Trauma and thrombosis in the DOAC era: promise and peril of direct oral anticoagulant use in injured patients

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Chapter 8. Discussion and Future Perspectives

Various clinical research questions were answered in the studies presented in this thesis. However, much remains to be discussed and explored in further research and writing. The published papers fit larger trends in academic trauma surgery that have influenced the questions asked, the study populations' definitions, and the exposures and interventions selected. Importantly, these trends also influence the uptake of scientific knowledge by regulatory bodies, professional associations and individual practitioners, which will be reflected upon in this Discussion.

Benefits, Harms and Uncertainty

Each decision for medical intervention requires *a priori* weighing of expected benefit vs. harm. Clinical research narrows the confidence intervals and improves physicians' decisions, but some degree of uncertainty always remains. The EMA and FDA restrict indications for medicines to specific populations for whom the harm-benefit assessment has been adequately studied. In the absence of an approved indication, we speak of off-label medication use, or of compassionate use when it concerns serious or life-threatening conditions.

In **Chapters 2 and 3** we studied the off-label chemical thromboprophylaxis (CTP) with DOACs in trauma patients with lower extremity fractures. Interestingly, a randomized controlled trial on patients with non-major orthopedic surgery found DOACs to be safe, and more effective than LMWHs.(1) Could these results be extrapolated to prescribe DOACs as CTP for patients with lower extremity fractures as well?

In the presence of evidence from elective surgery, the condition of equipoise may not hold. Equipoise in this context means either a) the treating physician (involved in a clinical trial) is genuinely uncertain over the relative therapeutic merits of DOACs and LMWH, or b)

there exists controversy in the expert medical community over preference of both options.(2) If there is no equipoise, exposing patients to potentially inferior care is unethical. Additionally, performing RCTs in unstable, bleeding trauma patients is complex, e.g. by requiring community consent. Elective surgery on the other hand greatly facilitates patient enrolment, baseline conditions and data capture. Such conditions are ideal for performing randomized evaluations - and obtaining research funding. To improve trauma care efficiently, we should consider under which conditions evidence from elective surgery can be extrapolated to trauma surgery.

Can we translate the superior efficacy and safety of DOACs in elective (nonmajor) orthopedic cases to trauma patients with orthopedic injuries? There are differences in patient population, timing and extent of surgery, and perioperative course. First, the risk of venous thromboembolism (VTE) is higher in major compared to nonmajor orthopedic injury. And, absent active hemorrhaging, the expected harms are similar, i.e. the rate of serious adverse events for DOACs is similar or lower than for LMWHs. Second, trauma and emergency surgery are, by definition, procedures that cannot be delayed beyond a certain time-window to avoid disability. The benefits of timely intervention are weighed against the consequences of suboptimal physiological factors in the acute or early posttraumatic setting, e.g. pro-inflammatory state, dysregulated coagulation, or hemodynamic instability. Many practices studied during elective surgery, such as anesthetic procedure, bleeding control, and infection prevention, have been adopted in emergency and trauma surgery without warranting additional clinical trials.

Evidently, some have translated the evidence from elective orthopedic surgery to CTP in trauma surgery (**Chapter 2**), with potentially equivalent effectiveness and safety as a result. Moreover, several RCTs have indicated at least equivalent effectiveness and safety (**Chapter 3**).(1,3,4) Equipoise may thus no longer hold. In my opinion, this justifies prescribing rivaroxaban, and potentially apixaban and dabigatran, for thromboprophylaxis

after hip fracture surgery and non-major orthopedic trauma in a study setting. The FDA and EMA may require full-scale randomized controlled trials in the process of approving these indications?

