PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk Factors for Persistent and New Chronic Opioid Use in Patients Undergoing Total Hip Arthroplasty: A Retrospective Cohort Study
AUTHORS	Inacio, Maria; Hansen, Craig; Pratt, Nicole; Graves, Steven; Roughead, Elizabeth

VERSION 1 - REVIEW

REVIEWER	Karim Ladha Department of Anesthesia, Toronto General Hospital and University of Toronto, Toronto, Ontario, Canada
REVIEW RETURNED	29-Dec-2015

GENERAL COMMENTS	The authors undertook a retrospective cohort study of patients undergoing THA and examined predictors of new and persistent chronic opioid use postoperatively. I would first like to commend the authors for their excellent study. Their investigation tackles a significant public health problem that is relevant to all perioperative clinicians and the work represents a needed contribution to the existing literature. I appreciated the fact that they chose to study an orthopedic procedure and included patients who were not opioid naïve, as other papers looking at persistent opioid use have excluded this patient population. However I do have a few concerns that I feel should be addressed and clarified before the manuscript is published. Major Concerns: 1) Definition of Opioid Use: a. The windows that define chronic opioid use are a little unclear to me. If a patient took no opioids in the immediate three months prior to surgery but had filled prescriptions 6-9 months before surgery would they still be included in the chronic opioid use cohort? Similarly, if they used opioids 9-12months after surgery but none 3-9 months after, would they be defined as chronic users? If the answer is yes, then maybe it would be better to shorten this window to the immediate periods before and after surgery. Perhaps do this as a sensitivity analysis? b. The term “continuous use” was not well defined. The authors should provide a little more detail on how this was calculated in their study. Was days supply simply taken from the database or was it

adjusted/calculated in some way? For example if a patient fills a prescription and the days supply is calculated as 14 days, what happens if they fill a prescription 20 days later? Are they not considered continuous users? Were gaps in the days supply allowed or did the prescriptions have to be overlapping?

Minor Concerns

1) In the results of the abstract, I think it makes more sense to present the percentage of patients who remained chronic users as 302/593 rather than as a percentage in the total cohort. Same for total new users. This is how it is presented under the strengths and limitations section.
2) I see that pre-surgical opioid use was a risk factor. However it is presented in 30 day increments rather than daily OME? Was daily OME included in the model and not found to be significant? The inclusion of preoperative opioid use as a risk factor is not described in the methods section and not listed in table 1 with the other risk factors considered.
3) One of the strengths in the summary states that the cohort was fully captured with no attrition but patients who had less than one year follow-up were excluded.
4) On page 6, line 59, I believe “affect” should be “effect”
5) The sentence on page 8 lines 12-17 is not clear and needs to be re-worded.
6) The authors did not have detailed data regarding what happened to a patient during their hospitalization i.e. complications, ICU stay, type of anesthesia, blood loss, or length of stay, discharge destination. I think this should probably be listed as a limitation.
7) How were patients who did not have one year of data prior to their surgery handled or did this scenario not occur?
8) When deciding whether a patient was exposed to additional analgesic medications as a risk factor eg. NSAID, during what period was this assessed? Was it defined as any prescription filled at any point during the year prior to surgery? Not sure if makes sense to consider an NSAID taken a year before surgery as equal to one taken a few days before.
9) It seems like having a previous hip surgery would be a confounder between some of the risk factors and taking opioids preoperatively. Was it adjusted for?
10) I find it hard to interpret the age in 10 year increments result when 95% of the cohort spanned a single 10 year increment.
11) In table 2, the heading states “for those who changed”. It is unclear what that means. Is this for patients who changed opioid groups pre and post THA? If so, then how could there be values for patients who remained in the chronic category during both time periods?

