Immediate total-body CT scanning versus conventional imaging and selective CT scanning in patients with severe trauma (REACT-2): a randomised controlled trial

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Summary

Background Published work suggests a survival benefit for patients with trauma who undergo total-body CT scanning during the initial trauma assessment; however, level 1 evidence is absent. We aimed to assess the effect of total-body CT scanning compared with the standard work-up on in-hospital mortality in patients with trauma.

Methods We undertook an international, multicentre, randomised controlled trial at four hospitals in the Netherlands and one in Switzerland. Patients aged 18 years or older with trauma with compromised vital parameters, clinical suspicion of life-threatening injuries, or severe injury were randomly assigned (1:1) by ALEA randomisation to immediate total-body CT scanning or to a standard work-up with conventional imaging supplemented with selective CT scanning. Neither doctors nor patients were masked to treatment allocation. The primary endpoint was in-hospital mortality, analysed in the intention-to-treat population and in subgroups of patients with polytrauma and those with traumatic brain injury. The χ^2 test was used to assess differences in mortality. This trial is registered with ClinicalTrials.gov, number NCT01523626.

Findings Between April 22, 2011, and Jan 1, 2014, 5475 patients were assessed for eligibility, 1403 of whom were randomly assigned: 702 to immediate total-body CT scanning and 701 to the standard work-up. 541 patients in the immediate total-body CT scanning group and 542 in the standard work-up group were included in the primary analysis. In-hospital mortality did not differ between groups (total-body CT 86 [16%] of 541 *vs* standard work-up 85 [16%] of 542; p=0·92). In-hospital mortality also did not differ between groups in subgroup analyses in patients with polytrauma (total-body CT 81 [22%] of 362 *vs* standard work-up 82 [25%] of 331; p=0·46) and traumatic brain injury (68 [38%] of 178 *vs* 66 [44%] of 151; p=0·31). Three serious adverse events were reported in patients in the total-body CT group (1%), one in the standard work-up group (<1%), and one in a patient who was excluded after random allocation. All five patients died.

Interpretation Diagnosing patients with an immediate total-body CT scan does not reduce in-hospital mortality compared with the standard radiological work-up. Because of the increased radiation dose, future research should focus on the selection of patients who will benefit from immediate total-body CT.

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Introduction

Total-body CT scanning is increasingly used in the primary assessment of patients with trauma, and is done according to Advanced Trauma Life Support (ATLS) guidelines.[1] CT scanning is accurate and safe for the detection of traumatic injuries.[2] A substantial advantage of total-body imaging compared with the standard work-up with radiographs, ultrasound, and selective CT scanning is the rapid and complete overview of life-threatening traumatic injuries. Time benefits in favour of total-body CT scanning compared with the standard work-up,[3–6] changes in treatment associated with total-body CT scanning,[7] and potential survival benefits of total-body CT scanning[3,8–13] have been described previously.

A potential disadvantage of total-body CT scanning of patients with trauma is the increased exposure to radiation.[14,15] As a side-effect, incidental (ie, unrelated to the trauma) findings are more frequently found with total-body CT scanning[16–18] than standard work-up. Despite the absence of level 1 scientific evidence for the use of total-body CT scanning in the assessment of patients with trauma,[2,19,20] an increasing number of trauma centres have incorporated this imaging strategy into their daily practice.[6,7,13,21] The total-body CT scan could be used as a supplemental instrument to standard radiological imaging or even as a replacement, without the need for previous conventional imaging (ie, radiographs and ultrasound).

Most previous studies retrospectively included a specific cohort of patients (eg, patients with polytrauma, defined as patients with an Injury Severity Score [ISS] of ≥16).[3,13] Because the ISS is calculated retrospectively at discharge, this parameter is not available in daily clinical practice and cannot be used as a triage method for the selection of severely injured patients. Therefore, intrinsic

Research in context

Evidence before this study

Before the start of REACT-2, we undertook a systematic review to assess the value of immediate total-body CT during the primary survey of injured patients compared with conventional radiographic imaging supplemented with selective CT. We did a systematic search of MEDLINE, Embase, Web of Science, and Cochrane Library databases. The search consisted of all articles published between 1947 and Nov 1, 2010, and terms searched for were ("fbct" or "tbct" or " whole body ct" or " total body ct" or "full body ct") OR (["whole body" or "total body" or "full body"] AND ["scan*" or "tomograph*" or "ct scan"]). These terms were combined with the following terms: "trauma" or "injur*" or "shock*" or "emerg*". All articles in English or Dutch were included. Reports were eligible if they contained original data that compared immediate total-body CT with conventional imaging supplemented with selective CT in injured patients. The main outcomes of interest were overall mortality and time in the emergency room. Four studies were included that described a total of 5470 patients; one study included 4621 patients (84%). All four studies were non-randomised cohort studies with retrospective data collection and were of proper methodological quality. Mortality was reported in three studies. Absolute mortality differed substantially between studies, but within studies mortality rates were comparable between immediate total-body CT and conventional imaging strategies (pooled odds ratio 0·91, 95% CI 0·79–1·05). After adjustment for confounders, one of the studies showed an increase in probability of survival in favour of patients with total-body CT. Time in the emergency room was described in three studies; in two emergency rooms, time was significantly shorter in patients who underwent immediate total-body CT (70 min *vs* 104 min; p=0·025; and 47 min *vs* 82 min; p<0·001). In conclusion, the substantial reduction in time in the emergency room is a promising feature of immediate total-body CT scanning, but well designed and larger randomised studies are needed to see how this will translate into clinical outcomes.

Added value of this study

Total-body imaging is theoretically so promising that several trauma centres around the world incorporated the total-body CT scan into their daily practice, without level 1 evidence. However, total-body CT scanning is associated with higher radiation exposure and health-care costs. REACT-2 showed that immediate total-body CT scanning is safe, shortens the time to end of imaging, and does not increase direct medical costs; however, it does not improve survival. REACT-2 is, to our knowledge, the first randomised trial on this topic and a substantial number of patients were included. Our study was well designed and patient characteristics were comparable between the randomly assigned cohorts. REACT-2 provided Oxford level 1a evidence to the question of whether use of the immediate total-body CT scan during assessment of trauma is justified.

