UNIL | Université de Lausanne
Faculty of Biology and Medicine

PROTOCOL SYNOPSIS

Sponsor / Sponsor-Investigator	Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
Study Title:	Prediction of massive transfusion in trauma patients in prehospital and in-hospital: Data from Swiss Trauma Registry (STR)
Acronym:	Massive transfusion Prediction Study (MTP Study)
Protocol Version and Date:	Version n°1, 11.09.2020
Trial registration:	*Swiss trauma Registry: NCT0352602* *MTP study: pending*
Study category and Rationale	Our study is an observational non-interventional study based on a multicentric swiss register (Swiss trauma Registry) based on retrospective anonymized data.
Clinical Phase:	No Clinical phase: Observational study

Background and Rationale:	Since the 2000s, many prognostic scores were developed to predict traumatic haemorrhage. Most of these studies were retrospectives based on registers. Due to missing data of death due to bleeding, these studies chose to predict the risk of massive transfusion as a surrogate of haemorrhagic death. These scores include clinical parameters (Vital signs), laboratory values (haemoglobin, lactate, Base excess) and/or imaging (CT or ultrasound) values. The scores showing best performance are the Trauma Associated Severe Hemorrhage (TASH) score, developed and validated on the German register (DGU-Register) (1, 2) and the ABC score developed and validated in the United States of America (3, 4). However, the majority of these scores cannot be applied at the scene of the injury due to the unavailability of laboratory and imaging values. Therefore, their clinical utility remains unclear. To overcome the need of diagnostic tests, authors have developed and recently validated a clinical prognostic score in identifying trauma patients with or at risk of significant haemorrhage based on predicted probabilities of death due to bleeding: BATT score (5). This score was developed from an international cohort using data from 271 Trauma Centres in 41 countries on 5 continents and uses first clinical parameters at initial assessment. The BATT score predicts death due to bleeding and has been validated on a large population in England and Wales. It could also predict massive transfusion, as a surrogate of haemorrhagic death, earlier at the scene of injury. Its feasibility and external validation would make its clinical utility superior to other scores while identifying a greater number of patients requiring early management.
Objective(s):	- External validation of pre-existing prognostic scores of traumatic haemorrhages at different times of care (Scene of Injury, admission at the trauma room) in order to assess their overall performance, discrimination and calibration in the prediction of massive transfusion and haemorrhagic death. - Comparison of score performances (Overall performance, discrimination and calibration).
Outcome(s):	<u>Primary study outcome :</u> - Massive transfusion defined by a transfusion equal to or greater than 10 Red blood cell (RBC) / 24 hours or ≥ 3 RBC in the first hour if available in the Swiss Trauma Registry. <u>Secondary study outcome :</u> - Death due to bleeding (if available in the registry) - Early death (< 24 hours) - Coagulopathy at admission defined by INR > 1.2, quick TP < 70% or Fibrinogen < 1.5 g/L (6,7,8)
Study design:	Observational non-interventional study based on a multicentric anonymized registry

Inclusion / Exclusion criteria:	Study population: All adult trauma patients treated at twelve Swiss trauma centres Level I from 01.01.2015 to 31.12.2019 with eligible criteria of the Swiss Trauma Registry (STR) are included. All data from the register are anonymised without any access to medical files. The identity of the trauma patients, date of birth, address and trauma scene location are unknown (as mandatory by the swiss law: Art. 2 ORH). Inclusion criteria: - Age > 16 years old - ISS (Injury Severity Score) ≥ 16 and/or AIS head (Abbreviated Injured scale) ≥ 3 Exclusion criteria: - Age < 16 years old - ISS < 16 and or AIS < 3 - Isolated Burns (including electric shock) or if the burn is clearly the primary injury - Patients arriving at the trauma room with no sign of life and no diagnostic/therapeutic measures have been initiated for them - Choking or hanging patient without any other injury. - Drowning patients

