Individual patient data meta-analysis in surgery. A systematic review.

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Abstract

Background
Compared to subgroup analyses in a single study or in a traditional meta-analysis, an individual patient data meta-analysis (IPDMA) offers important potential advantages. We studied how many IPDMA report on surgical interventions, how many of those surgical IPDMAs perform subgroup analyses, and whether these subgroup analyses have changed decision making in clinical practice.

Materials & methods
Surgical IPDMA were identified using a comprehensive literature search. The last search was conducted on April 24, 2012. For each IPDMA included, we obtained information using a standardized data extraction form, and the quality of reporting was assessed. We also checked whether results were implemented in clinical guidelines.

Results
Of all 583 identified IPDMA, 22 (4%) reported on a surgical intervention. 18 (82%) of these IPDMA presented subgroup analyses. Subgroups were mainly based on patient and disease characteristics. The median number of subgroup analyses was 3.5 (IQR 1.25-6.5). Statistical methods for subgroup analyses were mentioned in 11 (61%) surgical IPDMA. 36 (40%) of the total number of 90 subgroup analyses were performed on a non-significant overall effect estimate, whereas 49 (54%) were performed on a significant overall effect estimate. 8 (44%) of the 18 significant subgroups appeared to be implemented in clinical guidelines. The quality of reporting among surgical IPDMA varied from low to high quality.

Conclusion
Many of the surgical IPDMA performed subgroup analyses, but overall treatment effects were more often emphasized than subgroup effects. Although, most surgical IPDMA included in the present study have only recently been published, about half of the significant subgroups were already implemented in treatment guidelines.

Keywords: Individual patient data, meta-analysis, surgery, subgroup analysis, guidelines
Introduction

Surgery has advanced spectacularly in the past 50 years, but many advances have not come from carefully planned research using valid study designs [1]. Research on surgical interventions is associated with several methodological and practical challenges of which few, if any, apply only to surgery. Surgical innovation is especially demanding because many of these challenges coincide [2]. Perhaps this situation leads many surgeons to view randomized controlled trials (RCTs), although theoretically advantageous, to be too difficult and impractical to undertake, and even worse, irrelevant to their practice because of concerns about generalizability [2, 3].

The results of RCTs are usually implemented in practice by either treating or testing all patients in case of a “positive” study or treating or testing no one in case of a “negative” study. Clinicians intuitively know that this approach is oversimplified because in reality some patients benefit more than average whereas others do not benefit. This may explain why around 50% of the RCTs perform subgroup analyses [4, 5]. However, misleading claims about subgroup effects based on a single study are common [6].

Investigating subgroups is a highly relevant, but complex topic because of two interrelated concerns: failure to detect a relevant subgroup effect (false negative), and a misleading claim about a subgroup effect which in reality does not exist (false positive). Both of these problems can lead to suboptimal care for patients. Subgroup effects have been extensively and fiercely debated in the clinical, epidemiological and statistical literature, especially in the context of single trials or traditional meta-analyses based on published summary results [7-11].

Individual patient data meta-analyses (IPDMA) differ from traditional meta-analyses in that an IPD meta-analysis uses the “raw data” of individual patients from included studies instead of the published summary results of studies in a traditional meta-analysis [12]. Compared to subgroup analyses in a single study or in a traditional meta-analysis, an IPDMA offers important potential advantages, such as (1) improved flexibility and standardization of defining subgroups across studies, (2) more power compared to single studies and traditional meta-analyses, (3) higher validity of subgroup analyses by avoiding ecological bias and by
taking the distribution of other patient characteristics into account, (4) increased possibilities to perform more complex statistical analyses that better match the underlying data, and (5) opportunities to examine the consistency of subgroup effects across studies [13-17].

In this paper we present a systematic overview of all surgical IPDMA published. We studied the number and types of subgroup analyses performed, and whether these subgroups analyses influenced decision making in clinical practice.

**Materials & methods**

**Search**

A comprehensive literature search in PubMed, Embase, Web of Science, and the Cochrane Library was conducted to identify all IPDMA of randomized controlled trials. The last search was conducted on April 24th, 2012 (see Appendix A for detailed search strategy).

