**Measurement and evaluation of hip fracture care**
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# Optimal timing of hip fracture surgery

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## Abstract

There is an ongoing discussion about optimal timing for hip fracture surgery and much has been published about this subject. There is no literature-based consensus regarding the time frame in which a hip fracture patient should be operated on; nonetheless, the National Health Care Institute in the Netherlands has been using 'time to surgery' as a quality indicator since 2017. Analysis of the data from the Health and Youth Care Inspectorate on the quality indicator 'Percentage of patients operated on within one calendar day' showed that in Dutch hospitals 93% of the ASA grade 1-2 patients and 86% of the ASA grade > 2 patients were operated on within one calendar day. Delay of surgery due to preoperative optimization of the patient is not associated with an increased mortality. The chance of complications, such as pneumonia or pressure sores, does increase with delay of surgery.

## Introduction

An 88-year-old woman is admitted to the emergency department with a suspected hip fracture at 11 p.m. on a Tuesday evening. The patient has an extensive medical history including hypothyroidism, atrial fibrillation, hypertension, cardiac decompensation and cognitive disorders, for which she uses levothyroxine, phenprocoumon, hydrochlorothiazide and bisoprolol, respectively. Laboratory tests have revealed an electrolyte disorder, anaemia and excessive anticoagulation. The X-ray findings confirm that the patient has a hip fracture. According to the current guideline and quality standard, the patient's hip must be operated on by no later than Wednesday 12 midnight. Is it advisable to adhere to this time limit, or are there reasons to delay surgery? Is there an optimal time frame for the performance of hip fracture surgery and, if so, what is that time frame?

Hip fractures are common among elderly people. The average hip fracture patient is over 80 and shows extensive comorbidity [1]. Two Dutch guidelines provide a recommendation for time to surgery for hip fracture patients. The 2016 'Proximal Femur Fracture' guideline advises surgery on the day of admission or no later than the following calendar day [2]. The strength of evidence for this recommendation is classified as 'extremely low'. The 'Multidisciplinary Treatment of Frail Elderly During Surgical Procedures' guideline makes the same recommendation but allows for more time if necessary to optimize the patient's preoperative condition [3]. Legitimate reasons for delaying surgery are the treatment of: anaemia, anticoagulation, volume depletion, electrolyte imbalance, uncontrolled diabetes, uncontrolled heart failure, correctable cardiac arrhythmia or ischaemia, pneumonia and COPD exacerbation. The aim must be to treat these correctable comorbidities as soon as possible, i.e. within 24 hours [4].

## How often is the quality standard adhered to?

Until the end of 2012, time to surgery was a quality indicator in the 'Basic Set of Quality Indicators for Hospitals' of the Dutch Health and Youth Care Inspectorate (*Inspectie Gezondheidszorg en Jeugd* – IGJ). A patient had to be operated on within one calendar day after admission [5]. In 2017, this quality indicator was reinstated in a slightly modified form, the 'Transparency Calendar' of the National Health Care Institute (*Zorginstituut Nederland* – ZiNL) [6]. The indicator suggests the following: the shorter the time to surgery, the better the organization of hip fracture care and, hence, the higher the quality of care.

Analysis of the data of the IGJ quality indicator 'percentage of hip fractures operated on within one calendar day' from the 2012 Basic Set shows that, on average, Dutch hospitals operated on 93% of ASA grade 1-2 patients within one calendar day after admission (range: 71-100) (Figure 1a) [5]. The average with ASA grade > 2 patients was 86% (range: 59-100) (Figure 1b) [5]. Patient characteristics thus seem to influence the time to surgery.

*Figure 1a. Percentage of ASA 1-2 patients operated on the day of admission or the following day, at hospital level*