Measurements and procedures:	**Predictive Variables:** Demographics: Age, gender, type of accident, mechanism of Injury (penetrating/blunt), Hospital (anonymised by number), Date and time of accident. Prehospital settings: Arrival on scene (paramedics, date/time and medics, date/time), type of transport: physician staffed ambulance/helicopter, Firsts clinical measures recorded: Systolic blood pressure (SBP), Respiratory rate (RR), Heart Rate (HR), Pulse Oximetry, Glasgow coma scale, temperature, cardiopulmonary reanimation, Drugs Use: Tranexamic acid (Date/time) and vasoactive, early death before arriving to the hospital. In-hospital settings (trauma room): Hospital arrival (date/hour), Firsts measures: Systolic blood pressure (SBP), Respiratory rate (RR), Heart Rate (HR), Pulse Oximetry, Glasgow coma scale, temperature, cardiopulmonary reanimation, Biological parameters: haemoglobin, Platelets, lactates, Base excess, TP (sec and %), INR, PTT, Fibrinogen, Drugs use: Tranexamic acid (date/time), vasoactive, Vitamin K, Fibrinogen, Prothrombin complex concentrate, rFVIIa, Red blood cell (number in the first hour, date/hour of each Red blood cell), platelets units, fresh frozen plasma. Imaging: type of imaging, results: positive or negative for free fluid, date/time of imaging. Diagnosis: AIS final, ISS final, Medical past, use of anticoagulant/antiaggregant before trauma Outcome: Date/time of death, Early death (<12 hours), Early death (<24 hours), number of red blood cell in 24 hours, Massive transfusion (defined as ≥ 10 red blood cells in the first 24 hours). Depending of the availability of requested variables in the registry, we will ask for complementary variables. Comparison: Performance comparison of pre-existing scores (TASH, ABC and BATT scores) in term of overall performance, discrimination and calibration. Evaluation of clinical utility and feasibility in prehospital settings and emergency admission.
Intervention:	Comparison of score performances (Overall performance, discrimination and calibration)
Control Intervention (if applicable):	No group controls
Number of Participants with Rationale:	The number of participants will depend of the Swiss Trauma Registry Database. We project to include 10'000 participants for our study. A post-hoc power calculation will be performed.
Study Duration:	11 months
Study Schedule:	From August 2020 to June 2021

Investigator(s):	**Professor Pierre-Nicolas Carron** **Study Director** Service des Urgences Centre hospitalier Universitaire Vaudois (CHUV) Rue du Bugnon 46 CH-1011 Lausanne Email : Pierre-Nicolas.Carron@chuv.ch **Doctor François-Xavier Ageron** **Study Director** Service des Urgences Centre hospitalier Universitaire Vaudois (CHUV) Rue du Bugnon 46 CH-1011 Lausanne Email : Francois-Xavier.Ageron@chuv.ch **Alan Costa** **Principal investigator** Service des Urgences Centre hospitalier Universitaire Vaudois (CHUV) Rue du Bugnon 46 CH-1011 Lausanne Email : Alan.Costa@chuv.ch
Study Centre(s):	Multi-centre study including 12 Swiss Trauma Centre included in the Swiss Trauma Registry (Centre Hospitalier Universitaire Vaudois, Hôpitaux universitaire Genevois, Inselspital Bern, Universitätsspital Basel, Universitätsspital Zürich, Kantonsspital St. Gallen, Luzerner Kantonsspital, Kantonsspital Aarau, Kantonsspital Graubünden, Kantonsspital Winterthur, EOC – Ospedale Regionale di Lugano, Gesundheitsnetwerk Wallis – Standort Sion)
Statistical Considerations:	Comparison between scores: - Overall performance: Brier score - Discrimination: C-statistic, AUROC curve and calculation of likelihood ratio, sensitivity and specificity. - Calibration: Global calibration, calibration curve with intercept and slope calibration. Missing data: To estimate baseline risk for the full dataset, we will replace missing predictors using multiple imputation by chained equation. Please referring to the Statistical Analysis Plan
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

