Clinical Evidence, Practice Guidelines, and β-Blocker Utilization Before Major Noncardiac Surgery

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Background—Largely on the basis of 2 randomized trials published in the 1990s, β-blockers were initially promoted as an evidence-based intervention for preventing cardiac complications of noncardiac surgery. However, subsequent studies raised concerns about a widespread use of perioperative β-blockade. Little is known regarding how this changing evidence influenced the use of perioperative β-blockers in clinical practice.

Methods and Results—We conducted a population-based, time-series analysis (April 1999 to March 2010) among residents of Ontario, Canada (age 66 years and older), to evaluate the influence of research publications and practice guidelines on rates of new β-blocker prescriptions before major elective noncardiac surgery. In an analysis of 249,828 procedures, the rate of new β-blocker prescriptions increased from 26.3 per 1000 procedures in April 1999 to 62.7 per 1000 procedures in the first quarter of 2005, after which it decreased to 19.7 per 1000 procedures by March 2010. We observed a marked decrease in prescriptions (P=0.004) during early 2005, without any preceding publications that raised concerns about perioperative β-blockade. There was no change (P=0.98) in prescription rates after the May 2008 publication of a multicenter, randomized trial that showed increased mortality from perioperative β-blockade. Prescribing trends remain unchanged after revisions of related practice guidelines in 2002 (P=0.28) and 2006 (P=0.53).

Conclusions—After a period characterized by increasing adoption of preoperative β-blockade between 1999 and 2005, prescriptions rates subsequently fell from 2005 to 2010. Further research is needed to understand the basis for these changes, which are only partially explained by evidence of potential harm. (Circ Cardiovasc Qual Outcomes. 2012; 5:558-565.)

Key Words: surgery □ β-blockers □ coronary artery disease □ health services research

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Most recently, the publication of the results of Perioperative Ischemic Evaluation (POISE) trial in May 2008 raised more concerns about the safety of perioperative β-blockade. This multicenter RCT showed that individuals randomly assigned to receive β-blockers before surgery had a reduced risk of postoperative myocardial infarction but increased risk of significant hypotension, stroke, and death. The surprising results generated considerable debate (Nainggolan L. POISE β-blockers continues.

Published, debate on perioperative results generated considerable debate (Nainggolan L. POISE β-blockers continues.

http://www.theheart.org/article/864785.do) and led to further changes in practice guidelines. Specifically, the 2009 ACC/AHA guidelines only made moderate to strong recommendations for perioperative β-blockade in patients considered to be at highest risk for postoperative cardiac events.2

Despite such important changes in clinical evidence and guideline recommendations, relatively little is known about their influence on physicians’ prescribing of β-blockers before surgery. We therefore conducted a population-based, time-series study in Ontario, Canada, to assess trends in β-blocker use for noncardiac surgery and evaluate shifts in practice potentially attributable to changes in clinical evidence or guidelines recommendations.

WHAT IS KNOWN

• Largely on the basis of 2 randomized trials published in the 1990s, β-blockers were initially promoted for preventing cardiac complications of noncardiac surgery.
• Subsequent research cast doubts on both the efficacy and safety of perioperative β-blockade.

WHAT THE STUDY ADDS

• The mean rate of new β-blocker prescriptions before major elective noncardiac surgery in Ontario, Canada, between 1999 and 2010 was low, at 40.3 per 1000 procedures.
• The rate of new β-blocker prescriptions initially rose from 1999 to early 2005, after which it declined from 2005 to 2010.
• These changing prescribing trends were consistent across patients over varying perioperative cardiac risk but were not explained by the publication of new clinical evidence or revised practice guidelines.

Methods

A population-based, cross-sectional, time-series analysis was conducted in Ontario, Canada, using the following linked administrative databases: the Discharge Abstract Database of the Canadian Institute for Health Information (hospital admissions), the Ontario Health Insurance Plan database (physician service claims), the Registered Persons Database (demographics and vital statistics), and the Ontario Drug Benefit database (prescription medications for individuals aged older than 65 years). The approximately 13 million residents of Ontario have universal access to physician and hospital services through a publicly funded healthcare program. The research ethics board at Sunnybrook Health Sciences Centre approved this study.

We identified specific elective noncardiac surgeries performed between April 1, 1999, and March 31, 2010, on Ontario residents who were aged 66 years or older: abdominal aortic aneurysm repair, carotid endarterectomy, peripheral vascular bypass, total hip replacement, total knee replacement, large bowel resection, partial liver resection, Whipple procedure, pneumonectomy, pulmonary lobectomy, gastrectomy, esophagectomy, nephrectomy, and cystectomy. These procedures are intermediate to high risk and are previously described in the Discharge Abstract Database.13,14 Procedural information in the Discharge Abstract Database is very accurate.15 An age restriction of 66 years was imposed because data on outpatient medication prescriptions were only available for individuals aged 65 years or older, and a 1-year look-back period was used to ascertain preoperative medication use.

Patients were categorized on the basis of their perioperative cardiac risk. We estimated their risk using the Revised Cardiac Risk Index (RCRI),20 which consists of 6 equally weighted components: coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes, renal insufficiency, and high-risk surgery (major vascular, intraperitoneal, or intrathoracic procedures). As previously proposed, low-risk was defined as a RCRI score of zero or intermediate-risk as a score of 1 to 2, and high-risk as a score of 3 or more.21 Using the Discharge Abstract Database, we identified the presence of coronary artery disease, congestive heart failure, cerebrovascular disease, and renal insufficiency based on International Classification of Diseases codes (9th or 10th Revisions) from hospitalizations within 3 years before surgery.22 Additionally, validated algorithms were used to ascertain diabetes,23 and the Ontario Health Insurance Plan database was used to identify patients who required dialysis before surgery. We also used the Discharge Abstract Database and Registered Persons Database to identify any perioperative 30-day deaths.

The Ontario Drug Benefit database was used to identify outpatient prescriptions for orally administered β-blockers (except sotalol) before each surgical procedure. We excluded sotalol because it is typically used to suppress cardiac arrhythmias, as opposed to preventing cardiac ischemia. Prescription information in Ontario Drug Benefit database is very accurate.24 Practice guidelines recommend that perioperative β-blockade be initiated several days to weeks before surgery,15,25,26 with further suggestions to initiate therapy 7 or more days before surgery.22 Notably, many surgical patients in Ontario who warrant perioperative β-blockade may be able to initiate therapy well before their surgeries. Specifically, once they have been deemed to require surgery, the time required for 90% to undergo our scheduled procedures is 58 days for cancer surgery, 104 days for vascular surgery, and 192 days for orthopedic surgery (Ontario Ministry of Health and Long-Term Care. Ontario Wait Times: Wait Time for Surgery, MRIs and CTs. Available at http://waittimes.hco-on.ca/en/search/surgery/adult). In addition, 91% of preoperative medical consultations, which are the physician encounters where preoperative β-blocker therapy is most likely to be initiated, occur within 60 days before surgery, as compared with 84% within 30 days before surgery.26 For the purpose of the primary analysis, we therefore defined new perioperative β-blocker use as initiation of therapy within 60 days before surgery. Specifically, new perioperative β-blocker prescriptions were identified on the basis of (1) 1 or more prescriptions within 60 days before hospital admission and (2) no prescriptions between 61 and 365 days before admission. To evaluate whether trends in new perioperative β-blocker use were distinct from trends in patients’ other cardiovascular medications, we used the same database to identify statin and nonperoperative β-blocker prescriptions. Statin use was defined based on the presence of 1 or more statin prescriptions within 100 days before hospital admission. These prescriptions were classified as new preoperative use based on the same algorithm described for new β-blocker prescriptions. Otherwise, the prescriptions were classified as nonperioperative use. Nonperioperative β-blocker use was defined based on the presence of either (1) 1 or more prescriptions between 61 to 100 days before hospital admission or (2) 1 or more prescriptions within 60 days before hospital admission, in conjunction with 1 or more prescriptions between 61 to 365 days before admission.