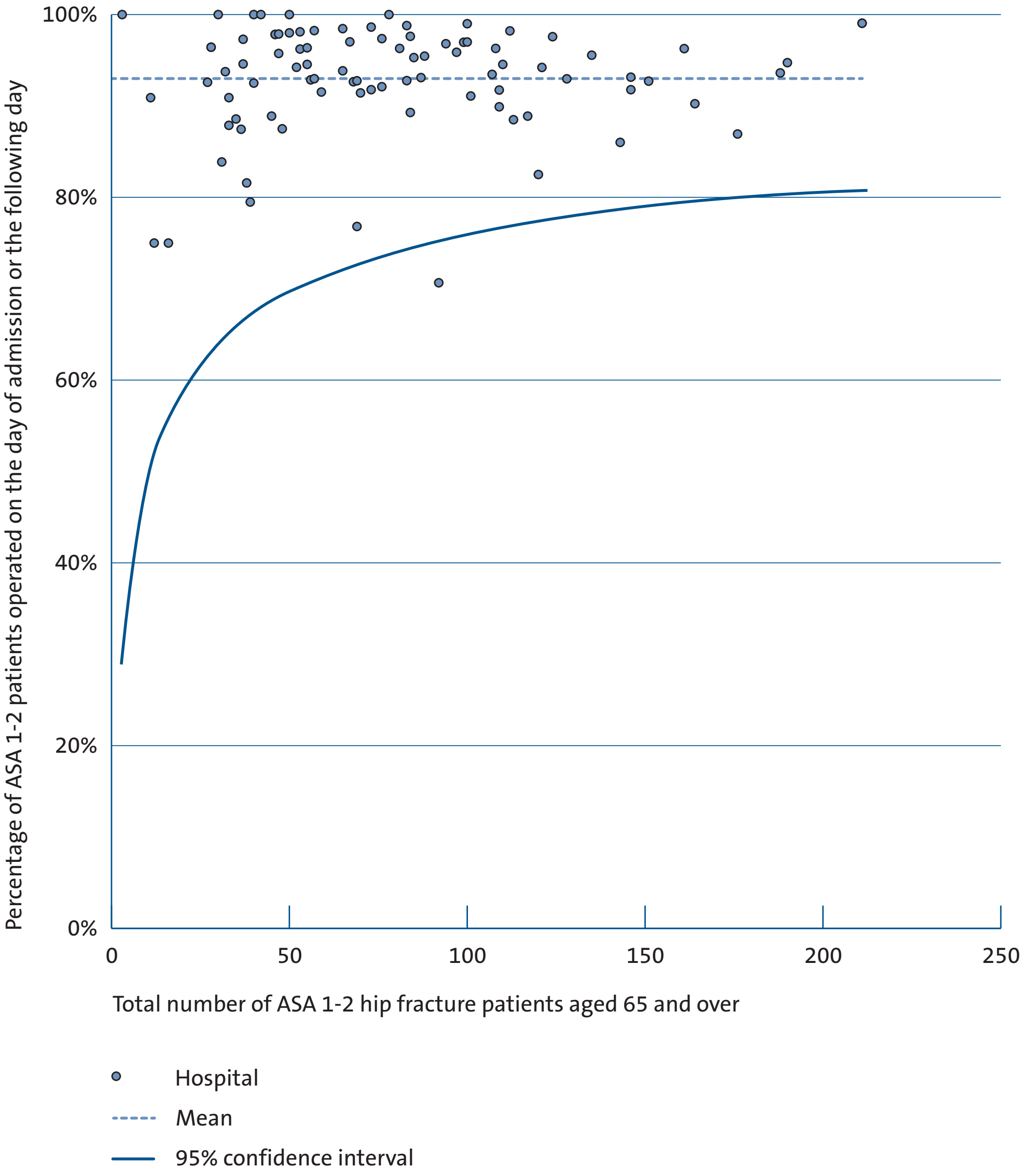
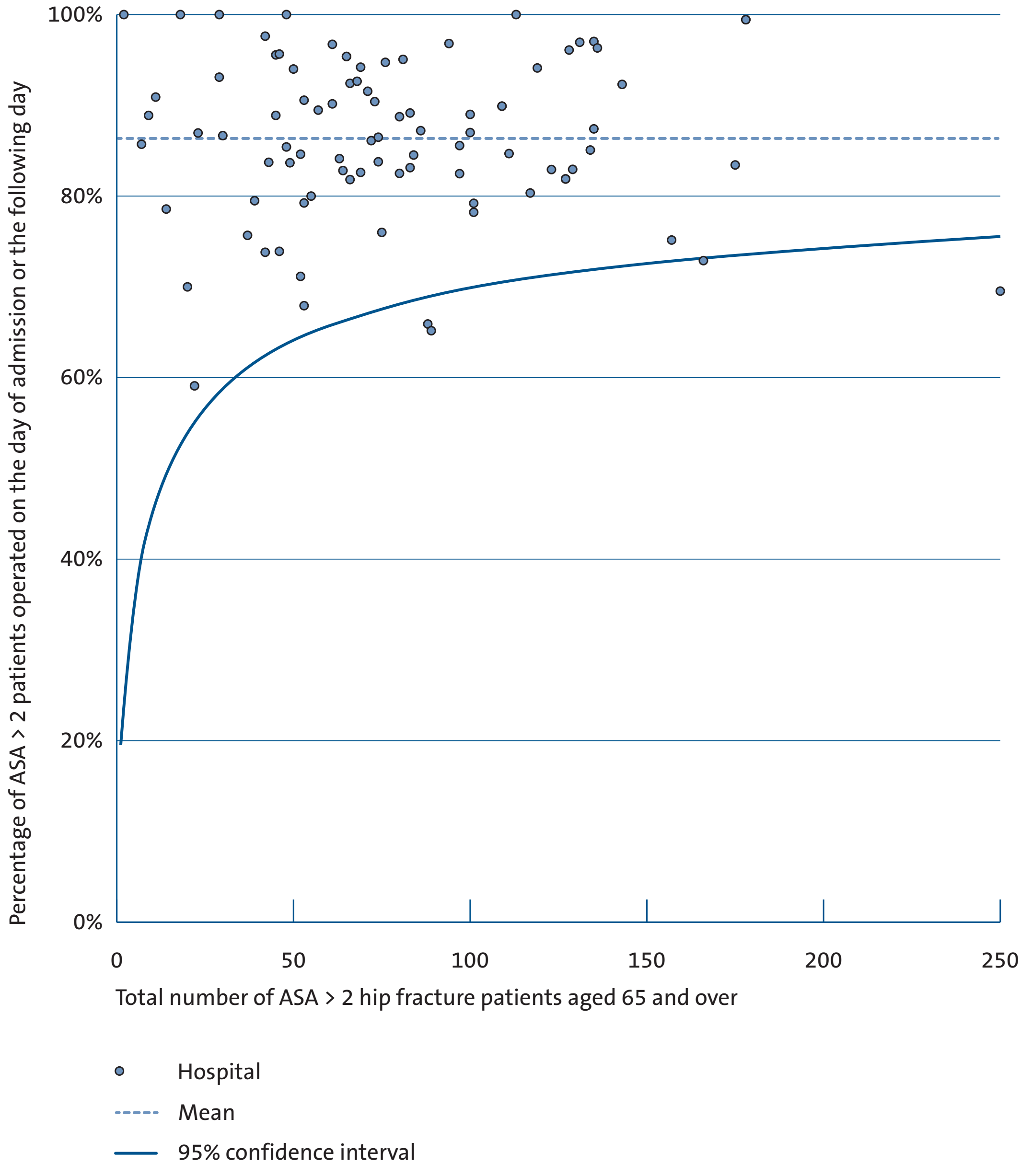