There is also increasing evidence that not all orthopedic trauma patients require CTP. On the one hand, this is caused by advances in care, including shorter operative durations, and earlier mobilization and rehabilitation.(5) On the other hand, risk assessment prior to starting CTP is becoming more personalized. Physicians can incorporate more patient-specific factors to predict individual benefit-harm trade-offs, as opposed to making standardized decisions for generalized populations. Current CTP algorithms do not include personalized prediction in trauma patients in a way the HAS-BLED and CHADS-VASc scores are used for prescribing anticoagulants in nonvalvular atrial fibrillation.(46–48)(6,7)

Various tools to predict VTE risk and innovation exist. For example, the L-TRIP score can be used for patients who require lower leg immobilization after orthopedic trauma.(8) The Trauma Outcomes Predictor predicts VTE, among many other complications, in the broad trauma population, but does not relate to CTP decisions.(9) The oldest and best known VTE risk prediction tool in surgery is the Caprini score, which similarly does not influence CTP decision-making.(10) In addition to narrowing and specifying the indication for CTP, the types of antithrombotics prescribed are changing. Where patients traditionally received LMWH, new evidence cautiously suggests equivalence of ‘weaker’ antithrombotics such as aspirin, even in patients at higher risk of VTE.(11)

Geriatric trauma

The advancement of trauma geriatrics as a science and subspecialty is another trend, resulting from both demographic change and ‘personalized medicine’. Questions answered in this thesis predominantly concerned geriatric trauma populations. They will represent an increasingly large proportion of patient volume in trauma systems globally as populations

become older and more frail. Geriatric trauma is already increasingly common and a leading cause of death in rich, Western countries such as the USA, with 1 in 4 older adults falling each year, and 1 in 5 of those sustaining injuries requiring hospital care, representing up to 10% of annual hospital admissions.(12,13)

Elderly trauma patients present with distinct problems and goals, which requires an even more holistic approach from trauma care professionals. Altered physiology, comorbidity and polypharmacy each contribute to the complexity of managing geriatric trauma cases.(14) Extent and severity of injuries are often incongruent with injury mechanism due to the declining quality of soft tissues, bone, vasculature and the brain.(15,16) Moreover, physiological reserve and compensatory mechanisms are blunted in elderly patients, altering patient presentation (e.g. late or absent tachycardia, tachypnea) and leading to more rapid decline.(17,18) Deterioration of renal, cardiac and pulmonary function all contribute to a lower tolerance of hypovolemia and higher incidence of shock.

Care for injured older patients is improving, with guidelines established, and evidence of improving survival over time and with increasing institutional exposure in some but not all countries studied.(19–24) Goals-of-care discussions, however, remain a necessary aspect of care for geriatric patients as surviving patients rarely return to their pre-injury levels of functioning.(25) Such conversations tend to occur when confronted when a patient's situation is considered unsalvageable, and not routinely.(26) As injury is typically unanticipated, goals-of-care discussions could be encouraged in outpatient setting, with advanced directives in trauma mentioned explicitly.

Thankfully, prognostication of survival and long term functional ability are accurate, as both are essential for such shared decisions.(27) For instance, patients may prefer not to have fractures fixed if the prognosis after trauma is particularly poor, with negligible functional gain or improvement to quality of life.(28) Similarly, anticoagulated TBI patients,

their proxies and treating physician may weigh the necessity of neurosurgical interventions or high-risk medication such as reversal agents against expected functional outcomes.

Polypharmacy and Pharmacosurveillance

Polypharmacy in geriatric trauma patients is the norm, rather than a rare occurrence. More than half of elderly patients use five or more medications, most commonly neuropsychiatric agents, anticoagulants, diuretics and cardiac medication.(29) All have systemic effects, further altering the physiology of patients, and impacting the odds of survival. For beta-blockers, both protective and deleterious effects were reported, warranting further research.(30) Pre-injury statins were demonstrated to independently predict multi-organ failure.(31) Neuropsychiatric medication was associated with significantly higher mortality.(32) NSAIDs were shown to correlate with lower rates of trauma coagulopathy.(33) Patients with pre-injury ACE inhibitor use had higher mortality rates, both isolated and in combination with calcium channel blockers and/or beta blockers.(34) Further research into compound effects of chronically used medication will improve clinicians' ability to assess and stratify the risk from polypharmacy.

Academic trauma surgeons study associations between pre-injury medication and outcomes in 'real world' cohorts, which falls victim to methodological imperfections. Chiefly, confounding by indication and selection bias impact such studies: patients without an indication for chronic use of the studied medication are not an adequate comparator. To overcome this and enable valid risk-benefit assessment of high risk medication, pharmaceutical companies should be required to report on safety in the case of trauma in future trials.