Implications of all the available evidence

Findings from REACT-2 show that the immediate total-body CT scan should be used cautiously in clinical practice. Although we noted no survival benefit, there was no increase in medical costs and there was a time benefit in favour of total-body CT scanning. In severely injured patients in whom CT examinations of several body regions were expected, total-body CT scanning was beneficial since such patients received a similar or higher radiation dose with the standard work-up. Future studies should aim to optimise the selection criteria for total-body CT in severely injured patients. REACT-2 showed the difficulty of trying to establish beforehand which patients are severely injured, as opposed to selecting patients with polytrauma retrospectively, when results of radiography are known and an Injury Severity Score is already attributed to the patient. The injury mechanism, vital parameters, and clinical suspicion of potential injuries as used in REACT-2 are a good, but certainly not the ideal, starting point for future studies. Another point of interest is whether the total-body CT scan should be used as a supplement to or as a replacement for conventional imaging. Even in haemodynamically compromised patients, the total-body CT scan could be a safe or even preferred imaging method. If conventional imaging can be omitted, radiation exposure in total-body CT will further decline and more time will be saved. However, large prospective series of haemodynamically unstable patient cohorts should be done to provide information on the transition point between those who are unstable but stable enough for a total-body CT scan and those who are too unstable to undertake a total-body CT scan. Another important group are patients with severe traumatic brain injury, especially if combined with injuries in other body regions. The rapid and detailed information on the absence or presence, and severity, of injuries provided by the total-body CT scan might direct important therapeutic decisions.

methodological limitations and the risk of selection bias are confounders in these studies. The need for a randomised clinical trial has been highlighted[3] and was the primary conclusion of all systematic reviews.[2,19,20,22–24]

We undertook a randomised clinical trial (REACT-2) to examine the effect of immediate total-body CT scanning as part of the primary assessment of patients with severe trauma on in-hospital mortality, and compared it with that of the standard work-up of conventional imaging supplemented with selective CT scanning.

For the **trial protocol** see http://bmcemergmed.biomedcentral.com/articles/10.1186/1471-227X-12-4

Methods

The trial protocol can be found online.

Study design and patients

In REACT-2, an international, multicentre, randomised controlled trial, we compared immediate total-body CT scanning with a standard work-up with conventional imaging supplemented by selective CT scanning in patients with severe trauma. The design of REACT-2 has been described previously.[25]

Patients were enrolled at four hospitals in the Netherlands and one hospital in Switzerland. All participating sites were level 1 trauma centres and academic teaching hospitals. A trauma survey was done by a team consisting of the following well-trained members: a trauma team leader (trauma surgeon or surgical resident in training), an anaesthesiologist, a radiologist, and support staff. Every new member of the trauma team received training for the study procedures and local trauma protocols. Trauma teams received feedback on study procedures by local trial staff within 1 working day of the trauma survey in relation to study procedures.

Eligibility criteria were chosen with the aim of enrolling a trauma population with potentially severe injuries. Patients aged 18 years or older with compromised vital parameters, clinical suspicion of life-threatening injuries, or severe injury were eligible. The appendix includes a complete list of inclusion and exclusion criteria.

This study was approved by the medical ethics committee at each participating centre. Informed consent was obtained at the earliest opportunity after the trauma work-up and is described later.

Randomisation and masking

Eligible patients were identified at initial presentation in the trauma room and informed consent was temporarily waived. Subsequently, patients were randomly assigned (1:1) by trained trauma leaders, stratified by centre, to either immediate total-body CT scanning without previous conventional imaging or to the standard work-up, with ALEA randomisation software available at an iPad or desktop PC in the trauma room. Neither doctors nor patients were masked to treatment allocation.

Patients who were included by mistake because they did not fulfil the inclusion criteria, as assessed by a member of the study group as soon as possible after the moment of inclusion, were classed as exclusions after randomisation. When a mistake was suspected, the trauma team leader and the research investigator at the specific sites were contacted. In consultation with these people, the decision was made whether a patient should be classed as an exclusion after randomisation.

Procedures

Potential life-saving interventions during the primary survey and before imaging included securing the airway by intubation, obtaining intravenous access, chest tube insertion, pericardiocentesis, and haemorrhage control measures. Indications for selective CT scanning in the standard work-up group were predefined according to local protocols (appendix). The multidetector CT scanner was located in the trauma room or in a room adjacent to the emergency department. Subsequent medical care was provided according to local protocols on the basis of international trauma care standards.

The protocol for the intervention (total-body CT) group consisted of a two-step acquisition (from vertex to pubic symphysis) without gantry angulations, starting with a non-enhanced CT of the head and neck with arms alongside the trunk. The second scan covered the chest, abdomen, and pelvis. The preferred technique for the second scan was split-bolus intravenous contrast imaging immediately after raising the arms alongside the head.[26] CT scanners at the participating sites were all 64-slice multidetector row CT scanners. The standard radiological trauma work-up was done according to ATLS guidelines.[1] Chest and pelvic radiographs and focused assessment with sonography in trauma were done during the ATLS-based primary survey. After further assessment and resuscitation during the secondary survey, a selective CT scan could be made from individual body regions, with segmented acquisition of the respective body regions.

Hypotension was defined as a systolic blood pressure below 90 mm Hg upon arrival at the trauma room.[27] Patients with traumatic brain injury (TBI) were defined as having a Glasgow Coma Scale score below 9 at presentation and an Abbreviated Injury Scale head score of 3 or above. Patients with polytrauma were defined as those with an ISS of 16 or above. Trauma ISS (TRISS) was used to calculate the probability of survival (coefficients for blunt trauma were b0 –0·4499, b1 0·8085, b2 –0·0835, and b3 –1·7430; coefficients for penetrating trauma were b0 –2·5355, b1 0·9934, b2 –0·0651, and b3 –1·1360).[28]

See Online for appendix

At the earliest possible moment after the trauma work-up, the patient or their legal representative was informed about REACT-2 and written informed consent was requested. All patients for whom written informed consent could be obtained were sent three questionnaires (EuroQol-5D-3L, Health Utilities Index Mark 3, and a questionnaire derived from the Dutch Health and Labour Questionnaire for cost-effectiveness analysis)[25] at 3, 6, and 12 months after the trauma. Outcomes of the questionnaires will be described in a separate report on the cost-effectiveness of total-body CT versus standard work-up. Patients for whom written informed consent could not be obtained, despite all efforts, were included in the intention-to-treat analysis, but not in analyses of patient questionnaire responses (approved by the central medical ethics committee at the Academic Medical Center, Amsterdam, Netherlands, and the Dutch Central Committee on Research Involving Human Subjects). Data at the 3-month, 6-month, and 12-month follow-ups were prospectively collected from clinical and outpatient reports in the hospital databases. If no information could be obtained from these databases, the patient or their family doctor, or both, were contacted by telephone by one of the study investigators or research nurses. If a patient was transferred to another hospital, data from that hospital were also included in the analyses.