*Figure 1b. Percentage of ASA > 2 patients operated on the day of admission or the following day, at hospital level*

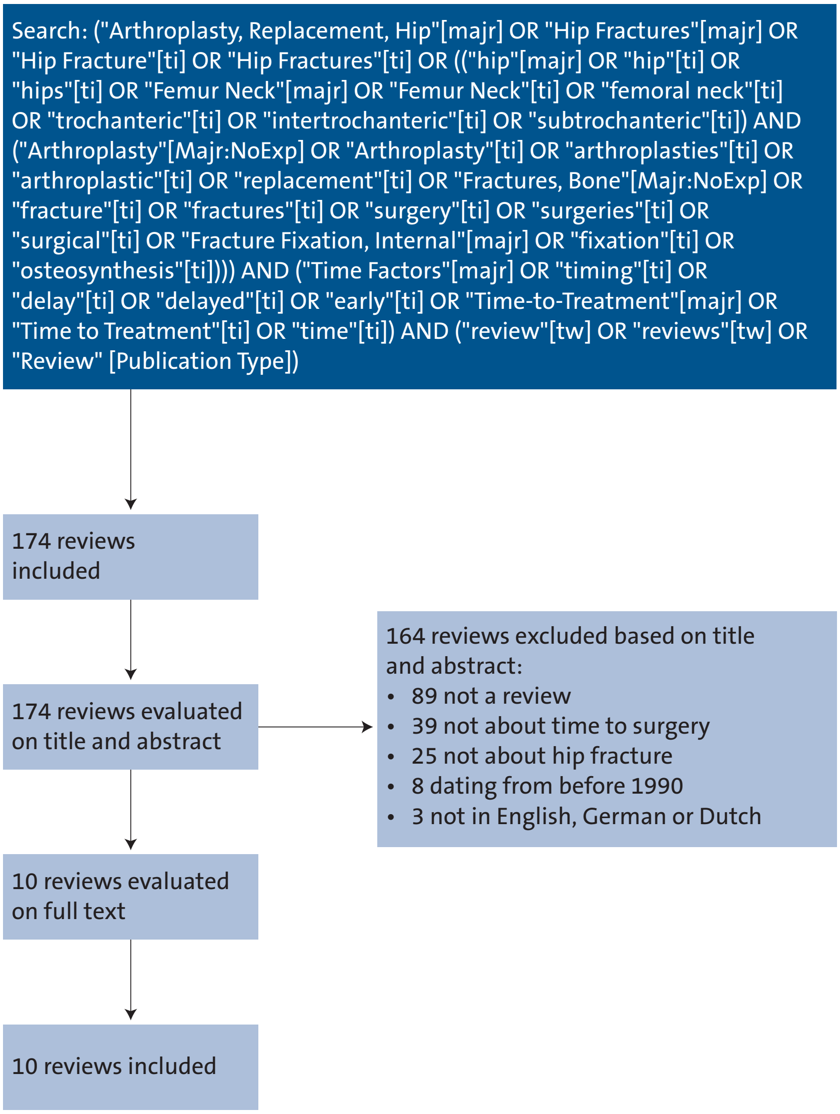



## What is the optimal time to surgery?

Much has been published about the optimal time to surgery for hip fracture patients. In 2007, the Dutch Journal of Medicine (*Nederlands Tijdschrift voor Geneeskunde)* published the results of two Dutch retrospective cohort studies assessing whether operating more than 24 hours after admission influenced the occurrence of complications. One cohort (n = 217) displayed a higher incidence of pneumonia among patients operated more than 24 hours after admission, but this was not the case in the other cohort (n = 446) [7,8]. These cohort studies were subsequently put in a broader perspective based on five international publications, resulting in the conclusion that unnecessary delay of surgery should be avoided [9].

Ten years later the optimal time to surgery is still a subject of discussion. To obtain a comprehensive summary of literature, we searched in PubMed for systematic and narrative reviews and meta-analyses about the time to surgery for hip fracture patients. Our search was restricted to English-, German- and Dutch-language articles published from January 1990 to September 2018. Articles about patients with multiple injuries were also excluded. The full search instruction and flowchart of the selection of articles are shown in Figure 2. The selection was performed by one researcher (VB).

*Figure 2. Search in PubMed and flowchart of study selection*



In total ten reviews published between 2008 and 2018, including six meta-analyses, met the inclusion criteria [10-19]. The cut-off points for the time to surgery varied from 6 to 168 hours after admission. The applied outcome measures were: mortality, complications (pneumonia, pressure sores, deep venous thrombosis, pulmonary embolism, blood transfusion, avascular femoral head necrosis, non-union and duration of pain), length of hospital stay, postoperative discharge to home, quality of life and functional outcome (see Table 1). The reviews were ranked for quality by one researcher (SV) based on the R-AMSTAR tool, with scores ranging from 13 to 36 on a scale of 11 to 44 points (see Table 1) [20]. The strength of evidence of the ten reviews was low, as most evidence was exclusively based on non-randomized studies. The ten reviews described the results of 108 different studies, but the reviews differed considerably regarding the inclusion of individual studies (see Appendix 1).