Unfortunately, safety in traumatic injury is an afterthought in regulatory processes. Regulatory agencies should update their safety frameworks to require pharmaceutical companies to include safety in trauma as study endpoints in phase 3 studies. This is

especially warranted for drug categories known or expected to impact a patient's (neuro)physiology, and those frequently prescribed to populations at high risk of injury, such as frail and elderly patients.

Although 5% of elderly patients seek care for injuries annually, it may be unrealistic to require all future phase 3 studies to be powered on safety outcomes in trauma.(12) Post-marketing studies of safety (**Chapters 4 to 6**) are a first-best solution to the absence of such data, especially if based on multi-institutional or national databases containing dose, patient presentation and patient-important outcomes. Alternatively, relevant information could be drawn from pre-clinical studies, ex-vivo blood analysis and/or from trauma registry data linked to trial participants.

Regulatory Developments

Another noteworthy trend is the changing regulatory landscape. **Chapters 7 and 8** were necessitated by the remarkable decision to accept a one-armed, open label trial phase 3 (ANNEXA-4) of andexanet alfa for accelerated approval on (FDA: May 3, 2018,EMA April 26, 2019). The ANNEXA investigators argued that it was unethical to compare andexanet alfa to placebo or usual care, since phase 2 studies (ANNEXA-A and -R) showed high rates of factor Xa activity reversal in plasma of healthy volunteers.(35)

This example fits a trend of lifecycle regulation, with drugs increasingly being approved through accelerated or emergency pathways, and more often without traditional scientific rigor such as double blinding, randomization, and confirmation trials.(36–38) Use of proxy outcomes, and post-approval safety events are also increasingly common, especially in drugs approved under accelerated pathways.(38) Accelerated approval for andexanet alfa was conditional on a randomized trial comparing it to usual care. This trial ("ANNEXA-I", NCT03661528) was to provide essential information on the benefit-cost assessment. The trial and its results are illustrative of the changing regulatory landscape and its failings.

ANNEXA-I randomized 530 patients and was stopped early because the primary endpoint was reached at interim analysis of 452 patients. Hemostatic efficacy (<35% hematoma expansion and <7 increase in National Institutes of Health Stroke Scale at 12 hours, and no rescue therapy between 3-12 hours) was achieved in 63.9% of patients in the andexanet alfa cohort compared with 52.4% in the usual care group (85% of which received PCC).(39) Interestingly, in this trial studying life-threatening bleeding, survival was a safety outcome, not an effectiveness outcome. The study was underpowered to study mortality, and reported “no appreciable differences in death and neurological functioning between groups after 30 days”. Andexanet alfa was again demonstrated to be prothrombotic: 10.3% of andexanet alfa-treated patients experienced thrombotic events (TE) vs 5.6% with usual care (TE incidence increased 4.6 per 100 patients, p = .048). The small sample and less than convincing, results leave significant room for debate on the benefit-cost ratio. I urge the authors to compare Andexanet alfa versus PCC in this study cohort, and estimate the net clinical benefit of both.

While not approved by FDA or EMA for the reversal of factor Xa inhibitors, previous research demonstrated that PCC (Kcentra, Beriplex, Octaplex, Cofact) completely reversed rivaroxaban’s effect on prothrombin time.(40) Its clinical use and effectiveness was widely reported, with clinical guidelines recommending its use as early as 2012.(41–47) Despite this, the ANNEXA-4 investigators argued that an RCT comparing andexanet alfa to PCC was unethical. Considering common clinical use, I argue it is unethical to not compare these drugs.

Big, Real-World Data

Gathering the information required for risk-benefit assessments of new drugs is increasingly left to post-marketing analyses. While disappointing post-marketing studies may lead to drug withdrawal, this shift in regulatory environment changes the research landscape.