**Selection**

In first instance, titles and abstracts were screened to identify eligible IPDMA. Selection of potential eligible IPDMA was restricted to IPD obtained from RCTs comparing surgical interventions. Patients had to be randomized over a surgical intervention in at least one treatment arm, and the surgical procedures had to be performed under general, spinal, epidural or regional anesthesia. IPDMA regarding drug eluting medical devices and surgical trials in which a drug was the comparison were excluded. Full text papers were retrieved when meta-analytic techniques for individual patient data of RCTs were used. IPDMA using the same dataset or combination of datasets, studying/addressing different questions/subgroups were included. If obvious duplicate papers were available, the most elaborate paper was included.

**Data extraction and analysis**

Data from all included surgical IPDMA were extracted with respect to specific characteristics, that is publication year, number of included trials and patients, domain, type
of intervention, comparison, outcome measured, and number, type, justification, methods, and results in relation to the overall effect estimate of the subgroups studied.

We classified 5 types of subgroups, patient characteristics (e.g. age or gender), disease characteristics (e.g. severity or co-morbidity), household characteristics (e.g. socioeconomic status or smoking), intervention characteristics (e.g. type of intervention or dose), and other characteristics (e.g. quality of included trials or trial effect). Justification for subgroups analyses was categorized as based on literature, clinical experience, biological mechanism, or no justification.

We also assessed the quality of reporting of all selected IPDMAs. IPDMAs on RCTs should be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. Since this guideline is not specific to IPDMA, it has been suggested that some additional information should be reported, for instance why the IPDMA approach was initiated, whether there was a protocol for the IPDMA project, and whether a one step or a two step analysis was performed [12]. We judged the quality of reporting based on 7 of the 18 items suggested by Riley et al.[12] relevant for surgical IPDMA. Two independent reviewers (GH and MMR) selected eligible surgical IPDMA and extracted data. Any disagreements were resolved by consensus.

Finally, we reviewed available clinical guidelines for recommendations based on significant results of subgroup analyses from IPDMA to determine the extent to which these results were implemented in clinical guidelines. We conducted a PubMed search for fields ‘patients’ (e.g. carotid stenosis), ‘intervention’ (e.g. carotid stenting) and ‘comparison’ (e.g. endarterectomy), extracted from IPDMA with significant subgroup analyses, and limited our search to “Practice Guideline”. We only included publications in English. We also searched the National Library of Guidelines (http://guidance.nice.org.uk/), and the National Guideline Clearinghouse (http://www.guidelines.gov/).

Results

Search
In the search for IPDMA, 3597 potential eligible papers were identified. After studying the abstracts, 583 papers, published between 1991 and 2012, indeed reported an IPDMA. After detailed evaluation, 22 (4%) IPDMA reported on a surgical intervention and met our inclusion criteria (Fig. 1).

Of the 22 surgical IPDMA, 12 focused on cardiovascular interventions, 3 on inguinal hernia repair, 3 on gynecological interventions, 2 on orthopedic interventions, 1 on a gastroenterological intervention, and 1 on ventilation tubes for otitis media (Table 1). The surgical IPDMA papers were published between 2005 and 2012. 18 (82%) of the 22 surgical IPDMA tried to identify subgroups of patients that benefit more or less from the surgical intervention.

The remaining non-surgical IPDMA predominantly focused on cancer, cardiovascular disease, and diabetes, and most assessed whether a treatment or intervention was effective, often in subgroups of patients. Before 2000 only a few IPDMA were published, whereas a considerable rise in the number of published IPDMA is seen between 2005 and 2012 (Fig. 2). This growth is most likely the result of an increased awareness the potential advantages of IPDMA, and the initiation of collaborations to specifically perform such studies.