Outcomes

The primary endpoint was in-hospital mortality, defined as mortality during the index hospital admission after trauma, including in patients who were transferred to

another hospital after initial admission at one of the participating sites. Secondary endpoints were 24-h mortality, 30-day mortality, clinically relevant time intervals during the trauma survey, duration of stay and number of ventilation days for patients admitted to the intensive care unit, readmission within 6 months, radiation exposure, complications, number of patients who received at least one blood transfusion, and hospital costs.

Clinically relevant time intervals were defined as imaging time, time to diagnosis of life-threatening injuries, and total time spent in the trauma room. Time intervals were prospectively registered by the trauma team by one-click or touch buttons on a PC or iPad, starting immediately after the patient entered the trauma room. Imaging time was defined as the time from arrival in the trauma room until the end of imaging in the trauma room. Time to diagnosis was defined as the time at arrival to the time all life-threatening injuries were diagnosed according to the trauma team leader, in accordance with the radiologist.

The cumulative radiation dose was defined as the sum of all effective doses from all radiological imaging strategies (eg, radiographs and CT scans), calculated for all radiological examinations done in the trauma room and for the complete index admission. The radiation dose was estimated based on the dose catalogue of Mettler and colleagues.[29] With respect to the radiation dose, radiographs of the clavicle were regarded as radiographs of the arms; radiographs of the face and dental panoramic orthopantomography were regarded as radiographs of the skull; and a retrograde urethrogram was regarded as a pelvic radiograph. The dose for radiographs of the thoracolumbar transition was not provided by Mettler and colleagues,[29] and was therefore estimated as the mean for a thoracic spine radiograph and a lumbar spine radiograph (1·25 mSv). Because mean doses for the CT protocols used in a trauma setting were not readily available in the published work, we calculated representative radiation doses for single-pass CT scans of various body regions on the basis of optimised trauma CT protocols at one of the study sites (Academic Medical Center; appendix).[30] This trauma resuscitation room has a sliding gantry 64-slice CT scanner (Sensation 64, Siemens Medical Solutions, Forchheim, Germany) with a multifunctional, radiolucent trauma resuscitation table. Doses of CT scans of the legs, arms, hands, and feet were excluded from the analysis. To calculate effective doses, we used the ImPACT CT Dosimetry spreadsheet. Fluoroscopies were excluded because they were not used for diagnostic examinations leading to treatment decisions, which was the limit of the scope of our study.

For the **ImPACT CT Dosimetry spreadsheet** see http://www.impactscan.org/ctdosimetry.htm

Complications were classified according to the Clavien-Dindo Classification for surgical patients.[31] Hospital costs were assessed at 6 months for Dutch patients only; complete data collection on the use of hospital resources in the patients outside the Netherlands consistent with the way these data were collected in Dutch centres was not possible. The Dutch assessment included the costs for all diagnostic and therapeutic procedures in the trauma room, intensive care unit, and general ward during the index admission. We further included the costs of inpatient and outpatient hospital consultations, repeat hospital admissions, and diagnostic and therapeutic procedures during the 6 months of follow-up. Costs for a stay in a nursing home or rehabilitation centre, other than rehabilitation in the index hospitals, were excluded from this analysis. Data on health-care volume (ie, all included health-care components mentioned for which the costs were calculated) in the Dutch index hospitals for all hospital admissions were gathered uniformly from the hospital information systems. Unit costs were expressed in euros for the base year 2013; unit costs from other calendar years were price indexed using the national general consumer price indices, as published by Statistics Netherlands.[32] Patients who died in hospital were analysed for all outcomes except those that were derived from patients' questionnaires.

Safety outcomes were the assessment of serious adverse events. A serious adverse event was defined as a life-threatening event during scanning. Every serious adverse event was reported to the research coordinators (JCS and KT) and the medical ethics committee within 24 h.

Statistical analysis

539 patients per group were needed for detection of a difference in mortality of 5% with a power of 80% and a two-sided alpha of 5%. Details of the power analysis have been described previously.[25] The statistical analyses were done by the study investigators and independently by a clinical epidemiologist not involved in the trial. The continuous data with a normal distribution are expressed as means and SDs, whereas the non-normally distributed data are presented as medians with IQRs. We used independent sample *t* tests to compare parametric continuous data (patient characteristics: pulse and systolic blood pressure; outcomes: none) and Mann-Whitney *U* tests for non-parametric continuous data (patient characteristics: age, respiratory rate, Glasgow Coma Scale score, triage Revised Trauma Score, Revised Trauma Score, laboratory results, ISS, and TRISS; outcomes: time intervals, radiation exposure, and duration of intensive care unit stay). We used the χ^2 test and Fisher's exact test to compare categorical variables (patient characteristics: sex, type of trauma, trauma mechanism, comorbidity, drug treatment, hypotension at admission, Abbreviated Injury Scale score, polytrauma, and patients with TBI; outcomes: mortality, complications, transfusion requirements, and serious adverse events). A p value of less than 0·05 was deemed statistically significant.

The primary analyses were done according to the intention-to-treat principle. Subgroups were prespecified

(patients with polytrauma, severe TBI, and penetrating injury) and analysed when appropriate (ie, if the sample size was sufficient for analysis).

We assessed differences in hospital costs between total-body CT scanning and the standard work-up by non-parametric bootstrapping, drawing 1000 samples of the same size as the original sample separately for each group with replacement (ie, a patient can be drawn more than once to be included in a bootstrap sample) and calculating the 95% CIs for the mean differences after correction for bias and acceleration.[33] Cost-effectiveness and cost-utility analyses will be reported separately, together with data on 1-year survival and quality of life.

We did post-hoc per-protocol analyses of primary and secondary outcomes that excluded crossovers (ie, patients who received the opposite intervention to the one they had been allocated). Supplementary post-hoc analyses to account for the presence of missing data and for treatment centre effects were also done.

After 275 (26%), 550 (51%), and 700 (65%) patients were included, we did preplanned unmasked interim analyses for the assessment of safety rules. No formal stopping rules were prespecified. Instead, the data and safety monitoring board assessed the data and each serious adverse event and decided whether the trial should be continued.

To comply with Good Clinical Practice guidelines,[34] we made a monitoring plan. Data monitoring was done in February, 2013, and was repeated after enrolment ended on Jan 1, 2014.