REVIEWER	Craig T Hartrick, MD Oakland University, USA Speakers' Bureau - The Medicines Company
REVIEW RETURNED	25-Jan-2016

GENERAL COMMENTS	The authors have attempted to address an important issue, the long-term use of opioids following a common surgical procedure. They state that patients are exposed to opioids for a long period of time after hip arthroplasty as a fact. They then present data to show this is likely true for only a minority of patients. They state that hip arthroplasty patients are at risk for misuse of opioids also as a fact. Misuse, i.e. use other than as prescribed, is however not assessed. In fact, in this work, all opioids were presumed to have been taken exactly as prescribed. Consequently, the ensuing discussions about "narcotic" use (presumably they mean opioid use), prescription, prescription habits, misuse and abuse become difficult and strained. The authors, and others, have pointed out the prevalence of persistence of pain following hip arthroplasty. The finding that only 2% became new chronic opioid users is then perhaps a pleasant surprise. The reasons provided for persistent pain, other than female sex, as provided are understandable as alternative reasons for opioid prescription (back pain, migraine, etc.). The lack of association in the "new" chronic users with other well known predictors making opioid treatment risky (psychiatric co-morbibities, alcohol abuse, opioid abuse, etc.) is likely controlled for and reflected in those with chronic opioid use both before and after surgery. It may also reflect the ability of physicians to recognize red flags and/or use instruments such as the Opioid Risk Tool before contemplating long-term opioid prescription. Retrospective studies suffer from many failings that can introduce bias. This study, having taken place over a long period of time, suffers in particular from changing prescribing habits over the decade, increasing awareness of the risks of opioid prescription, changing surgical practices over the decade including the introduction of minimally invasive techniques, and changing rehabilitation practices, all affecting opioid use. The study size is not very large considering the time frame for data collection, the many variables contributing to analgesic requirements, and the relatively low proportion of patients receiving opioid prescription long-term. No sample size determination was provided to examine any specific outcome measure. Nevertheless many interesting findings can be derived from database analyses, even when performed retrospectively. However, for meaningful conclusions to be derived, the definitions used need to be clearly defined. This study defines chronic use as 90 days of continuous use or 120 days of non-continuous use. Use, however, is only assumed based upon prescription history. It is unknown if the medications were used, misused, or discarded. What is meant by continuous use and discontinuous use is not defined. When discussing issues related to tolerance development, for example, certain doses over a given period of time are strictly defined. Here apparently any dose at any frequency might qualify as "non-continuous" use (or more accurately, non-continuous prescription). Clearly intermittent use (prescription) for undefined reasons, might not necessarily lead to any serious consequences. The authors then

	proceed to describe assignment into “chronic”, “some”, and “none” categories without any definition as to how the cut-offs were set. The Tables provide some suggestion as to presumed opioid equivalents calculated, but the rules for grouping as a categorical variable is not provided, nor is the rationale given for doing so. This reviewer has a difficult time being confident in the conclusions drawn without a better understanding of the definitions of continuous “use” (prescription), non-continuous “use”(prescription), as well as “chronic” and “some” use (prescription). The discussion should focus on the facts rather than assumptions about risk for misuse and abuse without relating these findings back to known risk factors for these conditions.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Karim Ladha
Institution and Country
Department of Anesthesia, Toronto General Hospital and University of Toronto, Toronto, Ontario, Canada
Please state any competing interests or state ‘None declared’:
None declared
Please leave your comments for the authors below Please see attached file.

The authors undertook a retrospective cohort study of patients undergoing THA and examined predictors of new and persistent chronic opioid use postoperatively. I would first like to commend the authors for their excellent study. Their investigation tackles a significant public health problem that is relevant to all perioperative clinicians and the work represents a needed contribution to the existing literature. I appreciated the fact that they chose to study an orthopedic procedure and included patients who were not opioid naïve, as other papers looking at persistent opioid use have excluded this patient population. However I do have a few concerns that I feel should be addressed and clarified before the manuscript is published.
Response: Thank you for your comments.

Major Concerns:
1) Definition of Opioid Use:
a. The windows that define chronic opioid use are a little unclear to me. If a patient took no opioids in the immediate three months prior to surgery but had filled prescriptions 6-9 months before surgery would they still be included in the chronic opioid use cohort?
Response: Yes, this is correct.
Similarly, if they used opioids 9-12months after surgery but none 3-9 months after, would they be defined as chronic users? If the answer is yes, then maybe it would be better to shorten this window to the immediate periods before and after surgery. Perhaps do this as a sensitivity analysis?
Response: Yes, this is also correct. A priori we decided on the 3-12 months post-surgical period as our window of exposure because of the lack of recommended periods for this assessment, difficult in doing so for surgical populations,1 and because of recent post- surgical chronic opioid studies. 2,3 Additionally, from a quality use of medicine’s perspective we regard this time period as a conservative/inclusive period for chronic opioid use ascertainment. Per the reviewer’s suggestion we evaluated the number of patients who were identified as chronic users using only days 91-270 and it was 196/302=65% of the persistent users and 84/196=44% of new chronic users. These numbers do not include patients who started being chronic users during this shorter exposure period. Our

estimates of risk factors for persistent and new chronic user were mostly consistent when using this shorter time windown, with a few risk factors no longer being significant and wider confidence intervals as expected since we reduced our number of events. No factors changed direction of association. No changes were made to the manuscript at this time.