Summary of IPDMA using IPD (or part of IPD) from the same trials

Of the 12 IPDMA that focused on a cardiovascular intervention, 4 IPDMA [19-22] used individual patient data from the same 22 trials (6763 patients) evaluating the clinical effects of primary percutaneous coronary intervention versus in-hospital fibrinolysis. In 3 IPDMA [23-25], comparing routine invasive strategies with selective invasive strategies in 5467 patients with non-ST segment elevation acute coronary syndromes, data from the same 3 trials (FRISC II, ICTUS, and RITA-3) were used. In addition, of the 3 IPDMA that focused on inguinal hernia repair one IPDMA [26] presented a combination of the data used in the other 2 IPDMA [27, 28].

Number, justification, type, and methods of subgroups analyses in surgical IPDMA
In 18 (82%) of the full set of surgical IPDМА assessed, subgroup analyses were performed to examine whether certain patients benefit more from a specific treatment than others. The median number of subgroups studied in these IPDМА was 3.5 (range 1-16, IQR=5.25 (1.25-6.5)). In 12 (67%) of the 18 surgical IPDМА that studied subgroups a justification for subgroup analyses was mentioned. Scientific literature was used for justification in these studies.

The types of subgroups studied varied. 15 (83%) IPDМА studied patient characteristics, 5 (28%) studied household characteristics, 15 (83%) studied disease characteristics, and 6 (33%) studied intervention-related subgroups. Subgroups related to study or trial effects were studied in 3 (17%) IPDМА. No IPDМА studied subgroups related to the quality of the included trials, for example concealment of allocation, blinding or completeness of follow-up. 12 (55%) IPDМА stratified their analysis per trial before pooling the results (two step analysis). Statistical methods for subgroup analyses were mentioned in 11 (61%) of the 18 IPDМА performing subgroup analyses. All IPDМА that mentioned statistical methods for subgroup analysis used interaction tests.

Only 5 (28%) surgical IPDМА mentioned the power of the subgroup analyses. Three IPDМА reported that their studies were underpowered to detect subgroup effects, 1 IPDМА reported that their study was well powered to detect subgroups effects, however, did fail to show differences in subgroups, and 1 IPDМА mentioned differences in power between different subgroups, but not whether these were over- or underpowered.

36 (40%) of the total number of 90 subgroups analyses were performed on a non-significant or inconclusive overall effect estimate, whereas 49 (54%) were performed on a significant overall effect estimate. Of the subgroup analyses performed on non-significant or inconclusive overall results, 5 (14%) became significant. 9 (18%) of those performed on IPDМА with a significant overall result remained significant. 1 IPDМА did not report an overall effect estimate and only presented results of subgroup analyses, 4 out of 5 subgroups being significant [29].

8 (67%) of the 12 surgical IPDМА with significant subgroups reported on what the
implications of these significant results of their subgroup analyses were for clinical practice. Mainly, the importance of differentiating when evaluating the efficacy and safety of new medical and interventional treatments, and translating these findings in treatment recommendations were emphasized. Moreover, it was reported that the influence of certain subgroups had not been reported previously, that findings concurred with recent recommendations or guidelines, and that subgroups not per se needed to be an exclusion criterion for treatment. 8 (44%) of the 18 significant subgroups were implemented in clinical guidelines.

Quality of reporting

The quality of reporting of the surgical IPDMA varied (Fig. 3). More than half of the IPDMA failed to report whether or not there was a protocol for the IPDMA project available. The reason why the IPD approach was initiated and the numbers of patients within each of the original studies were generally well reported. For 17 (77%) IPDMA, the process used to identify relevant studies for the IPDMA were reported. Details on the statistical analysis were reported in 16 (73%) IPDMA, however, details on the identification process and statistical analysis were not described in 1 IPDMA (4%), and were unclear in the remaining 5 (23%) IPDMA.

Discussion

Our systematic review of all surgical IPDMA published so far provides an overview of the potential advantages of IPD (see boxes for examples). In 18 (82%) of the full set of 22 surgical IPDMA assessed, subgroup analyses were performed to examine whether certain patients benefit more from a specific treatment than others. 8 (67%) of the 12 surgical IPDMA with significant subgroups reported on what the implications of their findings were for clinical practice. 44% (8 out of 18) of the significant subgroups were implemented in clinical guidelines.