This trial is registered with ClinicalTrials.gov, number NCT01523626.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, and had no access to the study data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patient enrolment began on April 22, 2011, and ended on Jan 1, 2014. 5475 patients were assessed for eligibility, 3860 of whom were excluded and 212 inclusions were missed (figure 1). Thus, 1403 patients were randomly assigned: 702 to total-body CT scanning and 701 to standard work-up. 203 patients were excluded after random allocation (appendix). 541 patients in the total-body CT scan group and 542 in the standard work-up group were included in the primary analysis.

Six (1%) of 702 patients assigned to the total-body CT group compared with 18 (3%) of 701 assigned to the standard work-up group crossed over (p=0·21). Other protocol violations, not classified as crossovers by the steering committee, occurred in 49 (9%) of 541 patients in the total-body CT group and 62 (11%) of 542 in the standard work-up group who were included in the primary analysis (p=0·20; appendix).

Table 1 shows the demographics and baseline clinical characteristics of the patients who were included in the primary analysis. The groups were comparable for all characteristics except for the number of patients with polytrauma (total-body CT 362 [67%] of 541 *vs* standard work-up 331 [61%] of 542), median haemoglobin concentration (129 g/L [IQR 113–142] *vs* 133 g/L [120–145]), and median haematocrit concentration (38 L/L

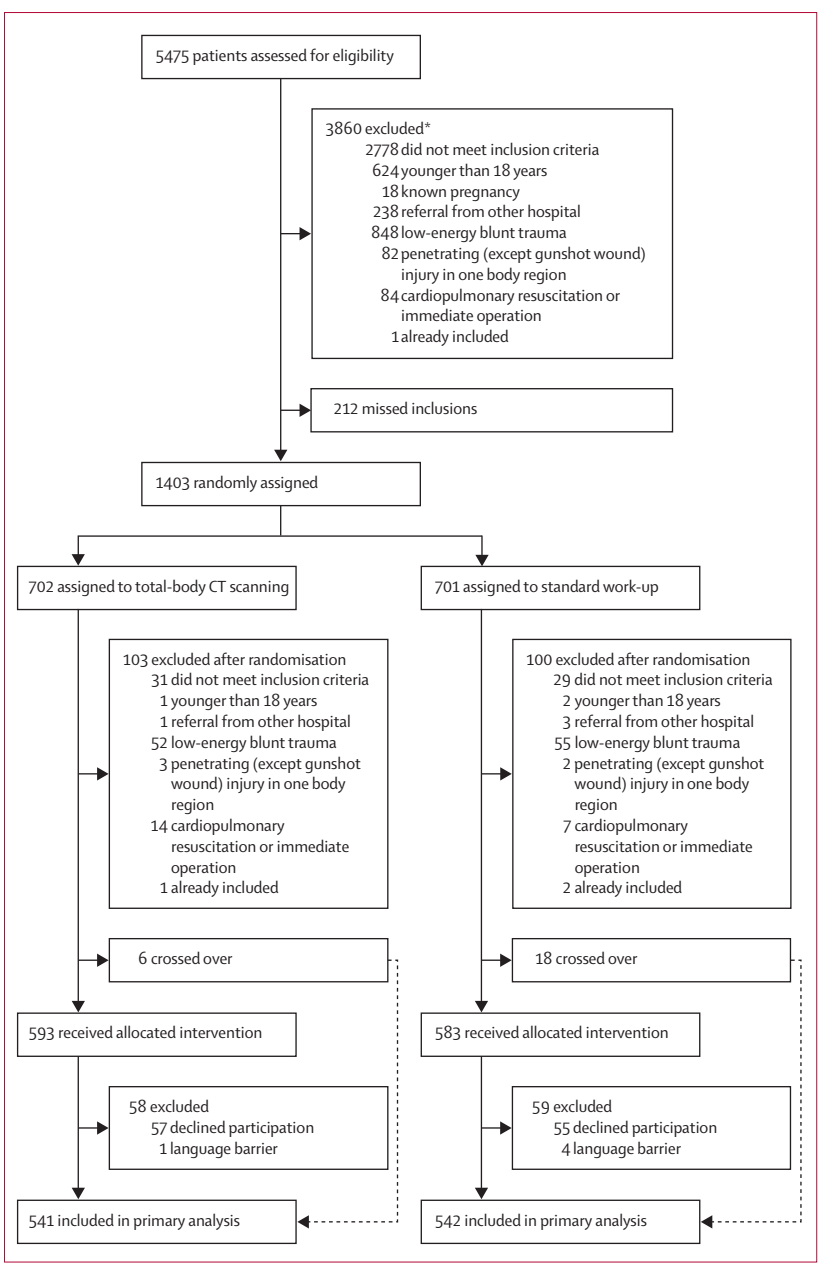

Figure 1: **Trial profile**
Missed inclusions are patients who fulfilled the inclusion criteria but were not included by mistake. *Patients could have more than one reason for exclusion.