Accelerated and emergency approval are only provisional guarantees of safety and efficacy. In this new dynamic, physicians have more autonomy and a more difficult task weighing harms and benefits before prescribing. It constitutes a partial transfer of responsibility from manufacturers to clinicians. Evidently, clinical researchers need guidance, and they study the impacts of these decisions on best they can: in a multitude of smaller, one-armed observational cohorts (**Chapter 8)**.

The use of such 'real world data' in academic medicine science is rapidly evolving. Large-scale, high-quality data collection in institutional and national databases allows for powerful causal inference studies, prediction modelling and clinical benchmarking. Several projects in this thesis (**Chapters 2, 4 & 6**) were possible because of standardized collection of high quality data on trauma care. Large databases such as TQIP and NSQIP enable the pursuit of surgical research questions not easily studied in prospective or randomized studies due to rare exposures, treatments or outcomes.

Use of routine healthcare data is also associated with methodological challenges. First, researchers depend on the quality and availability of relevant datapoints and variables. This means regular use of proxy variables, as opposed to ideal outcome variables, introducing new assumptions. It also necessitates handling of missing data. In practice, this is commonly done and in various different ways, ranging from unrefined - and inappropriate - mean value imputation to more sophisticated methods, but more often than not incompletely or incorrectly performed.(48,49) Imputation is imperfect, and readers and reviewers must be acutely aware of the underlying quality of databases used.

Second, comparison of treatments in real world data is heavily confounded by indication. It is virtually impossible to ascertain the exact rationale for treatment choices. Researchers employ advanced statistics in attempts to overcome this with multivariable regression models, inverse probability weighting, propensity scores et cetera. These

techniques may partially correct the effect size of confounding, and convince reviewers, but they do not truly remove its effects.

Third, researchers and reviewers still gaining experience may omit important steps in the analysis, reporting and review process of large database research.(50,51) Uniform requirement and enforcement of reporting standards, such as STROBE-RECORD, by journals and senior researchers could easily prevent the publication of incomplete research.(52)

Further research

In true academic fashion, answering one question raised countless more. Most relate to further decreasing the burden of VTE in trauma. VTE is, even today, considered the most common preventable cause of mortality, and the most important patient safety issue.(53,54) Improvement efforts of CTP should focus on optimal patient selection, drug selection, timing, and improving medication adherence.

Chemical thromboprophylaxis in trauma patients

First, I believe the evidence base (**Chapters 2 and 3**) supports initiating a randomized controlled trial comparing apixaban or rivaroxaban to LMWHs in trauma patients with an indication for chemical thromboprophylaxis. Currently published studies support at least equipoise between FXaI's and LMWH, with a potential superiority concerning the main outcome of symptomatic VTE and adverse events, most importantly patient-reported and/or clinically relevant bleeding complications.

The choice between anticoagulant agents is not solely influenced by efficacy and safety; factors such as patient acceptance, tolerance, and persistence weigh in. I propose prospectively studying a cohort of patients with lower extremity fractures prescribed LMWHs.

Patient acceptance will be assessed through surveys measuring satisfaction with the chosen anticoagulant regimen and tolerance will be evaluated by monitoring adverse events related to medication use. Additionally, persistence will be measured by tracking medication adherence (% of days covered) and persistence (days between first and last dose) over the prescribed treatment duration. This study can serve as a baseline in a well-defined population where it is expected that DOACs eventually become standard of care.

In addition, I propose modelling the necessary DOAC price reduction to reach cost-effectiveness parity of FXaIs and LMWH in different countries for the main indications: NVAF, VTE and postoperative CTP. *Nota bene*, some DOAC preparations may already be cheaper (cost of daily dosing in select indications) than LMWH in some countries, but empirical evidence on pharmaceutical pricing is missing. FXaI patents will transpire in the next five years (as of March 2024: apixaban US: 2026 and EU: 2027, rivaroxaban US: 2028 EU: 2026). Generic formulations have already been developed, and will likely be distributed immediately given the large market for these drugs. Availability of generic competitors will create competition, driving the price down and thus increasing the cost-effectiveness of FXaIs. Further, by comparing different scenarios of price evolution, e.g. based on historical average price reduction after patent expiry, or drug category-specific trends, one could estimate the money saved by substitution of LMWH by FXaIs in these indications.