Although many IPDMA performed subgroup analyses, the overall treatment was usually the
main focus of the paper. Only occasionally subgroup analyses were emphasized. In surgical IPDMA, similar to IPDMA in general [30], subgroups were often based on patient and disease characteristics. The median number of subgroups has been reported to range from 2 to 4, the maximum number of subgroups from 15 up to 50 [6, 31-33], which is comparable to our findings. Justification of subgroup analyses, the methods used to perform subgroup analyses, and power calculations for performing subgroup analyses are often not reported in IPDMA [6, 31-36]. However, eleven (65%) of the IPDMA included in our study justified at least one of the subgroups on which they reported, scientific literature being the mode of justification used. This is in line with other studies that found that clinical experience or biochemical justification is rare [32, 34, 37]. Others showed that the proportion of studies that used interaction tests for at least one of their subgroups ranges from 10% to 56% [6, 31-36], which is slightly lower compared to our findings. So far, few studies mentioned the importance of the power of subgroup analyses [6, 32, 38, 39], and reported that many reports put too much emphasis on subgroup analyses that commonly lacked statistical power. This is in agreement with the results of the present study.

To the best of our knowledge we are the first to study surgical IPDMA, and illustrate the merits of this method within surgery. However, some potential limitations should also be discussed. First, our literature search for surgical IPDMA was limited to IPDMA with IPD obtained from RCTs comparing surgical interventions, excluding IPDMA regarding drug eluting medical devices and surgical trials in which a drug was the comparison, and records were limited to the English language. We, however, believe that our review provides a good representation of the method within the surgical field. Second, reporting bias could not be entirely excluded, since reporting of subgroup effects in scientific publications might be influenced by reviewers’ and editors’ opinions. Third, as most studies mentioned multiple subgroups, a clustering effect might occur for reporting on justification and statistical methods. Therefore, the results were reported on study level instead of individual subgroup level. Fourth, the time from publication to implementation of a result into a guideline or clinical practice can be highly variable, and sometimes takes even more than 10 years [40],
Most surgical IPDMA included in the present study have only recently been published, and time to possible implementation has been rather short. Therefore, we might have underestimated the implementation of IPDMA results into guidelines and/or clinical practice. Despite the recommendations available on reporting clinical trials and meta-analyses, such as PRISMA [18], these guidelines have not been specifically developed for IPDMA. The development of a generally accepted guideline for reporting on IPDMA including subgroup analyses should therefore be encouraged. This seems the only option to really improve the reporting, analyses, and claims and applicability of subgroup effects in clinical research.

In conclusion, one of the challenges in medicine is to rationally implement available therapies in clinical practice, in the appropriate patients at the appropriate time. Findings from IPDMA might provide insight into opportunities to improve evidence based treatment decisions for patients. IPDMA is an extremely powerful tool if used correctly and provides the most definitive synthesis of the available evidence, also for potential subgroups. Clinicians in specialty groups, such as surgeons, need to be aware that contributing data from individual patients is certainly as important as conducting original research.

Two examples of differences in conclusions with regard to how patient-level characteristics modify treatment effect

Box 1: Effectiveness of coronary artery bypass grafting vs. percutaneous coronary interventions for multivessel disease

A two step meta-analysis of individual patient data from 7812 patients included in ten randomized trials comparing coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) in patients with multivessel coronary artery, showed a similar overall treatment effect on long-term mortality after CABG and PCI [41]. However, in diabetic patients mortality was substantially lower in the CABG group than in the PCI group (HR 0.70, 95%CI 0.56 to 0.87). Mortality was similar between groups in patients without diabetes (HR 0.98, 95%CI 0.86 to 1.12; p=0.01 for interaction). Patient age modified the
effect of treatment on mortality with hazard ratios of 1.25 (95% CI 0.94 to 1.66) in patients younger than 55 years, 0.90 (95% CI 0.75 to 1.09) in patients aged 55-64 years, and 0.82 (95% CI 0.70 to 0.97) in patients 65 years and older (p=0.002 for interaction). Treatment effect was not modified by other subgroups. CABG might be a better option for patients aged 65 years or older and patients with diabetes since mortality was found to be lower in these subgroups. These results have been implemented in clinical guidelines.

Box 2: Effectiveness of routine vs. selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome

An individual patient data meta-analysis of three randomized trials of routine versus selective invasive strategies in patients with non-ST-segment elevation acute coronary syndrome showed that a routine invasive strategy resulted in significantly less cardiovascular deaths (CV deaths) or nonfatal myocardial infarctions (MIs) compared to selective invasive strategies [25]. The authors used patient’s baseline characteristics to develop a multivariable risk prediction model. A simplified integer risk score was derived from the risk prediction model to predict a patient’s 5-year probability of CV death or MI, and the patients were categorized into 3 risk groups (low, intermediate, and high risk).

The treatment effect was similar between groups in patients with low (HR 0.80 (95% CI 0.63 to 1.02)) and intermediate (HR 0.81 (95% CI 0.66 to 1.01)) risk scores. In patients with high risk scores treatment favored routine over selective invasive strategies (HR 0.68 (95% CI 0.53 to 0.86)). There were 2.0% (95% CI -4.1% to 0.1%) and 3.8% (95% CI -7.4% to -0.1%) absolute risk reductions in CV death or MI in the low and intermediate risk groups and an 11.1% (95% CI -18.4% to -3.8%) absolute risk reduction in the highest risk patients. The multivariable risk prediction model has not yet been implemented in clinical guidelines.

Competing interests

The authors declare that they have no competing interests.
Authors' contributions

GH prepared the protocol with guidance from HG, CvL, and MR. GH and MR developed the search strategies. GH and MR selected relevant studies and extracted data; All authors participated in screening/extraction for the initial unpublished version of the review. GH carried out the analysis and prepared the manuscript with input from all authors. All authors read and approved the final manuscript.

References


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51. Staples MP, Kallmes DF, Comstock BA, Jarvik JG, Osborne RH, Heagerty PJ, Buchbinder R: **Effectiveness of vertebroplasty using individual patient data from two randomised placebo controlled trials: meta-analysis.** *BMJ* 2011, **343**:d3952.
Legends

Fig. 1  Flowchart of study selection process for IPDMA of surgical interventions.

Fig. 2  Number of applied IPDMA published up to April 2012,* as identified by a systematic review of PubMed, Embase, Web of Science, and the Cochrane Library. *Thirty seven IPDMA published in 2012 were identified up to 24 April 2012, when the review was conducted.

Fig. 3  Quality of IPDMA reporting surgical interventions. Numbers inside bars are numbers of studies.

Table 1  Characteristics of the 22 identified surgical IPDMA
## Table 1.