	Total-body CT		Standard work-up	
	Number of patients	Data	Number of patients	Data
Age (years)	541	42 (27–59)	542	45 (26–59)
Sex	541		542	
Male		413 (76%)		411 (76%)
Female		128 (24%)		131 (24%)
Blunt trauma	541	530 (98%)	542	534 (99%)
Fall from height	530	170 (32%)	534	178 (33%)
Motor vehicle collision, patient as occupant	530	201 (38%)	534	190 (36%)
Motor vehicle collision, patient as cyclist	530	65 (12%)	534	60 (11%)
Motor vehicle collision, patient as pedestrian	530	29 (5%)	534	45 (8%)
Other	530	65 (12%)	534	61 (11%)
Comorbidity				
ASA I or II	517	495 (96%)	521	501 (96%)
ASA III, IV, or V	517	22 (4%)	521	20 (4%)
Relevant drug treatment				
Coumarin derivatives	505	17 (3%)	516	14 (3%)
Thrombocyte aggregation inhibitors	505	38 (8%)	516	28 (5%)
Insulin	505	4 (1%)	516	3 (1%)
Vital parameters before hospital admission				
Respiratory rate (per min)	323	17 (14–20)	317	16 (14–20)
Pulse (beats per min)	470	90 (25)	478	88 (24)
Systolic blood pressure (mm Hg)	451	133 (31)	459	134 (31)
Glasgow Coma Scale score (points)	528	14 (6–15)	533	14 (6–15)
Triage Revised Trauma Score	316	6·90 (5·03–7·84)	302	7·69 (5·03–7·84)
In-hospital vital parameters				
Respiratory rate (per min)	330	16 (14–20)	339	16 (13–20)
Pulse (beats per min)	528	88 (22)	531	87 (22)
Systolic blood pressure (mm Hg)	530	131 (26)	530	131 (29)
Hypotension at admission	530	38 (7%)	530	44 (8%)
Glasgow Coma Scale score (points)	541	13 (3–15)	542	13 (3–15)
Revised Trauma Score	322	6·90 (4·09–7·84)	329	7·55 (4·09–7·84)
Laboratory results				
Haemoglobin concentration (g/L)	531	129 (113–142)	537	133 (120–145)
Haematocrit concentration (L/L)	478	38 (34–41)	488	39 (35–42)
pH	491	7·34 (7·28–7·38)	488	7·35 (7·29–7·39)
Base excess concentration (mmol/L)	491	−2·1 (−4·7 to −0·5)	490	−2·1 (−5·1 to −0·1)
Abbreviated Injury Scale ≥3				
Head	541	247 (46%)	542	218 (40%)
Chest	541	229 (42%)	542	206 (38%)
Abdomen	541	49 (9%)	542	67 (12%)
Arms, legs, hand, and feet	541	150 (28%)	542	154 (28%)
Injury Severity Score (points)	541	20 (10–29)	542	19 (9–29)
Patients with polytrauma	541	362 (67%)	542	331 (61%)
Patients with traumatic brain injury	541	178 (32·9)	542	151 (27·9)
Trauma and Injury Severity Score, survival probability	317	0·93 (0·65–0·98)	301	0·94 (0·70–0·99)

Data are median (IQR), number (%), or mean (SD). Some percentages do not add up to 100 because of rounding. ASA=American Society of Anesthesiologists.

Table 1: **Demographics and baseline clinical characteristics**

[IQR 34–41] *vs* 39 L/L [35–42]). Median ISS (total-body CT 20 [IQR 10–29] *vs* standard work-up 19 [9–29]) did not differ between groups. Figure 2 shows the distribution of the ISS across four score categories.

Table 2 provides primary and secondary endpoint data. We noted no significant difference in in-hospital mortality between groups (86 [16%] of 541 in the total-body CT group *vs* 85 [16%] of 542 in the standard work-up

group; p=0·92). Mortality also did not differ between groups in subgroup analyses of patients with polytrauma and TBI (table 2; figure 3). We did not do the preplanned subgroup analysis for penetrating injuries because of the small group size (n=19).

Median radiation exposure in the trauma room was higher in patients in the total-body CT group (20·9 mSv, IQR 20·6–20·9) than in those in the standard work-up group (20·6 mSv, 9·9–22·1; p<0·0001), and was also higher in the total-body CT group during total hospital admission (21·0 mSv [20·9–25·2] *vs* 20·6 mSv [11·8–27·6]; p<0·0001). In the standard work-up group, more patients were exposed to a lower radiation dose—242 (45%) of 542 patients had a radiation dose that was lower than the lowest dose of 20 mSv in patients who underwent a total-body CT scan. In the standard work-up group 250 (46%) of 542 patients underwent sequential segmental CT scans of all body regions, comprising a total-body CT scan in the end.

Median time to end of imaging was decreased in patients in the total-body CT group compared with the standard work-up group (30 min [IQR 24–40] *vs* 37 min [28–52]; p<0·0001), as was time to diagnosis (50 min [38–68] *vs* 58 min [42–78]; p=0·001). We identified weak evidence of a decrease in median time spent in the trauma room in patients in the total-body CT group (63 min [IQR 47–102]) compared with those in the standard work-up group (72 min [50–109]; p=0·067). The hospital costs of the hospital stay were €24 967 (95% CI 21 880–28 752) for the total-body CT group and €26 995 (23 326–30 908) for the standard work-up group (p=0·44). The proportion of patients who received blood transfusions (147 [27%] of 540 *vs* 150 [28%] of 542) did not differ between groups.

Five serious adverse events, defined as a life-threatening event during scanning, were reported during the course of the trial: three (1%) in the total-body CT group, one (<1%) in the standard work-up group, and one in a patient who was excluded after random allocation (appendix). All five serious adverse events resulted in death of the patient. The median age of the patients with a serious adverse event was 81 years (range 74–86). All patients were haemodynamically unstable on admission. The decision to proceed with a CT scan was made carefully in all cases, and the trauma team anticipated a potential serious adverse event in each case.

In post-hoc analyses adjusted for centre, unbalanced baseline characteristics, and the presence of missing data, the difference between groups in in-hospital mortality remained non-significant (appendix). After multiple imputation, most time reductions in favour of total-body CT compared with standard work-up among patients with TBI for time to end of imaging and among all patients and patients with polytrauma for time to diagnosis remained significant (appendix). Although a difference among patients with polytrauma for time spent at the emergency department was still present after adjustment for centre and baseline characteristics, no significant pattern was noted after multiple imputation (appendix).

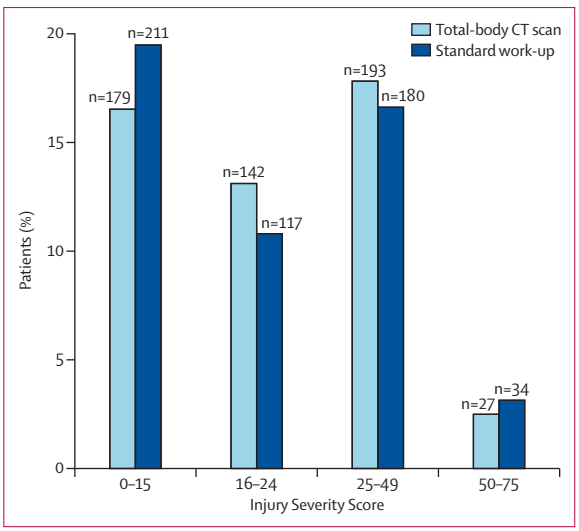

Figure 2: **Distribution of the Injury Severity Score**

In a post-hoc per-protocol analysis, 24 patients who crossed over (ie, who received the opposite intervention to which they had been allocated) were excluded. No significant differences in outcome were found for all endpoints (data not shown).

Discussion

In this randomised multicentre trial, we found no significant difference in-hospital mortality in patients with severe trauma who underwent immediate total-body CT scanning compared with the standard work-up with conventional imaging and selective CT scanning. The radiation dose was increased in patients in the total-body CT group, and substantially more patients in the standard work-up group received a lower radiation dose. Time to diagnosis and time to end of imaging in the trauma room were shorter with total-body CT scanning than with standard work-up.