The timing of anticoagulation in different trauma population is also of interest. Clot development is gradual, and initiation of anticoagulation at different stages may have differential effects on symptomatic VTE incidence. In patients presenting with traumatic hemorrhaging, optimal timing of CTP balances the greatest VTE risk reduction without exacerbating existing hemorrhage. Published research mostly studied TBI, and compared ‘early’ and ‘late’ thromboprophylaxis, employing fixed dichotomies at 48 of 72 hours. The resulting formulation of the Parkland Protocol, and later the modified Berne-Norwood criteria, recommends timing of CTP based on TBI presentations, suggests early treatment and 24

hour repeat evaluation.(55) Randomized evaluations and multicenter prospective cohort studies have not been able to reach sufficient sample size, to show with high fidelity whether these cutoffs are optimal.(56,57) Studies of optimal CTP timing in other trauma subpopulations, such as long bone fractures and nonoperative blunt abdominal organ injury similarly relied on cutoffs of early/late, had small sample size or were further limited by lack of imaging results.(58–61) Although guidelines recommend starting CTP in polytrauma "as early as hemorrhage risk allows", there have been no studies in this subpopulation.(62,63)

I thus propose a national registry-based evaluation of CTP praxis – agent and timing - in patients with relative contraindications to early CTP (e.g. presentation with active hemorrhage, need for intracranial pressure monitoring) across the major subpopulations of study: isolated TBI, isolated orthopedic trauma, isolated abdominal organ injury, and polytrauma. Analyzing the hourly association between CTP timing and symptomatic VTE incidence, as well as hemorrhagic complications will illustrate risks and benefits attributable to prophylactic anticoagulation. Individual hospital identifiers, as well as hospital types (trauma center designation, teaching status, urbanity, size, etc.) can be used as instrumental variables to separate practice variation and case mix from the association between CTP timing and outcomes.

Pre-injury exposure to DOACs

High quality evidence on the optimal treatment of DOAC-exposed trauma patients is scarce, owing to limited sample sizes and methodological imperfections. Wide variability was reported for management of DOAC-associated trauma, for instance in the rate of surgical intervention in DOAC-associated tICH is common (3-33%).(64) Whether this reflects practice variation or case mix differences has not been sufficiently validated.

To this end, I propose a national registry-based study in the Netherlands comparing all patients chronically prescribed FXaIs, DTIs or VKA for the most common indications –

NVAF, VTE and postoperative CTP. Patient presentation (injury pattern and severity, GCS, age, comorbidity, frailty, comedication, etc.), as well as baseline risk of VTE and bleeding outcomes (CHADS-Vas2Sc and HAS-BLED) can be used to control for confounding by indication in the analysis of risk associated to anticoagulant type. Temporal trends since the introduction of DOACs can be performed to analyze the evolution of physician prescribing patterns. In addition, I would analyze how increasing exposure to and experience with DOAC-anticoagulated trauma patients may have changed risk-adjusted odds of surgical intervention, reversal agent use, thrombotic and bleeding outcomes, mortality and long-term physical functioning in VKA- and DOAC-anticoagulated trauma patients. Instrumental variable analysis using hospital characteristics can further reduce the risk of confounding in this study.

Single institution studies from other countries showed reversal and neurosurgery rates differed significantly within DOAC-TBI cohorts, and between anticoagulant types.(64) Comparing institutional trauma registries with detailed neuroimaging reports, one could study indications for surgery such as unilateral swelling, contusions, extradural or subdural hemorrhage, and midline shift to assess if these are equally associated with neurosurgery rates and outcomes in DOAC-associated TBI compared to VKA-associated TBI. Similarly, clinical presentation should be correlated with reversal agent use, dosing and outcomes. Both reversal and neurosurgery rates have not been studied extensively in the Netherlands, and ideally variations found in national data should be accompanied by granular data and interpretation.