<table>
<thead>
<tr>
<th>Author &amp; year</th>
<th>No. RCTs</th>
<th>No. of patients</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jørgenson et al. 2007 [42]</td>
<td>7</td>
<td>2091</td>
<td>Women with cervical insufficiency</td>
<td>Cervical cerclage</td>
<td>Expectant management, no cerclage</td>
<td>Primary Pregnancy loss or neonatal death before discharge from hospital Secondary Preterm delivery &amp; maternal morbidity</td>
<td>Obstetric history, cervical length</td>
</tr>
<tr>
<td>Hlatky et al. 2009 [41]</td>
<td>10</td>
<td>7812</td>
<td>Patients with multivessel coronary disease</td>
<td>Coronary artery bypass graft</td>
<td>Percutaneous coronary intervention</td>
<td>All cause mortality Age, sex, diabetes, smoking, hypertension, hypercholesterolaemia, PVD, stability of symptoms, previous MI, heart failure, LV function, no. of diseased vessel, proximal LAD, balloon versus stent</td>
<td></td>
</tr>
<tr>
<td>Daniels et al. 2010 [43]</td>
<td>5</td>
<td>862</td>
<td>Patients with chronic pelvic pain</td>
<td>Laparoscopic uterosacral nerve ablation (LUNA)</td>
<td>No LUNA</td>
<td>Derived measure of worst pain level experienced Presence of visual pathology, site of pain, age, parity</td>
<td></td>
</tr>
<tr>
<td>Burzotta et al. 2009 [44]</td>
<td>11</td>
<td>2686</td>
<td>Patients with ST-elevation myocardial infarction (STEMI)</td>
<td>Percutaneous coronary intervention with thrombectomy</td>
<td>Standard percutaneous coronary intervention</td>
<td>Primary All cause mortality Secondary Survival free from MI, TLR or TVR, major adverse coronary events (MACE), death+MI Manual vs. non-manual thrombectomy devices, diabetes, primary vs. rescue PCI, treated vs. non-treated with IIb/IIIa-inhibitors, ischaemic time, infarct related artery, pre-PCI TIMI flow</td>
<td></td>
</tr>
<tr>
<td>Carotid Stenting Trialists’ Collaboration 2010 [45]</td>
<td>3</td>
<td>3433</td>
<td>Patients with symptomatic carotid stenosis</td>
<td>Carotid stenting</td>
<td>Endarterectomy</td>
<td>Primary Any stroke or death Secondary Disabling stroke or death, all cause death, any stroke, myocardial infarction, severe local haematoma, severe wound infection Age, sex, diabetes, hypertension, SBP, hypercholesterolaemia, smoking, coronary heart disease, peripheral artery disease, most recent ipsilateral ischaemic event, history of stroke, degree of ipsilateral ischaemic stroke, contralateral severe carotid stenosis</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Patients with</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Primary Outcomes</td>
<td>Secondary Outcomes</td>
<td></td>
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<tr>
<td>Middleton et al. 2010 [46]</td>
<td>17</td>
<td>2814</td>
<td>Patients with heavy menstrual bleeding</td>
<td>Hysterectomy, endometrial destruction (1st &amp; 2nd generation), levonorgestrel releasing intra-uterine system (MIRENA)</td>
<td>Endometrial destruction (1st &amp; 2nd generation), levonorgestrel releasing intra-uterine system (MIRENA)</td>
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<tr>
<td>Mercado et al. 2005 [47]</td>
<td>4</td>
<td>3051</td>
<td>Patients with multi-system coronary artery disease</td>
<td>Percutaneous coronary intervention with multiple stenting</td>
<td>Coronary artery bypass graft</td>
<td></td>
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<td>Boersma et al. 2006 [19]</td>
<td>22</td>
<td>6767</td>
<td>Patients with acute myocardial infarction</td>
<td>PCI</td>
<td>Fibrinolysis</td>
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<td>Timmer et al. 2007 [22]</td>
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<td>6315</td>
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<td>PCI</td>
<td>Fibrinolysis</td>
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<td>6767</td>
<td>Patients with acute myocardial infarction</td>
<td>Primary PCI</td>
<td>Fibrinolysis</td>
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<td>6767</td>
<td>Patients with acute myocardial infarction</td>
<td>Primary PCI</td>
<td>Fibrinolysis</td>
<td></td>
<td></td>
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<tr>
<td>Fox et al. 2010 [25]</td>
<td>3</td>
<td>5467</td>
<td>Patients with non-ST-elevation</td>
<td>Routine invasive strategy</td>
<td>Selective invasive strategy</td>
<td>Primary</td>
<td></td>
</tr>
</tbody>
</table>

or occlusion, treatment within 14 days, patients recruited per center, center recruitment rate

Uterine cavity length, age, presence of fibroids/polyps, parity, baseline bleeding score

Dissatisfaction rates

Primary

Composite of death, MI, or stroke at 1 year FU

Secondary

Death, composite of death or MI, repeat revascularization, composite of death, MI, stroke, and repeat revascularization

Age, gender, diabetes, smoking, number of diseased vessels

All cause mortality

Death, recurrent MI, death or recurrent MI, stroke

Age, sex, diabetes, prior MI, MI location, heart rate, SBP, fibrinolytic agent, front-loaded tPA, size volume

All cause mortality

Primary

All cause mortality

Secondary

reMI, stroke, composite of all cause mortality or reMI, composite of all cause mortality, reMI, or stroke