1. Macrae WA. Chronic pain after surgery. British journal of anaesthesia. Jul 2001;87(1):88-98.
2. Raebel MA, Newcomer SR, Reifler LM, et al. Chronic use of opioid medications before and after bariatric surgery. JAMA. Oct 2 2013;310(13):1369-1376.
3. Raebel MA, Newcomer SR, Bayliss EA, et al. Chronic opioid use emerging after bariatric surgery. Pharmacoepidemiology and drug safety. Dec 2014;23(12):1247-1257.

b. The term “continuous use” was not well defined. The authors should provide a little more detail on how this was calculated in their study. Was days supply simply taken from the database or was it adjusted/calculated in some way? For example if a patient fills a prescription and the days supply is calculated as 14 days, what happens if they fill a prescription 20 days later? Are they not considered continuous users? Were gaps in the days supply allowed or did the prescriptions have to be overlapping?

Response: We apologize for the lack of clarity. We changed the method section, see top of page 7 to include more detail on definition of chronic use and how it was calculated. See edited text: “Chronic opioid use was defined as having any number of opioid prescriptions, or dosing, for at least 90 days continuously or opioid prescriptions for 120 non-consecutive days. The number of days was obtained from the number of units supplied. No gap days between one prescription supply and another were allowed when determining consecutive prescription of opioids.”

The median number of opioid prescriptions was 15 (interquartile range 11-20) for chronic users pre-THA and only 5% of this cohort had 7 or less prescriptions during the period. Similarly, the cohort defined as chronic users after THA surgery had a median number of 15 (interquartile range 12-22) prescriptions for opioids and 5% of them had less than 8 prescriptions, indicating that these were cohorts with a high number of prescriptions.

Minor Concerns

1) In the results of the abstract, I think it makes more sense to present the percentage of patients who remained chronic users as 302/593 rather than as a percentage in the total cohort. Samefor total new users. This is how it is presented under the strengths and limitations section.

Response: We agree with the reviewer and edited the abstract.

2) I see that pre-surgical opioid use was a risk factor. However it is presented in 30 day increments rather than daily OME? Was daily OME included in the model and not found to be significant? The inclusion of preoperative opioid use as a risk factor is not described in the methods section and not listed in table 1 with the other risk factors considered.

Response: We appreciate the reviewer’s suggestion and included this in our analysis. The amount of daily opioid use prior to surgery was not statistically significantly associated with persistent chronic use after surgery after we included this in the model with a new specification of our days of opioid exposure variable and adjusting for all other factors- please see table 3 for this edit, the reported numbers in the abstract and results. All other variable estimates remained consistent after the addition of this variable to our model (all statistical assumptions were also checked and met). We also edited the methods to mention that we included these in our analysis (page 8).

3) One of the strengths in the summary states that the cohort was fully captured with no attrition but patients who had less than one year follow-up were excluded.

Response: We apologize for the lack of clarify. We only excluded 1 patient that had only 363 days of follow up. We only selected patients into our cohort who had at least one year follow up after their surgery so we would have their complete medication history for that time period and properly classify their outcomes. There was, however, that one patient that did not have quite one year follow up and

we decided to exclude him. We hope that this clarifies to the reviewer our selection criteria.

4) On page 6, line 59, I believe “affect” should be “effect”
Response: This was edited.

5) The sentence on page 8 lines 12-17 is not clear and needs to be re-worded.
Response: We edited this sentence in the statistical analysis section per your request.

6) The authors did not have detailed data regarding what happened to a patient during their hospitalization i.e. complications, ICU stay, type of anesthesia, blood loss, or length of stay, discharge destination. I think this should probably be listed as a limitation.
Response: We agree with the reviewer and edited page 13, end of third paragraph to add this.