During the past few years, several, mostly retrospective, studies have shown an association between total-body CT scanning and survival in patients with trauma, as was summarised in six systematic reviews.[2,19,20,22–24] Huber-Wagner and colleagues[3,13] have repeatedly shown a decrease in absolute mortality and an increase in the probability of survival in patients with polytrauma (ISS ≥16) from the German Trauma Registry who had received a total-body CT scan compared with non-total-body CT. The major difference between this study and REACT-2 is that the studies by Huber-Wagner and colleagues[3,13] are retrospective. Huber-Wagner and colleagues used a risk-adjusted approach and multivariate analysis to adjust for possible confounders. As yet, no consensus exists regarding the appropriate selection criteria for patients eligible for a total-body CT

	Total-body CT		Standard work-up		p value
	Number of patients	Data	Number of patients	Data	
Mortality					
In-hospital mortality					
All patients, ITT (primary endpoint)	541	86 (16%)	542	85 (16%)	0·92*
Patients with polytrauma	362	81 (22%)	331	82 (25%)	0·46*
Patients with TBI	178	68 (38%)	151	66 (44%)	0·31*
24-h mortality					
All patients, ITT	541	43 (8%)	542	33 (6%)	0·23*
Patients with polytrauma	362	41 (11%)	331	33 (10%)	0·56*
Patients with severe TBI	178	37 (21%)	151	27 (18%)	0·51*
30-day mortality					
All patients, ITT	487	81 (17%)	497	78 (16%)	0·69*
Patients with polytrauma	335	76 (23%)	312	75 (24%)	0·69*
Patients with severe TBI	171	66 (39%)	146	60 (41%)	0·65*
Time intervals (min)					
Time to end of imaging					
All patients, ITT	429	30 (24–40)	424	37 (28–52)	<0·0001†
Patients with polytrauma	289	32 (24–41)	253	38 (29–53)	<0·0001†
Patients with TBI	148	31 (23–41)	117	35 (27–47)	0·007†
Time to diagnosis of life-threatening injuries					
All patients, ITT	415	50 (38–68)	410	58 (42–78)	0·001†
Patients with polytrauma	276	52 (40–69)	245	63 (45–81)	0·001†
Patients with TBI	141	49 (39–63)	114	54 (41–73)	0·070†
Time in trauma room					
All patients, ITT	423	63 (47–102)	416	72 (50–109)	0·067†
Patients with polytrauma	285	69 (49–109)	252	82 (57–119)	0·011†
Patients with TBI	144	66 (49–95)	119	74 (52–114)	0·083†
Radiation exposure (mSv)‡					
In the trauma resuscitation room					
All patients, ITT	520	20·9 (20·6–20·9)	531	20·6 (9·9–22·1)	<0·0001†
Patients with polytrauma	346	20·9 (20·1–20·9)	323	20·6 (17·6–22·7)	0·27†
Patients with TBI	172	20·9 (20·0–20·9)	146	20·6 (10·5–22·4)	0·040†
Total during hospital stay					
All patients, ITT	520	21·0 (20·9–25·2)	531	20·6 (11·8–27·6)	<0·0001†
Patients with polytrauma	346	22·3 (20·7–26·5)	323	22·5 (20·0–33·1)	0·77†
Patients with TBI	172	22·7 (20·6–26·4)	146	21·4 (15·1–29·1)	0·068†
Hospital outcomes					
Hospital costs (€)	479	24 967 (95% CI 21 880–28 752)	488	26 995 (95% CI 23 326–30 908)	0·44
Complications	541	129 (24%)	540	124 (23%)	0·73*
Blood transfusions in hospital§	540	147 (27%)	542	150 (28%)	0·91*
Duration of stay¶					
Days in intensive care unit	286	3 (1–8)	295	3 (1–8)	0·83†
Ventilation days	286	2 (1–5)	295	1 (1–6)	0·78†
Readmission within 6 months‖	395	67 (17%)	412	44 (11%)	0·01*
Serious adverse events (safety endpoint)**	541	3 (1%)	542	1 (<1%)	0·37††

Data are number (%) or median (IQR), unless otherwise specified. The primary and safety endpoints are specified; all other endpoints are secondary. ITT=intention to treat. TBI=traumatic brain injury. *χ^2 test. †Mann-Whitney *U* test. ‡Patients who died in the emergency department (six [1%] of 541 patients in the total-body CT group *vs* four [1%] of 542 in the standard work-up group) and those with incomplete follow-up for radiation exposure (15 [3%] *vs* seven [1%]) were excluded. §Packed cells, thrombocytes, or plasma. ¶Excluded patients who died during the initial admission (86 patients in the total-body CT group and 85 in the standard work-up group). ‖Excluded patients with incomplete follow-up for readmissions (60 in the total-body CT group and 45 in the standard work-up group). **One other serious adverse event occurred in a patient who was excluded after random allocation. The appendix includes details of the serious adverse events. ††Fisher's exact test.

Table 2: **Primary and secondary endpoints**

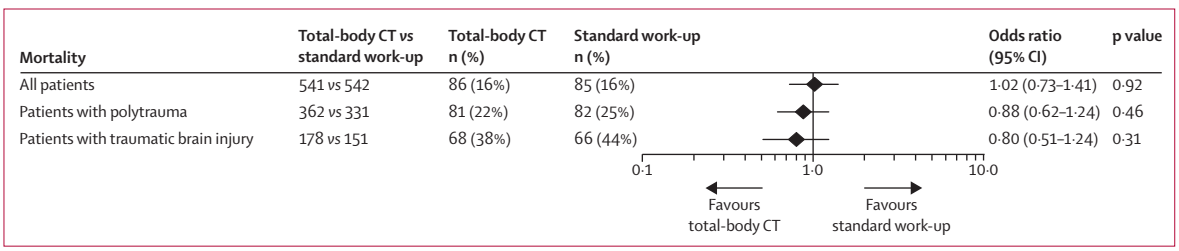

Figure 3: **Subgroup analyses of in-hospital mortality**

scan. In some centres, the trauma team leader decides whether to select a patient for total-body CT,[11,35] whereas in other centres the selection is made on the basis of a three-tiered structure with vital parameters, clinical suspicion of specific injuries, and injury mechanisms,[5,36] as was used in the present study. As a consequence of our randomised design, we included a substantial number of patients with an ISS lower than 16 (390 [36%]). The trial reflects the realities of daily practice and the difficulties in preventing over-triage or under-triage, but possibly confounds the association between survival and total-body CT scanning. Although severely injured patients can be expected to benefit most from the rapid and detailed overview provided by a total-body CT scan, the differences between the two randomised groups might be reduced because of the high number of patients with less severe injuries. Nevertheless, the subgroup analyses in patients with polytrauma and TBI also revealed no differences in in-hospital mortality. Further refinement of appropriate selection criteria is a challenge for future studies.