High risk patients

Primary

High-risk groups based on baseline
<table>
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<tr>
<th>Study References</th>
<th>n</th>
<th>n</th>
<th>Primary End Points</th>
<th>Secondary End Points</th>
<th>Procedure/Characteristics</th>
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<td>Damman et al. 2012 [23]</td>
<td>3</td>
<td>5469</td>
<td>Composite of CV death or nonfatal MI</td>
<td>All-cause death, nonfatal MI alone</td>
<td>Age, gender, baseline risk</td>
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<tr>
<td>Damman et al. 2012 [24]</td>
<td>3</td>
<td>5467</td>
<td>Composite of CV death or nonfatal MI</td>
<td>All-cause mortality</td>
<td>Procedure-related vs. spontaneous MI</td>
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<td>Biau et al. 2009 [48]</td>
<td>6</td>
<td>423</td>
<td>All cause mortality</td>
<td>Gender, age at surgery, trial effect</td>
<td></td>
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<tr>
<td>Rovers et al. 2005 [49]</td>
<td>7</td>
<td>1234</td>
<td>Positive pivot shift test</td>
<td>Gender, age at surgery, trial effect</td>
<td></td>
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<tr>
<td>Salerno et al. 2007 [50]</td>
<td>4</td>
<td>305</td>
<td>Death from any cause before LT</td>
<td>Hearing level at baseline, history of acute otitis media, upper respiratory infections, attending day care, socioeconomic status, siblings, season, history of breast feeding, parental smoking</td>
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<td>Staples et al. 2011 [51]</td>
<td>2</td>
<td>209</td>
<td>Scores for pain and function</td>
<td>Onset of pain, pain scores at baseline</td>
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<td>McCormack et al. 2003 [27]</td>
<td>25</td>
<td>4185</td>
<td>Open repair</td>
<td>NA</td>
<td></td>
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<tr>
<td>Study</td>
<td>N</td>
<td>Patients with clinical diagnosis of groin hernia for whom surgical management was judged appropriate</td>
<td>Mesh technique</td>
<td>Non-mesh technique</td>
<td>Duration of operation, ‘opposite’ method initiated, conversion, haematoma, seroma, wound/superficial infection, serious complications, length of postoperative hospital stay, time to return to usual activities, persisting pain, persisting numbness, hernia recurrence, known death</td>
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</tr>
<tr>
<td>Scott et al. 2002 [28]</td>
<td>11</td>
<td>3347</td>
<td>Mesh technique</td>
<td>Non-mesh technique</td>
<td>Duration of operation, ‘opposite’ method initiated, conversion, haematoma, seroma, wound/superficial infection, serious complications, length of postoperative hospital stay, time to return to usual activities, persisting pain, persisting numbness, hernia recurrence, known death</td>
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<tr>
<td>Gregson et al. 2012 [29]</td>
<td>8</td>
<td>2186</td>
<td>Surgery</td>
<td>Conservative treatment</td>
<td>Unfavorable outcome</td>
</tr>
</tbody>
</table>
3,597 records identified through database searching
- PubMed 2,015 records
- Embase 921 records
- Web of Science 522 records
- Cochrane Library 139 records

2,433 records after removal of duplicates

583 potentially eligible IPDMA identified and screened

1,850 records excluded
- Cohort, case report, or case-control instead of RCT
- Methodological or tutorial review
- Objective differed too much from IPDMA
- Duplicate publications
- Conference abstracts & protocols
- Animal studies

541 IPDMA excluded
- Non-surgical

42 full-text surgical IPDMA retrieved for detailed evaluation

20 surgical IPDMA excluded
- No IPDMA
- Duplicate publications

22 surgical IPDMA included

18 surgical IPDMA with subgroup analysis

4 surgical IPDMA without subgroup analysis
Figure 2
Figure 3

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Additional files provided with this submission:

Additional file 1: Appendix A.doc, 25K
http://www.systematicreviewsjournal.com/imedia/1936759618154121/supp1.doc