7) How were patients who did not have one year of data prior to their surgery handled or did this scenario not occur?
Response: All patients had at least one year of prior history. Our medication data from the Australian DVA starts in 1/1/2000 and our cohort of joint replacement patients in this study started in 1/1/2001.

8) When deciding whether a patient was exposed to additional analgesic medications as a risk factor eg. NSAID, during what period was this assessed? Was it defined as any prescription filled at any point during the year prior to surgery? Not sure if makes sense to consider an NSAID taken a year before surgery as equal to one taken a few days before.
Response: We considered any prescription filled the year prior to surgery as someone that was considered an NSAID user. We choose this because wanted to use the same window of exposure that we used to determine the chronic use of opioids in our cohort.

9) It seems like having a previous hip surgery would be a confounder between some of the risk factors and taking opioids preoperatively. Was it adjusted for?
Response: Because of the possibility of confounding, we did not include patients in our sample who had either a hip or knee surgery the year before or after the index procedure included in this study. See page 6, 2nd line of 2nd paragraph. We also checked wether having had a hip surgery more than one year before or after the surgery was a confounder and it was not.

10) I find it hard to interpret the age in 10 year increments result when 95% of the cohort spanned a single 10 year increment.
Response: We edited the estimates to report in 1 year increments (OR=0.96, 95%CI 0.94-0.99). See edits in abstract, results section and table 3.

11) In table 2, the heading states “for those who changed”. It is unclear what that means. Is this for patients who changed opioid groups pre and post THA? If so, then how could there be values for patients who remained in the chronic category during both time periods?
Response: We removed the heading to avoid confusion. The information presented in these rows of the table has both the pre- and post-totals and the change in mean OME and days of opioid use in all the possible groups. For example, in the case of patients who were chronic users pre surgery and remained chronic users after- their mean number of days using opioids prior to THA was 189.9 (185.9, 193.9), after THA their mean number of days using opioids was 193.0 (188.8, 197.1), and the adjusted mean change was 2.6 (-2.3, 7.5). We found this information important for descriptive purposes.

Reviewer Name
Craig T Hartrick, MD
Institution and Country

Oakland University, USA
Please state any competing interests or state ‘None declared’:
Speakers' Bureau - The Medicines Company

The authors have attempted to address an important issue, the long-term use of opioids following a common surgical procedure. They state that patients are exposed to opioids for a long period of time after hip arthroplasty as a fact. They then present data to show this is likely true for only a minority of patients. They state that hip arthroplasty patients are at risk for misuse of opioids also as a fact. Misuse, i.e. use other than as prescribed, is however not assessed. In fact, in this work, all opioids were presumed to have been taken exactly as prescribed. Consequently, the ensuing discussions about “narcotic” use (presumably they mean opioid use), prescription, prescription habits, misuse and abuse become difficult and strained.
Response: We apologize for the confusion. We corrected the wording misuse (other than in the introduction as a reference to the potential problems with opioid use) to say abuse, which was our intended goal. We also replaced the word narcotic with opioid in page 6. We hope that his clarified our intent and discussion.

The authors, and others, have pointed out the prevalence of persistence of pain following hip arthroplasty. The finding that only 2% became new chronic opioid users is then perhaps a pleasant surprise. The reasons provided for persistent pain, other than female sex, as provided are understandable as alternative reasons for opioid prescription (back pain, migraine, etc.). The lack of association in the “new” chronic users with other well known predictors making opioid treatment risky (psychiatric co-morbibities, alcohol abuse, opioid abuse, etc.) is likely controlled for and reflected in those with chronic opioid use both before and after surgery. It may also reflect the ability of physicians to recognize red flags and/or use instruments such as the Opioid Risk Tool before contemplating long-term opioid prescription.
Response: We agree with the reviewer and added this page 12 when we discussed the risk factors for new chronic opioid use. See text added: ”Finally, some established risk factors for chronic opioid use, including psychiatric co-morbidities, alcohol and substance abuse, were not observed in our study. It is likely that these co-morbidities were either well managed in these patients or the higher risk of opioid abuse in them was recognized and properly managed by their providers.“

Retrospective studies suffer from many failings that can introduce bias. This study, having taken place over a long period of time, suffers in particular from changing prescribing habits over the decade, increasing awareness of the risks of opioid prescription, changing surgical practices over the decade including the introduction of minimally invasive techniques, and changing rehabilitation practices, all affecting opioid use.
Response: We edited the limitations paragraph to include that residual confounding due to certain non-measured variables could impact our estimations. See page 13, last sentence: ”… other confounding variables that we were unable to assess, such as body mass index, psychological well-being, function status, prescribers’ preferences, as well as information regarding the index surgery such as intra-operative complications, anaesthesia, length of stay, and discharge destination, could affect the relationship between the risk factors we identified for persistent or new chronic use of opioid.”

The study size is not very large considering the time frame for data collection, the many variables contributing to analgesic requirements, and the relatively low proportion of patients receiving opioid prescription long-term. No sample size determination was provided to examine any specific outcome measure.
Response: This was an exploratory analysis using existing data and therefore a-priori sample size calculation was not conducted. We agree that we could be underpowered to detect some of the weaker possible risk factors and this is a limitation of our study. We added this to the limitations

paragraph (see page 14): “Also, it is possible that due to the relatively low proportion of patients with some of the risk factors assessed we may have been underpowered to detect associations between these factors and the likelihood of chronic or persistent opioid use. “

Nevertheless many interesting findings can be derived from database analyses, even when performed retrospectively. However, for meaningful conclusions to be derived, the definitions used need to be clearly defined. This study defines chronic use as 90 days of continuous use or 120 days of non-continuous use. Use, however, is only assumed based upon prescription history. It is unknown if the medications were used, misused, or discarded. What is meant by continuous use and discontinuous use is not defined. When discussing issues related to tolerance development, for example, certain doses over a given period of time are strictly defined. Here apparently any dose at any frequency might qualify as “non-continuous” use (or more accurately, non-continuous prescription). Clearly intermittent use (prescription) for undefined reasons, might not necessarily lead to any serious consequences. The authors then proceed to describe assignment into “chronic”, “some”, and “none” categories without any definition as to how the cut-offs were set. The Tables provide some suggestion as to presumed opioid equivalents calculated, but the rules for grouping as a categorical variable is not provided, nor is the rationale given for doing so.
Response: We apologize for the lack of clarity and have edited the methods to include more detail on how the chronic use was defined. See edited text in page 7: “Chronic opioid use was defined as having any number of opioid prescriptions, or dosing, for at least 90 days continuously or opioid prescriptions for 120 non-consecutive days.” We would like to note that the median number of opioid prescriptions was 15 (interquartile range 11-20) for chronic users pre-THA and 5% of this cohort had 7 or less prescriptions during the period. Similarly, the cohort defined as chronic users after THA surgery had a median number of 15 (interquartile range 12-22) prescriptions for opioids and 5% of them had less than 8 prescriptions, indicating that these were cohorts with high prescription frequency.

This reviewer has a difficult time being confident in the conclusions drawn without a better understanding of the definitions of continuous “use” (prescription), non-continuous “use”(prescription), as well as “chronic” and “some” use (prescription). The discussion should focus on the facts rather than assumptions about risk for misuse and abuse without relating these findings back to known risk factors for these conditions.
Response: We hope that our clarification of how the chronic users were defined (see comment above) satisfies the reviewer. We also edited the discussion to remove any mention of opioid misuse as this was not evaluated in this study. In addition, we added more on the limitations of using opioid data in this study population and on the type of data that we had for our study (i.e. prescriptions only). See page 13: “Additionally, our observational study used prescriptions to measure opioid use in this cohort of patients; therefore we do not know whether patients were compliant to medication instructions.”

VERSION 2 – REVIEW

REVIEWER	Karim Ladha Department of Anesthesia, Toronto General Hospital and University of Toronto, Toronto, Canada
REVIEW RETURNED	11-Mar-2016

GENERAL COMMENTS	I would like to congratulate the authors on the excellent revision. Again, I think this paper will be a significant contribution to the existing literature. I just have a few small point that should be addressed.