The need to limit the radiation dose is another important factor in deciding which patients might benefit from an immediate total-body CT scan. CT scanning is associated with a high radiation dose, which could contribute to an increased lifetime risk of cancer.[15] In the present study, over 40% of patients in the standard work-up group had a radiation dose below the lowest radiation dose of patients who underwent a total-body CT scan. The substantial number of patients in the standard work-up group who had a low radiation dose might have been because 36% of patients in our study population did not have polytrauma.

The time benefit with the use of total-body CT has been reported previously.[25] In the present study, we also showed reductions in the time to end of imaging and, to a lesser extent, reductions in time to diagnosis after correction for centre and baseline characteristics, while simultaneously accounting for missing data. However, the registered time intervals seem to be long because a total-body CT scan can technically be obtained in 5 min. Explanations for this longer time interval might be that patient transfers, ATLS primary surveys, and life-saving interventions in the trauma room are time consuming, particularly in severely injured patients, or that registered time intervals lag behind the real time intervals.

Confidence in the safety of a total-body CT scan is a concern of the complete multidisciplinary trauma team. We found a low number of serious adverse events during the trial. Although all the serious adverse events occurred during CT scanning, a high risk of a serious adverse event was noted by the entire trauma team in these specific cases. We postulate that in the case of severe injuries combined with old age and a compromised medical history, with an associated low probability of survival, the trauma team sometimes accepts extra minutes of diagnostic time and proceeds with CT scanning to exclude salvageable injuries instead of undertaking potentially futile invasive procedures.

The limitations of this study should be acknowledged. First, 46% of patients in the standard work-up group underwent sequential segmental CT scans of all body regions, comprising a total-body CT scan in the end. This high percentage might introduce bias in the interpretation of our results, since the differences between groups with respect to mortality might be narrowed by the increased amount of non-immediate total-body CT scans in the standard work-up group. Although we discussed this finding, we aimed to keep the study as close to daily practice as possible and therefore did not demand that the participating centres change their local protocols for obtaining CT scans of specific body regions.

Second, the number of total-body CT scans in the standard work-up group might have been higher than in daily practice because trauma team members became more experienced during the course of the trial. An alternative to the present study design with respect to imaging protocols would have been to make all participating hospitals undertake a specific imaging and contrast administration protocol in both study groups. However, there is no solid scientific basis for the choice and preference of one imaging protocol over another, and participating hospitals would have had to change their practice, which would probably have increased the risk of protocol violations. Also, the introduction of a new protocol is associated with the usual learning curve disadvantages (eg, non-adherence because of unfamiliarity with the new protocol or refusal to work with a new protocol because of familiarity with the old protocol). Additionally, such a

forced use of imaging protocols would not take into account the wide variation in imaging protocols used worldwide, thereby limiting the external validity of the trial results.

Third, the calculation of direct medical costs was done for patients from the four Dutch hospitals. Although we could make a valid comparison between the groups, this limits the international generalisability of the absolute cost results.

Fourth, a common limitation in trauma care is the unmasked randomisation procedure. Selection bias was not possible, but both surgeons and patients were aware of the randomisation outcome. Furthermore, some subjectivity could not be prevented with respect to the inclusion and exclusion criteria. For example, establishing whether the trauma mechanism was high or low energy is not a measurable criterion. Defining these criteria gives an appearance of objectivity (eg, a high-energy trauma defined as motor vehicle collision at >50 km/h), whereas in daily practice individual interpretations by witnesses or ambulance personnel will occur. Our pragmatic design led to a substantial number of exclusions after random allocation because of inappropriate enrolment. We found a wide variety in the amount of exclusions after random allocation between the participating sites (appendix), which might be explained by differences in experience with the use of a total-body CT scan. Nevertheless, being too strict with regard to the inclusion criteria in an acute setting will lead to a higher rate of exclusion of patients who otherwise might have benefited from the total-body CT scan.

Lastly, similar arguments are applicable to the number of protocol violations. More experience with the use of a total-body CT scan might decrease the number of protocol violations. Protocol violations were not routinely described in previous studies, but that does not mean that they did not occur. The strength of the present study is the clear and detailed description of these violations, which were justified on the basis of clinical grounds in 32 (24%) of 135 cases (appendix).

To our knowledge, this is the first international multicentre randomised study of immediate total-body CT scanning in patients with severe trauma with prospective clinically based inclusion criteria. The overall design and stratification of randomisation by hospital ensured that the randomly assigned cohorts were similar in terms of patient characteristics, treatment methods, and previous probability of survival. Furthermore, the pragmatic design means that the results should be generalisable and thus applicable to the various trauma imaging settings worldwide. Finally, the detailed description of the study methods, including the variables that were missing in most studies, increases the chance of reproduction of the trial, which we encourage. Improvement of selection of patients who benefit from immediate total-body CT should be the subject of future research.

Contributors
JCS and KT gathered and analysed the data. JCS wrote the manuscript under the supervision of JCG. JCS and KT created the figures under the supervision of MGWD and JCG. MGWD did the cost analysis. LFMB contributed to the radiation dose calculation. All authors contributed to the study design, writing and editing of the manuscript, and the decision to submit for publication.

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Declaration of interests
We declare no competing interests.

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References

1 American College of Surgeons Committee on Trauma. ATLS Advanced Trauma Life Support program for doctors. Student Course Manual, 9th edn. Chicago, IL: American College of Surgeons, 2012.

2 Sierink JC, Saltzherr TP, Reitsma JB, Van Delden OM, Luitse JS, Goslings JC. Systematic review and meta-analysis of immediate total-body computed tomography compared with selective radiological imaging of injured patients. *Br J Surg* 2012; **99** (suppl 1): 52–58.

3 Huber-Wagner S, Lefering R, Qvick LM, et al. Effect of whole-body CT during trauma resuscitation on survival: a retrospective, multicentre study. *Lancet* 2009; **373:** 1455–61.