In sensitivity analyses, we used 2 alternative definitions of new β-blocker use, namely, (1) 1 or more prescriptions within 30 days before hospital admission or (2) 1 or more prescriptions within 7 days...
before hospital admission, in individuals who had not previously received any β-blockers within the year before surgery.

Analysis

Each year of the study period was divided into 3-month intervals (January to March, April to June, July to September, October to December). Surgeries were assigned to these intervals based on the date of hospital admission. We measured rates of preoperative β-blocker use, preoperative statin use, and 30-day mortality within each interval. Rates of new β-blocker use were calculated among individuals who were not previously using β-blockers, whereas rates of new statin use were calculated among individuals who were not previously using statins. Conversely, rates of nonoperative β-blocker and statin use were calculated among all patients. These rates were also calculated for subgroups based on RCRI score (low risk: zero points; intermediate-high risk: 1 or more points) and surgical procedure (vascular surgery; nonvascular surgery). The sample size was not large enough for a subgroup analysis of only high-risk patients with RCRI scores of 3 or more.

Patterns of preoperative β-blocker and statin use over the study period were examined using time-series analysis, which is a collection of techniques for modeling autocorrelation in temporally sequenced data. In the primary analysis, trends in rates of new β-blocker use, nonoperative β-blocker use, new statin use, nonoperative statin use, and 30-day mortality were separately examined. In secondary analyses, we examined trends in rates of new β-blocker use within strata defined by RCRI score and surgical procedure.

The association of selected publications with rates of new operative β-blocker use was assessed through intervention autoregressive integrated moving average (ARIMA) models with ramp functions. Ramp functions describe points in time when the trend in data gradually changes slope. The publications and guidelines that we considered a priori to have potentially influenced rates of new β-blocker prescriptions are described in the Table. We evaluated the appropriateness of the model assumptions by performing the augmented Dickey-Fuller test, calculating the Ljung-Box statistic at various lags, and assessing the autocorrelation, partial autocorrelation, and inverse autocorrelation functions. In sensitivity analyses, we reevaluated the impact of these same publications by using a different statistical approach, namely, segmented regression models within a “difference-in-differences” framework. These linear regression models tested for changes in the slope of a linear trend before and after a specific point in time. All statistical analyses were performed using SAS Version 9.2 (Cary, NC). A 2-sided probability value ≤0.05 was used to define statistical significance.

Results

The analysis included 249,828 procedures that were performed between April 1, 1999, and March 31, 2010. Of these procedures, 191,481 involved individuals who were not previously using β-blockers (characteristics presented in Online Data Supplement Table I). The overall rate of new preoperative β-blocker prescriptions during the study period was low (40.3 per 1000 procedures). The rate rose from 26.3 per 1000 procedures in April 1999 and peaked during the first quarter of 2005 (62.7 per 1000 procedures), after which it declined to 19.7 per 1000 procedures by March 2010 (Figure 1). Although rates of new β-blocker prescriptions were generally higher in intermediate- to high-risk patients as opposed to low-risk patients (Figure 2), similar temporal changes occurred in both subgroups. However, these patterns were specific to new β-blocker prescriptions. By comparison, rates of perioperative and nonoperative statin prescriptions rose consistently over the study period (Figures 1 and 3), whereas rates of nonoperative β-blocker prescriptions initially rose and reached a plateau by mid-2002 (Figure 3).