Such results can then be used to model population-level cost-benefit assessment of DOAC vs VKA for NVAF/VTE/CTP. As mentioned earlier in this thesis, at the time of regulatory approval for DOACs, reversal strategies were unavailable for spontaneous, procedure-related or traumatic bleeding. Patient-level cost-benefit ratio of DOAC use were certainly worse. But as exposure and experience builds, better outcomes are achieved in the

management of these patients, and the cost-benefit ratio may have improved commensurately. Based on Dutch national registry data, I suggest estimating cost-effectiveness using a Markov model looking at mortality, long term disability and thrombotic events, expressing the relative cost-effectiveness in $/QALY.

Reversal agents for FXaI-associated traumatic hemorrhage

As shown in **Chapter 8,** current evidence on optimal DOAC reversal strategies relies on observational, often retrospective cohort studies, or on one-armed open-label studies for experimental reversal agents. Not all patients will require reversal, but evidence on patient selection is lacking at present. Prescribing information presented to FDA and EMA recommends use in “patients with life-threatening or uncontrolled bleeding” - not further specified. Clinical studies assessing reversal agent effectiveness relied on the ISTH definition of acute major bleeding to include patients, i.e. “hemorrhage into critical organ spaces (intracranial, retroperitoneal, intra-abdominal etc.) or bleeding associated with hemoglobin drop of >1 g/dL.”(65–67) The American College of Cardiologists also offers limited detail beyond recommending andexanet alfa for patients with acute major bleeding and serum anti-FXa >75 ng/mL, (a)PCC if AA is unavailable, and activated charcoal if the last dose was within 2-4 hours.(68) A reduction in anti-Xa levels, however, was not correlated to clinical hemostasis (AUC=0.53), and neither was presenting anti-Xa concentration.(67,69)

Based on this evidence, anti-Xa levels could perhaps be left out of reversal decision algorithms. In addition to affected organ space, clinical signs of hemodynamic compromise and hemoglobin drop, clinicians rely on time-since-last-dose. This leaves ample room for clinician judgment and further research on useful criteria to improve patient selection. In injured patients, the possibility of operative hemostasis, injury mechanism and pattern, and pre-hospital use of blood products and tranexamic acid should always be considered. To test and validate factors, collect and compare institutional prescribing guidelines from international hospital systems. Consolidate commonalities in existing guidelines and longlist

all factors and decision-points that vary to deliberate by a FXa-inhibitor reversal guideline development group. Conclusions should be reached on at least 1) role of bleeding location, kidney and liver function in low versus high dose reversal, 2) dosing recommendations on (a)PCC if andexanet alfa is unavailable, and 3) hemodynamic criteria for reversal in intra-abdominal, intra-thoracic, pelvic, thigh and external bleeding. While ambitious and costly, a pre- versus post-implementing review of expanded guidance in all FXaI-exposed trauma patients is necessary, because of large potential cost-savings.

There is also merit in further study comparative effectiveness of andexanet alfa and PCC. Such real world evidence is essential for post-marketing surveillance of drugs under accelerated regulatory pathways. For instance, one could use institutional registries to perform target trial emulation of the ANNEXA-4 and ANNEXA-I studies at non-participating sites.(70) In addition, the effectiveness and safety of patients receiving andexanet alfa in combination with other procoagulant agents should be studied, as these patients were ineligible for ANNEXA-4 and ANNEXA-I.

Countries with willingness-to-pay thresholds for clinical benefit, such as The Netherlands, will be interested in the cost-effectiveness of andexanet alfa, PCC and non-PCC usual care. Previously published cost-effectiveness ratios for andexanet alfa ranged widely: an independent Canadian study found average discounted lifetime costs of $237,177 Canadian dollars for Andexanet and $177,871 Canadian dollars for PCC, while a second study co-authored and sponsored by Alexion (Andexanet alfa's manufacturer, red.) found incremental cost-effectiveness per quality-adjusted life-year gained of $35,872 from a third-party payer perspective and $40,997 from a societal perspective over 20 years.(71,72)

At present, modelling a €/QALY threshold is not possible, as patient-reported quality of life was not studied. I propose to model the cost-effectiveness of andexanet alfa and PCC basing expected utility values on ANNEXA-I and institutional outcomes.(39,73) