ARIMA parameters were estimated. We used the Akaike Information Criterion (AIC) to select between several appropriate preintervention models. Next, we ran diagnostic checks over the residuals of the models. The Ljung-box Chi-square test was used to evaluate if the residuals were white noise.

Results:

The preintervention series was stationary (ADF p-values <0.05). Therefore, we didn't need to apply any transformation or differentiation. The Chi-square test for white noise autocorrelation was not statistically significant for the first six autocorrelations (p=0.496). From examining the ACF and PACF plots for the data and according to the AIC criteria (AIC=242.5), the selected preintervention model was an ARIMA (0,0,2) (p=0: no autoregression (not related to the past points), d=0: no differentiation was needed (because no trend with time), q=2: moving average (MA) order two but MA only took on lag 2 (principle of parsimony). The autocorrelation check of residuals was not significant at lag 6 or more (p-value>0.1). This means that the residual was white noise and no additional information was required to be used to construct a more complex model.

B. Model of Intervention Variable:

Methods:

Next, a new data set was created and a new variable called "I" was created as a binary variable to denote the intervention (change of drug policy in September 2003). Having identified a feasible model with the baseline data (the model with the minimum AIC), that model was applied to the complete interrupted time series. The intervention effect was then added to the model, as a dummy variable coded as 1 for the intervention phase (after September 2003) and 0 for the baseline phase (before September 2003). The interrupted time series was used to test for the impact of the intervention due to the drug policy change. A test for the difference between phases of the experiment was then performed on these data using the traditional t-test statistic.

Results:

The intervention parameter (ω) representing a change in the series level was -3.78 and was statistically significant at alpha=0.05 with Pr>|t|=-2.43 and its standard error was 1.557, P-value=0.015. The estimate of the intervention variable (ω) was negative and statistically significant, therefore, an intervention effect was found to exist.

Parameter estimates, standard errors and p-values from the full segmented time series regression model

Variable	Parameter	Estimate	Standard Error	t Value	Approx Pr > |t|
Combined outcome	MU	15.31963	0.89411	17.13	<.0001
Combined outcome	MA1,1	-0.28738	0.12940	-2.22	0.0264
Drug policy change (step function)	ω	**-3.78441**	**1.55702**	**-2.43**	**0.0151**

MA=moving average

II. Summary of Analysis of Primary Outcome

The primary model of analysis for the study was the time series analysis. We initially compared the pre- and post-intervention composite event rates using Chi-square, although we recognized the limitations of this method with time-dependent data. To assist with the visual interpretation of the data on the figure, we fit two separate regression trend lines. For the regression models, we found that pre-policy, there was not a significant trend in the composite outcome (p=0.625), but there was a significant trend post-policy (p=0.070). We retained the time series analysis as our primary model of analysis, recognizing that regression was not the ideal statistical model for this data.