Qualitative inspection of trends in new preoperative β-blocker use (Figure 1) suggested a directional change in this trend during the first quarter of 2005, which was confirmed statistically (P<0.001). This directional change was also evident in subgroups of low-risk (P=0.006) and intermediate-to high-risk (P=0.005) patients (Figure 2). Conversely, qualitative inspection of prescription trends did not suggest any changes in prescribing patterns after the publication of the POISE trial in May 2008 (Figure 1 and 2), which was confirmed statistically for all patients (P=0.98), low-risk patients (P=0.95), and intermediate- to high-risk patients (P=0.89). Similarly, there was no evidence of a change in prescribing trends after the earlier presentation of these results at a major international scientific meeting (November 2007). Finally, there was no graphical or statistical evidence of a shift in prescribing trends after the publication of revised ACC/AHA practice guidelines in 2002 (P=0.28) and 2006 (P=0.53). These findings were also similar in the subgroups of low-risk and intermediate-to high-risk patients.

The study findings were qualitatively similar when the time-series analyses were repeated, using different definitions for new β-blocker use (Figure 4), subgroups of vascular surgical procedures (Online Data Supplement Figure 1), or segmented linear regression methods. In addition, there was no qualitative evidence of changes in 30-day mortality that coincided with shifts in rates of new β-blocker prescriptions (Figure 5).

Discussion

Rates of new β-blocker prescriptions before major elective noncardiac surgery in Ontario were relatively low and underwent marked changes between 1999 and 2010. In association with an early positive clinical trial, the use of preoperative β-blockers increased rapidly between 1999 and early 2005, after which it began to decline. This decline was not further influenced by either the publication of the POISE trial, a large RCT that demonstrated harm from perioperative β-blockade, or revisions of AHA/ACC practice guidelines that advised changes in β-blocker use.10,15

Past examinations of the diffusion of new research findings into clinical practice have typically emphasized delays in clinicians’ uptake of guideline recommendations and evidence-based practices. Conversely, some recent work has also described the potential for innovations with high degrees of intuitive appeal to diffuse rapidly into clinical practice, even if definitive proof of efficacy is lacking. In this present study, we observed a rapid adoption of preoperative β-blocker treatment after initial reports that suggested clinical efficacy. Notably, this trend in clinicians’ behavior occurred before similar recommendations by perioperative practice guidelines. The increased initiation of β-blocker use from 1999 to early 2005 was specific to the perioperative setting; by comparison, nonoperative β-blocker use among surgical patients plateaued in mid-2002. These differing prescribing patterns may be explained, in part, by 1999 Canadian practice guidelines recommending against β-blockers as first-line treatment for hypertension in individuals aged 60 years or older. Previous research has shown that in the nonoperative setting, these recommendations led to subsequent general
We also observed a previously undescribed shift from increasing to decreasing rates of new preoperative β-blocker prescriptions during early 2005. This shift was again specific to new β-blocker prescriptions. Newly published clinical evidence in peer-reviewed journals was unlikely to be the major basis for this shift, especially since it occurred before the publication of any studies that raised doubts about the efficacy of perioperative β-blockade, such as the POBBLE trial (April 2005),11 DiPOM trial (June 2006),12 MAVS trial (November 2006),13 and the cohort study by Lindenauer et al14 (July 2005). It is also unlikely that this shift was caused by general changes in prescribing patterns for β-blockers in decline in new β-blocker prescriptions among Ontario residents aged 65 years or older.40

We also observed a previously undescribed shift from increasing to decreasing rates of new preoperative β-blocker prescriptions during early 2005. This shift was again specific to new β-blocker prescriptions. Newly published clinical evidence in peer-reviewed journals was unlikely to be the major basis for this shift, especially since it occurred before the publication of any studies that raised doubts about the efficacy of perioperative β-blockade, such as the POBBLE trial (April 2005),11 DiPOM trial (June 2006),12 MAVS trial (November 2006),13 and the cohort study by Lindenauer et al14 (July 2005). It is also unlikely that this shift was caused by general changes in prescribing patterns for β-blockers in
the nonoperative setting. Specifically, rates of new prescriptions for β-blockers in the nonoperative setting began to decline in 1999. Nonetheless, it is possible that the presentation of some perioperative β-blocker studies at medical conferences could have been partially responsible for the shift in prescribing patterns during early 2005. Specifically, the results of the MAVS trial (June 2004) and DIPOM trial (November 2004) were presented at scientific meetings within the 6-month period preceding the shift. Perioperative physicians may have learnt about the findings presented at these conferences before their publication in print journals, either by attending the relevant conferences themselves, discussing with colleagues who attended these conferences, or reading web-based coverage of newly presented research at medical conferences. The relative contributions of these different mechanisms remain unclear and merit further research.