*Table 1. Overview of included systematic reviews and meta-analyses*

| Author and year | SR or MA | Number and type of studies | Intervention (I) / Comparison (C) | Outcome measure | Risk on outcome measure | Conclusion / recommendation | R[§] |
|---|---|---|---|---|---|---|---|
| Shiga et al.[10] 2008 | MA | 16 (5 pro, 11 retro) | I: OP < 24 hours<br>C: OP > 24 hours | 1. 30-day mortality<br>2. 1-year mortality | 1. C vs. I; OR 1.56, 95% CI 1.27–1.91<br>2. C vs. I; OR 1.45, 95% CI 0.57–3.72 | Surgery within 48 hours, as surgery after 48 hours is associated with higher 30-day and 1-year mortality. | 28 |
| | | | I: OP < 48 hours<br>C: OP > 48 hours | 1. 30-day mortality<br>2. 1-year mortality | 1. C vs. I; OR 1.41, 95% CI 1.29–1.54<br>2. C vs. I; OR 1.32, 95% CI 1.21–1.43 | | |
| | | | I: OP < 72 hours<br>C: OP > 72 hours | 1. 30-day mortality<br>2. 1-year mortality | 1. C vs. I; OR 1.56, 95% CI 1.24–1.96<br>2. C vs. I; OR 2.00, 95% CI 1.06–3.78 | | |
| Khan et al.[11] 2009 | SR | 52 (18 pro, 34 retro) | I: Early OP<br>C: Delayed OP (cut-off points: 24 and 168 hours) | 1. Mortality<br>2. Post-operative complications<br>3. Length of hospital stay<br>4. Percentage of patients able to go home | 1. Non-conclusive<br>2. Higher in C<br>3. Higher in C<br>4. Non-conclusive | Delayed surgery may influence occurrence of complications and length of hospital stay. Effect on mortality has not been proven. | 23 |

| Author and year | SR or MA | Number and type of studies | Intervention (I) / Comparison (C) | Outcome measure | Risk on outcome measure | Conclusion / recommendation | R§ |
|---|---|---|---|---|---|---|---|
| Simunovic et al.[12] 2010 | MA | 16 (pro) | I: Early OP<br>C: Delayed OP (cut-off points: 24, 48, 72 and 120 hours) | 1. 30-day mortality<br>2. 1-year mortality<br>3. Corrected mortality^◊<br>4. Pneumonia<br>5. Pressure sore<br>6. Deep venous thrombosis<br>7. Pulmonary embolism | 1. I vs. C; RR 0.90, 95% CI 0.71–1.13<br>2. I vs. C; RR 0.55, 95% CI 0.40–0.75<br>3. I vs. C; RR 0.81, 95% CI 0.68–0.96<br>4. I vs. C; RR 0.59, 95% CI 0.37–0.93<br>5. I vs. C; RR 0.48, 95% CI 0.34–0.69<br>6. I vs. C; RR 0.97, 95% CI 0.56–1.68<br>7. I vs. C; RR 0.77, 95% CI 0.17–2.58 | Surgery within 24 – 72 hours is associated with lower mortality, pneumonia and pressure sore rates. | 32 |
| Leung et al.[13] 2010 | SR | 42 (14 pro, 28 retro) | I: Early OP<br>C: Delayed OP (cut-off points: 6, 24, 48, 72 and 96 hours) | 1. 30-day mortality<br>2. 1-year mortality<br>3. Complications (infection, pressure sore)<br>4. Length of hospital stay | 1. Non-conclusive<br>2. Non-conclusive<br>3. Higher in C<br>4. Higher in C | Surgery within 24 hours is associated with less complications. | 14 |
| Panesar et al.[14] 2012 | SR | 6 (2 reviews, 2 pro, 2 retro) | I: Early OP<br>C: Delayed OP (cut-off points: 24, 48 and 72 hours) | 1. Mortality | 1. Non-conclusive | Unsure whether time to surgery is associated with mortality. | 14 |