	1) Strengths and limitations section, second bullet point, first sentence: I believe a word is missing from this sentence. 2) I still have an issue with the use of the term “no attrition” in the strengths and limitations section. Patients who died in the cohort were excluded, which could possibly cause a bias in the results. To say that there was no attrition in the summary, I feel is misleading. 3) Page 5, line 58: Maybe avoid the word abuse as per the comments of the other reviewer. It is also mentioned in the abstract. 4) Is there concern for the model being “over-fitted” given the number of predictors used? 5) Discussion, first sentence: I think it is confusing to state the risks as 3% and 2% as this is not how it was presented in the results section and it is unclear to me where these numbers came from. 6) I think what is interesting is that in the overall cohort the number of patients who were chronic uses dropped (6.2 vs 5.2%). Does this mean that as a healthcare system we benefit from patients undergoing joint arthroplasty?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Karim Ladha
Institution and Country
Department of Anesthesia, Toronto General Hospital and University of Toronto, Toronto, Canada
Please state any competing interests or state ‘None declared’:
None declared.

Please leave your comments for the authors below I would like to congratulate the authors on the excellent revision. Again, I think this paper will be a significant contribution to the existing literature. I just have a few small point that should be addressed.

1) Strengths and limitations section, second bullet point, first sentence: I believe a word is missing from this sentence.
Response: We corrected this sentence.

2) I still have an issue with the use of the term “no attrition” in the strengths and limitations section. Patients who died in the cohort were excluded, which could possibly cause a bias in the results. To say that there was no attrition in the summary, I feel is misleading.
Response: We understand the reviewer’s concern and edited the last bullet point in the strengths and limitations to say that only attrition related to death is encountered in our cohort. We hope that this satisfies the reviewer’s concern.

3) Page 5, line 58: Maybe avoid the word abuse as per the comments of the other reviewer. It is also mentioned in the abstract.
Response: We edited the abstract and this sentence to remove the word abuse.

4) Is there concern for the model being “over-fitted” given the number of predictors used?
Response: The persistent chronic user model was not a concern. But the new chronic model user was as it fit 36 variables, which meant 5.2 events/variable and was in the lower end of the acceptable number of events/variable. However, the model presented in the study had a good fit (Hosmer and Lemeshow goodness of fit test p=0.159) and calibration (c=0.80). We did investigate a reduced model where risk factors not significant (using p>0.2) in the multivariable model were removed. In this reduced model all parameter estimates for the risk factors identified were consistent with those

presented in our current model, and model had a similar goodness of test fit (p=0.138) and slightly lower calibration c=0.789. Therefore at this time no edits were made to the manuscript.

5) Discussion, first sentence: I think it is confusing to state the risks as 3% and 2% as this is not how it was presented in the results section and it is unclear to me where these numbers came from.
Response: We edited this sentence to present the information differently, see edits, page 12:
"In this large cohort of patients who had undergone THAs we determined that 6.2% of patients were chronic opioid users before surgery and 5.2% were chronic opioid use after. After THA, 61.4% of the chronic users of opioid had been chronic users before surgery and 38.6% of them were new chronic use after."

6) I think what is interesting is that in the overall cohort the number of patients who were chronic uses dropped (6.2 vs 5.2%). Does this mean that as a healthcare system we benefit from patients undergoing joint arthroplasty?
Response: There is substantial evidence that joint arthroplasty is a successful and cost effective treatment for end-stage arthritis because it provides most patients with pain relief, function gain, and reduces their need for certain health services.1-4 Chronic opioid use is one factor associated with the wellbeing of these patients and one that requires still much studying. From our study we determined that 51% of the patients who were chronic user prior to THA stopped being chronic users, which was a goal of the surgery and a significant accomplishment. But there were still 49% who continued to be chronic users, additionally, there were 190 (out of the 492 post-surgery chronic users) patients that were not chronic users prior that develop chronic use later, which are an area of concern and focus. No edits were made at this time to the manuscript.

1. Ethgen O, et al. Health-Related Quality of Life in Total Hip and Total Knee Arthroplasty. A Qualitative and Systematic Review of the Literature. J Bone Joint Surg Am. 2004 May;86-A(5):963-74.
2. Daigle ME, et al. The Cost-Effectiveness of Total Joint Arthroplasty: A Systematic Review of Published Literature. Best Pract Res Clin Rheumatol. 2012 Oct;26(5):649-58.
3. Corbett KL, et al. Population-Based Rates of Revision of Primary Total Hip Arthroplasty: A Systematic Review. PLoS One. 2010;5(10):e13520.
4. Learmonth ID, et al. The Operation of the Century: Total Hip Replacement. Lancet. 2007 Oct 27;370(9597):1508-19.