Although the shift from increasing to decreasing β-blocker use in early 2005 may have been partially attributable to the availability of new clinical evidence (albeit not in the print literature), it is unlikely that changes in clinical evidence were the only reason for this marked shift in prescribing practice. Another potential explanation, which requires evaluation by future research, is clinicians’ own observations of adverse events after preoperative β-blockade (eg, significant hypotension). Especially since perioperative β-blockers are associated with relatively common short-term adverse effects that
could be readily attributed to the new medication,\textsuperscript{16,41} the initial rising rates of perioperative $\beta$-blockade from 1999 to 2005 might have led to an increasing recognition of related adverse effects and subsequently dampened enthusiasm for these medications.

By comparison to the significant shift in prescribing trends in early 2005, we found no strong evidence of changes in prescribing practice after the release of the results of the POISE trial, either as a conference presentation (November 2007) or print publication (May 2008). There are several potential explanations for this observation. Given the preceding decline in $\beta$-blocker use, the POISE trial results may have only confirmed and supported ongoing trends in practice. In addition, controversy surrounding the interpretation of POISE trial, some of which related to its use of high fixed doses of $\beta$-blockers, may have lessened the clinical impact of the study findings. Finally, the results of the POISE trial may have most strongly influenced in-hospital initiation of $\beta$-blockers immediately before surgery, yet our data sources did not capture in-hospital medication use.

Although we identified important directional shifts in prescribing trends, these shifts occurred within the context of a low overall prescription rate for $\beta$-blockers, which ranged from 19.7 to 62.7 per 1000 procedures over the study period. This low prescription rate in our population-based study is consistent with other Ontario data sources. Specifically, Ellenberger et al.\textsuperscript{42} reported that the rate of new perioperative $\beta$-blocker prescriptions at 2 tertiary care Ontario hospitals was 58.2 per 1000 procedures; notably, these data included both in-hospital and outpatient prescriptions. This low prescription rate suggests that despite strong encouragement by proponents of patient safety,\textsuperscript{6–9} most clinicians remained reluctant to incorporate perioperative $\beta$-blockade into their clinical practice.

Our study also highlights the importance of research that seeks to describe and understand physicians’ adoption and abandonment of new medical therapies, especially within the context of rapid changes in the biomedical literature. The case of perioperative $\beta$-blockade serves as a model for understanding how clinical care might be altered when the results of early positive clinical trials are initially promoted enthusiastically but subsequently refuted by larger studies. Future research should therefore examine how clinical practice was altered in other settings associated with similar swings in evidence, such as intensive glucose control in the critically ill.\textsuperscript{43,44}

Our study has limitations. First, our data sources lacked information on $\beta$-blocker use occurring in-hospital or among individuals younger than 65 years. Thus, we could not capture de novo administration of $\beta$-blockers immediately before surgery, as might be performed by some anesthesiologists. Nonetheless, the absence of information on in-hospital
medication use is unlikely to explain the shift to a decreasing rate of outpatient β-blocker prescriptions in early 2005. However, it could have masked some of the impact from the results of the POISE trial and might have had a greater impact on in-hospital use of β-blockers. Second, the study population was not large enough to examine specific subgroups, such as high-risk patients with an RCRI score of 3 or more. It is conceivable that trends in β-blocker prescriptions may differ in these smaller subgroups.