| Author and year | SR or MA | Number and type of studies | Intervention (I) / Comparison (C) | Outcome measure | Risk on outcome measure | Conclusion / recommendation | R§ |
|---|---|---|---|---|---|---|---|
| Moja et al.[15] 2012 | MA | 35 (1 RCT, 14 pro, 20 retro) | I: Early OP<br>C: Delayed OP (cut-off points: 12, 24, 36, 48 and 96 hours) | 1. Mortality◊<br>2. Pressure sore | 1. I vs. C; OR 0.74, 95% CI 0.67–0.81<br>2. I vs. C; OR 0.48, 95% CI 0.38–0.60 | Surgery after 24 hours is associated with higher mortality and pressure sore rates. | 36 |
| | | | I: OP < 12 hours<br>C: OP > 12 hours | 1. Mortality◊ | 1. I vs. C; OR 0.84, 95% CI 0.57–1.23 | | |
| | | | I: OP < 24 hours<br>C: OP > 24 hours | 1. Mortality◊ | 1. I vs. C; OR 0.74, 95% CI 0.62–0.87 | | |
| | | | I: OP < 48 hours<br>C: OP > 48 hours | 1. Mortality◊ | 1. I vs. C; OR 0.75, 95% CI 0.68–0.81 | | |
| | | | I: OP < 96 hours<br>C: OP > 96 hours | 1. Mortality◊ | 1. I vs. C; OR 0.67, 95% CI 0.39–1.13 | | |
| Doleman et al.[16] 2015 | MA | 12 (1 pro, 11 retro) | I: Early OP (< 72 hours) and clopidogrel use<br>C: Early OP (< 72 hours) and no clopidogrel use | 1. Mortality#<br>2. 30-day mortality<br>3. Blood transfusion<br>4. Length of hospital stay | 1. I vs. C; OR 0.89, 95% CI 0.58–1.38<br>2. I vs. C; OR 1.10, 95% CI 0.48–2.54<br>3. I vs. C; OR 1.41, 95% CI 1.00–1.99<br>4. Not tested | Inconclusive about effect of early versus delayed surgery. Patients on clopidogrel can be operated within 3 days, although they run a higher risk of blood transfusion. | 27 |
| | | | I: Early OP and clopidogrel use<br>C: Delayed OP (cut-off points: 120 and 168 hours) and clopidogrel use | 1. Mortality<br>2. 30-day mortality<br>3. Blood transfusion<br>4. Length of hospital stay | 1. I vs. C; OR 0.61, 95% CI 0.11–3.25<br>2. Not tested<br>3. I vs. C; OR 0.44, 95% CI 0.15–1.30<br>4. I vs. C; mean difference -7.09 days, 95% CI -10.14 – -4.04 | | |

| Author and year | SR or MA | Number and type of studies | Intervention (I) / Comparison (C) | Outcome measure | Risk on outcome measure | Conclusion / recommendation | R§ |
|---|---|---|---|---|---|---|---|
| Papakostidis et al.[17] 2015 | MA | 7 (1 pro, 6 retro) | I: OP < 6 hours<br>C: OP > 6 hours | 1. Avascular necrosis<br>2. Non-union | 1. I vs. C; OR 0.53, 95% CI 0.07–3.93<br>2. I vs. C; OR 0.09, 95% CI 0.01–0.68 | Surgery after 24 hours is not associated with avascular necrosis, but may increase risk of non-union. | 30 |
| | | | I: OP < 12 hours<br>C: OP > 12 hours | 1. Avascular necrosis<br>2. Non-union | 1. I vs. C; OR 0.70, 95% CI 0.39–1.26<br>2. I vs. C; OR 0.89, 95% CI 0.14–5.68 | | |
| | | | I: OP < 24 hours<br>C: OP > 24 hours | 1. Avascular necrosis<br>2. Non-union | 1. I vs. C; OR 0.92, 95% CI 0.50–1.68<br>2. I vs. C; OR 0.33, 95% CI 0.16–0.69 | | |
| | | | I: OP < 6 hours<br>C: OP > 24 hours | 1. Avascular necrosis<br>2. Non-union | 1. I vs. C; OR 0.52, 95% CI 0.09–2.86<br>2. Not tested | | |
| Lewis et al.[18] 2016 | SR | 31 (4 reviews, 2 RCT, 12 pro, 13 retro) | I: Early OP<br>C: Delayed OP (cut-off points: 6, 12, 24, 36, 48 and 72 hours) | 1. Mortality<br>2. Complications<br>3. Length of hospital stay<br>4. Time of pain | 1. Non-conclusive<br>2. Higher in C<br>3. Longer in C<br>4. Longer in C | The longer surgery is delayed, the higher the chance of complications. | 13 |

| Author and year | SR or MA | Number and type of studies | Intervention (I) / Comparison (C) | Outcome measure | Risk on outcome measure | Conclusion / recommendation | R§ |
|---|---|---|---|---|---|---|---|
| Klestil et al.[19] 2018 | MA | 28 (pro) | I: Early OP<br>C: Delayed OP (cut-off points: 6, 24, 48 and 72 hours) | 1. Complications<br>2. Quality of life<br>3. Functional scores | 1. Not tested<br>2. Not tested<br>3. Not tested | Surgery within 48 hours is associated with lower mortality and complication rates; it is unknown whether this is also applicable to frail patients. | 34 |
| | | | I: OP < 24 hours<br>C: OP > 24 hours | 1. 30-day mortalityˆ<br>2. 1-year mortalityˆ<br>3. 30-day mortality<br>4. 1-year mortality | 1. Not tested<br>2. I vs. C RR 0.82, 95% CI 0.67–1.01<br>3. I vs. C RR 1.04, 95% CI 0.85–1.29<br>4. I vs. C RR 0.68, 95% CI 0.56–0.84 | | |
| | | | I: OP < 48 hours<br>C: OP > 48 hours | 1. 30-day mortalityˆ<br>2. 1-year mortalityˆ<br>3. 30-day mortality<br>4. 1-year mortality | 1. Not tested<br>2. I vs. C; RR 0.80, 95% CI 0.66–0.97<br>3. I vs. C; RR 0.78, 95% CI 0.62–0.98<br>4. I vs. C; RR 0.74, 95% CI 0.64–0.84 | | |

MA Meta-analysis
SR Systematic review
R R-AMSTAR score
RCT Randomized controlled trial
Pro Prospective cohort study
Retro Retrospective cohort study
OP Operation
OR Odds ratio
RR Risk ratio
CI Confidence interval
ˆ Corrected for ASA grade, age and gender
◊ Combined outcome measure for mortality: 30-day mortality and 1-year mortality
# Combined outcome measure for mortality: in-hospital mortality, 30-day mortality and 1-year mortality
§ Score of the methodological quality of systematic reviews / meta-analyses on an 11 to 44-point scale

## Mortality

Five meta-analyses and four systematic reviews used 'mortality' as an outcome measure [10-16,18,19]. Three meta-analyses stratified according to time to surgery (24, 48, 72 and 96 hours) [10,15,19]. Looking at a combined outcome measure of 30-day and 1-year mortality, surgery delayed more than 24 hours was found to have a higher mortality rate [15]. However, looking at the individual outcome measures, a delay of more than 24 hours was not found to be related to an increased mortality rate within 30 days, but patients whose surgery was delayed more than 48 hours did run an increased risk of mortality within 1 year [10,19]. In one meta-analysis the results were adjusted for patient characteristics such as age, gender and ASA grade [19].