Study Procedure/Flowchart with Timelines: Study specific Examinations have to be clearly identified

1st step :Request database to the Swiss trauma registry, redacting the statistical analysis plan and study registration on Clinicaltrials.org (August-September 2020)

2nd step: Statistical Analysis (October 2020)

3rd step: Results (December 2020)

4th step: Publication

Storage of Data-and Samples for Future Research Aims: no

Ethical Considerations:

1. Please describe the potential gain of new knowledge obtained with this study, and its meaning for patients/society.

Answer n°1:
Due to the study population (Swiss Trauma Registry) which is partly integrated into the German DGU-Register, we expect good transportability of the TASH score to the Swiss Trauma Registry in term of overall performance, discrimination and calibration. The ABC score should show lowers results in terms of discrimination due to his validation on small cohorts exclusively in north America. The new BATT score predicting death due to bleeding, has been validated on a large English Cohort of more than 100'000 patients. It identifies all patients with haemorrhage and not only patients who have received a massive transfusion subject to survival bias. In this context, the BATT score provides good discrimination with only simple physiological variables available on the trauma scene. In case of its external validation on the swiss trauma registry as part of our study, its feasibility would make its clinical utility superior to other pre-existing scores while identifying a greater number of patients requiring early management. Its application would activate a massive transfusion plan directly on the trauma scene and save precious time.

2. Please give an assessment of the benefit/risk relationship for the patient.
3. Please explain, why the methodology is also ethically appropriate to gain new generalizable knowledge (for ex. double-blind, placebo, sham, vulnerable subjects, emergency cases, partial information only etc.)

Answer n°2-3:
Due to the retrospective aspect of our observational study based on an anonymized register (identity, date of birth, trauma scene and hospital location unknown according to the swiss law: Art. 2 HRA), we don't identify any risk of being harmful to our population. In case of external validation of the scores, we identify benefits for the population in terms of trauma care. Without any risk for the patient, the potential gain of knowledge obtained with this study is high and will contribute to improve trauma care in respect of the fundamental principles of Medical ethics.

The most relevant References:

1) Yücel N, Lefering R, Maegele M, et al. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening haemorrhage after multiple trauma. The Journal of Trauma. 2006 Jun;60(6):1228-36
2) Maegele M, Lefering R, Wafaisade A, et al. Revalidation and update of the TASH-Score: a scoring system to predict the probability for massive transfusion as a surrogate for life-threatening haemorrhage after severe injury. *Vox Sang*. 2011;100(2):231-238.
3) Nunez TC, Voskresensky IV, Dossett LA, Shinall R, Dutton WD, Cotton BA. Early prediction of massive transfusion in trauma: simple as ABC?. *J Trauma*. 2009;66(2):346-352.
4) Cotton BA, Dossett LA, Haut ER, et al. Multicenter validation of a simplified score to predict massive transfusion in trauma. *J Trauma*. 2010;69 Suppl 1:S33-S39.
5) Ageron F-X, Gayet- Ageron A, Steyerberg E, et al. Prognostic model for traumatic death due to bleeding: cross-sectional international study. BMJ Open 2019; e026823. doi:10.1136/ bmjopen-2018-026823
6) Frith D, Goslings JC, Gaarder C, Maegele M, Cohen MJ, Allard S, Johansson PI, Stanworth S, Thiemermann C, Brohi K. Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. J Thromb Haemost 2010; 8: 1919–25.
7) Floccard B, Rugeri L, Faure A, et al. Early coagulopathy in trauma patients: an on-scene and hospital admission study. *Injury*. 2012;43(1):26-32. doi:10.1016/j.injury.2010.11.003
8) Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. *Curr Opin Crit Care*. 2007;13(6):680-685. doi:10.1097/MCC.0b013e3282f1e78f