Third, the 60-day window used to identify new preoperative β-blocker prescriptions in the primary analysis may be considered exceedingly long in jurisdictions with shorter waiting times for surgery. However, as described previously, this window is appropriate for the setting of the present study. In addition, our overall findings remained consistent in sensitivity analyses that used shorter time-windows for ascertaining new preoperative β-blocker use. Fourth, our results represent clinical practice within Ontario, a region where individuals aged 65 years or older have access to publicly funded prescription drug coverage and where several scientists leading the POISE trial are located. Thus, the generalizability of our results to other settings warrants further study.

Conclusions
In this population-based, time-series analysis, we found that rates of new β-blocker prescriptions before major elective noncardiac surgery in Ontario, while relatively low overall, underwent marked changes between 1999 and 2010. There was a statistical and qualitative evidence of a significant shift toward decreasing β-blocker use in early 2005 but no clear change in prescription rates that could be attributable to the publication of a large, randomized trial showing evidence of harm or to 2 prominent clinical practice guidelines published over the period. These findings highlight the importance of research that seeks to understand the processes underlying physicians’ adoption and abandonment of new medical therapies, as well as the potential benefits and harms of the ways in which information gained from randomized trials, observational studies, and practice guidelines inform medical decision-making.

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Disclosures
None.

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**SUPPLEMENTAL TABLE 1:** Characteristics of individuals who were not previously using beta-blockers (i.e. those with the potential to receive new preoperative beta-blocker prescriptions)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Cohort N = 191,481</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>104,098 (54.4%)</td>
</tr>
<tr>
<td>Age, year, mean (SD)</td>
<td>74.6 (5.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbid disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>17,214 (9.0%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3,890 (2.0%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5,788 (3.0%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>5,962 (3.1%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>15,482 (8.1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>135,372 (70.7%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>41,534 (21.7%)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>16,753 (8.7%)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>3,876 (2.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Revised Cardiac Risk Index score</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero points</td>
<td>92,768 (48.4%)</td>
</tr>
<tr>
<td>One point</td>
<td>70,740 (36.9%)</td>
</tr>
<tr>
<td>Two points</td>
<td>21,819 (11.4%)</td>
</tr>
<tr>
<td>Three points</td>
<td>4,752 (2.5%)</td>
</tr>
<tr>
<td>Four points</td>
<td>1,147 (0.6%)</td>
</tr>
<tr>
<td>Five or more points</td>
<td>255 (0.1%)</td>
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</table>

<table>
<thead>
<tr>
<th>Procedure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA repair</td>
<td>6,931 (3.6%)</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>5,512 (2.9%)</td>
</tr>
<tr>
<td>Peripheral vascular bypass</td>
<td>6,335 (3.3%)</td>
</tr>
<tr>
<td>Total hip replacement</td>
<td>46,049 (24.0%)</td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>77,872 (40.7%)</td>
</tr>
<tr>
<td>Procedure</td>
<td>Count</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Large bowel surgery</td>
<td>31,543</td>
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<tr>
<td>Liver resection</td>
<td>1,212</td>
</tr>
<tr>
<td>Whipple procedure</td>
<td>865</td>
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<tr>
<td>Pneumonectomy or lobectomy</td>
<td>5,436</td>
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<tr>
<td>Gastrectomy or esophagectomy</td>
<td>3,256</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>4,567</td>
</tr>
<tr>
<td>Cystectomy</td>
<td>1,903</td>
</tr>
</tbody>
</table>

Abbreviations: AAA, abdominal aortic aneurysm; SD, standard deviation
**Supplemental Figure 1:** Trends in new outpatient prescriptions for beta-blockers within 60 days before major elective vascular surgery procedures in Ontario

Rates of new beta-blocker prescriptions before elective vascular non-cardiac surgery in Ontario, Canada. These rates (per 1000 procedures) are reported for three-month periods from 1 April 1999 to 31 March 2010. The vertical lines represent the timing of publications that may have influenced rates of perioperative beta-blockade.