The two other meta-analyses made no stratification according to time to surgery but combined the different times, which varied from 24 to 168 hours [2,16]. One meta-analysis focused primarily on mortality; corrected for age, gender and ASA grade, surgery within 24 to 120 hours led to a statistically significant decline in mortality [12]. The other meta-analysis focused more on the use of an anticoagulant (clopidogrel) and its impact on mortality. Early surgery (within 72 hours) did not lead to increased mortality among clopidogrel users compared to non-users [16].

The authors of the four systematic reviews concluded that the individual studies did not demonstrate a causal relationship between time to surgery and mortality [11,13,14,18]. We therefore cannot make any recommendation for optimal time to surgery in relation to mortality. The researchers show that comorbidity influences the decision to delay surgery, and propose differentiating between healthy patients and patients with active medical problems [14]. The ASA classification can be used for this purpose: ASA 1-2 for healthy patients and ASA 3-4 for patients with active medical problems. Patients with active medical problems require preoperative optimization, while fit patients should be operated on as soon as possible [18,19].

## Complications

Complications was an outcome measure in five meta-analyses and three systematic reviews [11-13,15-19]. Two meta-analyses stratified according to time to surgery [17,19]. One meta-analysis centered on the relationship between time to surgery (6, 12 or 24 hours) and surgical complications with femoral head preservation (avascular femoral head necrosis and non-union) [17]. The time to surgery had no influence on the occurrence of avascular femoral head necrosis, but patients whose surgery was delayed more than 24 hours after admission ran a slightly increased risk of non-union. This may be an underestimation of the actual risk as patients with extensive co-morbidity are no longer eligible for femoral head preservation and are immediately treated with a femoral neck prosthesis. The authors of the other meta-analysis concluded that the cut-off values of the time to surgery differed to such an extent between the individual studies that pooled analyses were not possible [19].

The other three meta-analyses made no stratification according to time to surgery but grouped the outcomes, which varied from 24 to 168 hours. Patients whose surgery was not delayed ran an increased risk of pneumonia and pressure sores, but not of deep venous thrombosis, pulmonary embolism or blood transfusion [12,15,16]. Clopidogrel users who were operated within 72 hours received a blood transfusion more often than non-users [16]. The authors of the three reviews concluded that delaying surgery (varying from 24 to 96 hours) leads to more complications such as pneumonia, pressure sores and increased pain [11,13,18].

### Confounding by indication

Eight of the ten included reviews exclusively covered observational studies [10-14,16,17,19]. These studies were almost certainly affected by confounding by indication; patients with more comorbidity required more time for preoperative optimization, which probably reduced their chance of being operated on within a set time frame [21]. The extent to which preoperative optimization was the reason for delaying surgery could not be determined for the individual studies. Two meta-analyses attempted to adjust for patient characteristics, but it is unlikely that this eliminated all differences between early and late surgery [12,19]. In addition, three meta-analyses made no stratification according to time to surgery, which makes the results more difficult to interpret [12,15,16].

The literature describes two randomized studies, but neither had sufficient patients to detect statistically significant differences between groups [22,23]. One trial (n = 71) found no difference in mortality between patients whose surgery was delayed more or less than 48 hours [22]. In the other trial (n = 60) complications occurred more often among standard-care patients compared to accelerated-care patients (surgery within 6 hours) [23]. These results prompted the HIP ATTACK trial, a large multicenter, randomized study comprising 3,000 patients in 15 countries. This trial focuses primarily on the difference in postoperative complications and 90-day mortality between patients who were operated on within 6 hours after diagnosis and patients who received unspecified standard treatment. The results of this study are expected in the second half of 2019.

## What practical recommendations can we make?

Both the analysis of the IGJ quality indicator data and the literature study show that patients with more comorbidity are operated on later. The literature shows that patients should be operated on as soon as possible to reduce the risk of complications, but also that a delay of up to four to five days for preoperative optimization does not lead to increased mortality [18]. In other words, there is time for preoperative optimization, if necessary. The practical implication is that when using time to surgery as a care quality indicator, a distinction needs to be made between delay for patient optimization and delay due to inadequate hospital procedures. A longer time to surgery is only acceptable if the extra time is used for preoperative optimization.

The introduction of Direct Oral Anticoagulants (DOAC) is expected to increase the group of patients with active medical problems. The anticoagulation effect of most DOACs cannot yet be reversed, so it is necessary to wait for the patient’s coagulation to normalize. With patients using Rivaroxaban or Apixaban, it can take up to 48 hours before surgery can be performed safely. Clearly, therefore, the guideline to operate hip fracture patients within one calendar day after admission to hospital should not be applied too rigidly [2,3]. Hospitals, after all, might be tempted to operate patients too quickly, when still in suboptimal condition, to boost their score on the 'time to surgery' quality indicator. This would beat the purpose of the quality indicator.