4 Weninger P, Mauritz W, Fridrich P, et al. Emergency room management of patients with blunt major trauma: evaluation of the multislice computed tomography protocol exemplified by an urban trauma center. *J Trauma* 2007; **62:** 584–91.

5 Wurmb TE, Fruhwald P, Hopfner W, et al. Whole-body multislice computed tomography as the first line diagnostic tool in patients with multiple injuries: the focus on time. *J Trauma* 2009; **66:** 658–65.

6 Wurmb TE, Quaisser C, Balling H, et al. Whole-body multislice computed tomography (MSCT) improves trauma care in patients requiring surgery after multiple trauma. *Emerg Med J* 2011; **28:** 300–04.

7 Salim A, Sangthong B, Martin M, Brown C, Plurad D, Demetriades D. Whole body imaging in blunt multisystem trauma patients without obvious signs of injury: results of a prospective study. *Arch Surg* 2006; **141:** 468–73.

8 Kanz KG, Paul AO, Lefering R, et al. Trauma management incorporating focused assessment with computed tomography in trauma (FACTT)—potential effect on survival. *J Trauma Manag Outcomes* 2010; **4:** 4.

9 Kimura A, Tanaka N. Whole-body computed tomography is associated with decreased mortality in blunt trauma patients with moderate-to-severe consciousness disturbance: a multicenter, retrospective study. *J Trauma Acute Care Surg* 2013; **75:** 202–06.

10 Hutter M, Woltmann A, Hierholzer C, Gartner C, Buhren V, Stengel D. Association between a single-pass whole-body computed tomography policy and survival after blunt major trauma: a retrospective cohort study. *Scand J Trauma Resusc Emerg Med* 2011; **19:** 73.

11 Wada D, Nakamori Y, Yamakawa K, et al. Impact on survival of whole-body computed tomography before emergency bleeding control in patients with severe blunt trauma. *Crit Care* 2013; **17:** R178.

12 Yeguiayan JM, Yap A, Freysz M, et al. Impact of whole-body computed tomography on mortality and surgical management of severe blunt trauma. *Crit Care* 2012; **16:** R101.

13 Huber-Wagner S, Biberthaler P, Häberle S, et al. Whole-body CT in haemodynamically unstable severely injured patients—a retrospective, multicentre study. *PLoS One* 2013; **8:** e68880.

14 Brenner DJ, Elliston CD. Estimated radiation risks potentially associated with full-body CT screening. *Radiology* 2004; **232:** 735–38.

15 Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 2007; **357:** 2277–84.

16 Barrett TW, Schierling M, Zhou C, et al. Prevalence of incidental findings in trauma patients detected by computed tomography imaging. *Am J Emerg Med* 2009; **27:** 428–35.

17 Hoffstetter P, Herold T, Daneschnejad M, et al. Non-trauma-associated additional findings in whole-body CT examinations in patients with multiple trauma. *Rofo* 2008; **180:** 120–26 (in German).

18 Sierink JC, Saltzherr TP, Russchen MJ, et al. Incidental findings on total-body CT scans in trauma patients. *Injury* 2014; **45:** 840–44.

19 Healy DA, Hegarty A, Feeley I, Clarke-Moloney M, Grace PA, Walsh SR. Systematic review and meta-analysis of routine total body CT compared with selective CT in trauma patients. *Emerg Med J* 2014; **31:** 101–08.

20 van Vugt R, Kool DR, Deunk J, Edwards MJ. Effects on mortality, treatment, and time management as a result of routine use of total body computed tomography in blunt high-energy trauma patients. *J Trauma Acute Care Surg* 2012; **72:** 553–59.

21 Hilbert P, zur Nieden K, Hofmann GO, Hoeller I, Koch R, Stuttmann R. New aspects in the emergency room management of critically injured patients: a multi-slice CT-oriented care algorithm. *Injury* 2007; **38:** 552–58.

22 Caputo ND, Stahmer C, Lim G, Shah K. Whole-body computed tomographic scanning leads to better survival as opposed to selective scanning in trauma patients: a systematic review and meta-analysis. *J Trauma Acute Care Surg* 2014; **77:** 534–39.

23 Surendran A, Mori A, Varma DK, Gruen RL. Systematic review of the benefits and harms of whole-body computed tomography in the early management of multitrauma patients: are we getting the whole picture? *J Trauma Acute Care Surg* 2014; **76:** 1122–30.

24 Jiang L, Ma Y, Jiang S, et al. Comparison of whole-body computed tomography *vs* selective radiological imaging on outcomes in major trauma patients: a meta-analysis. *Scand J Trauma Resusc Emerg Med* 2014; **22:** 54.

25 Sierink JC, Saltzherr TP, Beenen LF, et al. A multicenter, randomized controlled trial of immediate total-body CT scanning in trauma patients (REACT-2). *BMC Emerg Med* 2012; **12:** 4.

26 Beenen LF, Sierink JC, Kolkman S, et al. Split bolus technique in polytrauma: a prospective study on scan protocols for trauma analysis. *Acta Radiol* 2015; **56:** 873–80.

27 Bruns B, Gentilello L, Elliott A, Shafi S. Prehospital hypotension redefined. *J Trauma* 2008; **65:** 1217–21.

28 Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. Trauma Score and the Injury Severity Score. *J Trauma* 1987; **27:** 370–78.

29 Mettler FA Jr, Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. *Radiology* 2008; **248:** 254–63.

30 Sierink JC, Saltzherr TP, Wirtz MR, Streekstra GJ, Beenen LF, Goslings JC. Radiation exposure before and after the introduction of a dedicated total-body CT protocol in multitrauma patients. *Emerg Radiol* 2013; **20:** 507–12.

31 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240:** 205–13.

32 Statline. Consumer prices; price index 2006 = 100. (in Dutch). http://statline.cbs.nl/StatWeb/publication/?PA=71311ned (accessed Nov 15, 2014).

33 Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. *Stat Med* 2000; **19:** 3219–36.

34 ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6 (R1), 1996. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf (accessed Dec 2, 2014).

35 Venugopal K, Kinghorn AF, Emordi CE, Atkinson PR, Kendall RJ. An evaluation of the use of whole-body computed tomography in trauma patients at a United Kingdom trauma centre. *Eur J Emerg Med* 2012; **19:** 193–95.

36 Sedlic A, Chingkoe CM, Tso DK, Galea-Soler S, Nicolaou S. Rapid imaging protocol in trauma: a whole-body dual-source CT scan. *Emerg Radiol* 2013; **20:** 401–08.