## Case continued

In the case of our 88-year-old patient, preoperative optimization is advisable. The optimization consists of the correction of active medical problems, such as electrolyte imbalance, anaemia and excessive anticoagulation. If the operation must be delayed until Thursday or Friday to optimize the patient, that is the correct procedure for this specific patient. But delay is not justified for every patient with comorbidity. Surgery should only be delayed if active medical problems so require. Patients without active medical problems should be operated on as quickly as possible.

## Conclusion

Much has been published about the optimal time to surgery for hip fracture patients. Almost all studies are observational, and are therefore almost certainly affected by confounding by indication. For this reason, the optimal time to surgery cannot be defined. It is clear that the risk of complications such as pneumonia and pressure sores increases the longer the surgery is delayed. Otherwise, mortality does not increase if surgery is delayed for preoperative optimization. In conclusion, patients with active medical problems require preoperative optimization, but patients without active medical problems should be operated on as soon as possible.

# Appendices

## Appendix 1. Overview of included studies grouped by study design

| | Shiga[10] 2008 (MA) | Khan[11] 2009 (SR) | Simu-novic[12] 2010 (MA) | Leung[13] 2010 (SR) | Pane-sar[14] 2012 (SR) | Moja[15] 2012 (MA) | Dole-man[16] 2015 (MA) | Papakos-tidis[17] 2015 (MA) | Lewis[18] 2016 (SR) | Klestil[19] 2018 (MA) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Randomized Clinical Trial** | | | | | | | | | | |
| Swanson, 1998 | | | | | | ■ | | | ■ | |
| Devereaux, 2014 | | | | | | | | | ■ | |
| **Prospective cohort study** | | | | | | | | | | |
| Davie, 1970 | | ■ | ■ | | | | | | | |
| Villar, 1986 | | ■ | | | | | | | | |
| Davis, 1987 | | ■ | | | | | | | | |
| Davis, 1988 | | ■ | ■ | | | ■ | | | | |
| Harries, 1991 | | ■ | ■ | ■ | | | | | | |
| Mullen, 1992 | | ■ | ■ | ■ | | ■ | | | ■ | |
| Parker, 1992 | ■ | ■ | ■ | ■ | | ■ | | | ■ | |
| Wood, 1992 | | ■ | | | | | | | | |
| Fox, 1994 | | ■ | | ■ | | | | | | |
| Todd, 1995 | | ■ | | | | | | | | |
| Zuckermann, 1995 | ■ | ■ | ■ | ■ | | | | | ■ | |
| Beringer, 1996 | | | ■ | | | | | | | |
| Smektala, 2000 | | | ■ | | | | | | | ■ |
| Dorotka, 2003 | | ■ | ■ | ■ | ■ | ■ | | | | ■ |
| Elliott, 2003 | ■ | ■ | ■ | ■ | | ■ | | | ■ | ■ |
| Doruk, 2004 | | ■ | ■ | ■ | | ■ | | | | |
| Orosz, 2004 | | ■ | ■ | ■ | ■ | ■ | | | ■ | ■ |
| Moran,2005 | ■ | ■ | ■ | ■ | | ■ | | | ■ | ■ |
| Siegmeth, 2005 | ■ | ■ | ■ | ■ | | ■ | | | ■ | ■ |
| Rae, 2007 | | ■ | ■ | ■ | | ■ | | | ■ | ■ |
| Al-ani, 2008 | | | | ■ | | ■ | | | | ■ |
| Holt, 2008 | | | | ■ | | ■ | | | ■ | |
| Smektala, 2008 | | | ■ | | | ■ | | | | ■ |
| Loizou, 2009 | | | | | | | | ■ | | |
| Vertelis, 2009 | | | | | | | | | | ■ |
| Yonezawa, 2009 | | | | | | | | | | ■ |
| Maggi, 2010 | | | | | | ■ | | | | ■ |
| Oztürk, 2010 | | | | | | | | | | ■ |

| | Shiga[10] 2008 (MA) | Khan[11] 2009 (SR) | Simu-novic[12] 2010 (MA) | Leung[13] 2010 (SR) | Pane-sar[14] 2012 (SR) | Moja[15] 2012 (MA) | Dole-man[16] 2015 (MA) | Papakos-tidis[17] 2015 (MA) | Lewis[18] 2016 (SR) | Klestil[19] 2018 (MA) |
|---|---|---|---|---|---|---|---|---|---|---|
| Thaler, 2010 | | | | | | | ■ | | | |
| Vidán, 2011 | | | | | | | | | | ■ |
| Kim, 2012 | | | | | | | | | | ■ |
| Pioli, 2012 | | | | | | | | | | ■ |
| Dailiana, 2013 | | | | | | | | | | ■ |
| Muhm, 2013 | | | | | | | | | | ■ |
| Poh, 2013 | | | | | | | | | | ■ |
| Trpeski, 2013 | | | | | | | | | | ■ |
| Uzoigwe, 2013 | | | | | | | | | ■ | |
| Hapuarachchi, 2014 | | | | | | | | | | ■ |
| Bretheron, 2015 | | | | | | | | | ■ | ■ |
| Mariconda, 2015 | | | | | | | | | ■ | ■ |
| Pajulammi, 2016 | | | | | | | | | | ■ |
| Lizaur-Utrilla, 2016 | | | | | | | | | | ■ |
| Butler, 2017 | | | | | | | | | | ■ |
| Crego-Vita, 2017 | | | | | | | | | | ■ |
| Kelly-Pettersson, 2017 | | | | | | | | | | ■ |
| **Retrospective cohort study** | | | | | | | | | | |
| Beals, 1972 | | ■ | | | | | | | | |
| McNeill, 1975 | | ■ | | | | | | | | |
| Kenzora, 1984 | | ■ | | ■ | | ■ | | | ■ | |
| Swiontokowski, 1984 | | | | | | | | ■ | | |
| Davidson, 1986 | | ■ | | | | | | | | |
| Manniger, 1989 | | | | | | | | ■ | | |
| Dolk, 1990 | | ■ | | | | | | | | |
| Eiskjaer, 1991 | | ■ | | | | | | | | |
| Bredahl, 1992 | | ■ | | ■ | | ■ | | | | |
| Hoerer, 1993 | | ■ | | ■ | | | | | | |
| Perez, 1995 | | ■ | | ■ | | | | | ■ | |
| Rogers, 1995 | | ■ | | ■ | | | | | | |
| Hamilton, 1996 | | ■ | | ■ | | | | | | |
| Roos, 1996 | | | | | | ■ | | | | |
| Hamlet, 1997 | | ■ | | ■ | | ■ | | | | |
| Hoenig, 1997 | | ■ | | ■ | | | | | | |
| Sexson, 1998 | | ■ | | | | ■ | | | | |
| Ho, 2000 | | | | ■ | | | | | | |

| | Shiga[10] 2008 (MA) | Khan[11] 2009 (SR) | Simu-novic[12] 2010 (MA) | Leung[13] 2010 (SR) | Pane-sar[14] 2012 (SR) | Moja[15] 2012 (MA) | Dole-man[16] 2015 (MA) | Papakos-tidis[17] 2015 (MA) | Lewis[18] 2016 (SR) | Klestil[19] 2018 (MA) |
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| Thomas, 2001 | | ■ | | ■ | | | | | | |
| Grimes, 2002 | ■ | ■ | | ■ | ■ | ■ | | | ■ | |
| Jain, 2002 | | | | | | | | ■ | | |
| Stoddart, 2002 | ■ | ■ | | ■ | | ■ | | | | |
| Cooper, 2003 | | ■ | | | | | | | | |
| Shabat, 2003 | | ■ | | ■ | | | | | | |
| Casaletto, 2004 | | ■ | | ■ | | | | | | |
| Gdalevich, 2004 | ■ | ■ | | ■ | | ■ | | | ■ | |
| Haiduckewych, 2004 | | | | | | | | ■ | | |
| Karaeminogullari, 2004 | | | | | | | | ■ | | |
| McGuire, 2004 | ■ | ■ | | ■ | | ■ | | | ■ | |
| Elder, 2005 | | ■ | | ■ | | | | | ■ | |
| Franzo, 2005 | ■ | ■ | | | | ■ | | | | |
| McLeod, 2005 | | ■ | | ■ | | | | | | |
| Sund, 2005 | ■ | ■ | | ■ | | ■ | | | | |
| Weller, 2005 | ■ | ■ | | ■ | | ■ | | | ■ | |
| Williams, 2005 | | ■ | | ■ | | | | | | |
| Bergeron, 2006 | ■ | ■ | | ■ | | ■ | | | | |
| Bottle, 2006 | ■ | ■ | | ■ | ■ | | | | ■ | |
| Mackenzie, 2006 | | ■ | | | | | | | | |
| Majumdar, 2006 | ■ | ■ | | ■ | | ■ | | | | |
| Novack, 2007 | ■ | ■ | | ■ | | ■ | | | | |
| Rademakers, 2007 | | ■ | | | | ■ | | | | |
| Radcliff, 2008 | | | | ■ | | ■ | | | | |
| Verbeek, 2008 | | | | ■ | | ■ | | | ■ | |
| Cox, 2009 | | | | | | | ■ | | | |
| Lefaivre, 2009 | | | | ■ | | | | | ■ | |
| Sim, 2009 | | | | | | | ■ | | | |
| Holt, 2010 | | | | | | | | | ■ | |
| Nydick, 2010 | | | | | | | ■ | | | |
| Caretta, 2011 | | | | | | ■ | | | | |
| Chechik, 2011 | | | | | | | ■ | | | |
| Peleg, 2011 | | | | | | ■ | | | | |
| Rodriguez-Fernandez, 2011 | | | | | | | | | ■ | |
| Chechik, 2012 | | | | | | | ■ | | | |
| Collinge, 2012 | | | | | | | ■ | | | |

| | Shiga[10] 2008 (MA) | Khan[11] 2009 (SR) | Simu-novic[12] 2010 (MA) | Leung[13] 2010 (SR) | Pane-sar[14] 2012 (SR) | Moja[15] 2012 (MA) | Dole-man[16] 2015 (MA) | Papakos-tidis[17] 2015 (MA) | Lewis[18] 2016 (SR) | Klestil[19] 2018 (MA) |
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| Razik, 2012 | | | | | | | | | | |
| Wallace, 2012 | | | | | | | | | | |
| Feely, 2013 | | | | | | | | | | |
| Hossain, 2013 | | | | | | | | | | |
| Wordsworth, 2013 | | | | | | | | | | |
| Belmont, 2014 | | | | | | | | | | |
| Manaqibwala, 2014 | | | | | | | | | | |

MA Meta-analysis

SR Systematic review

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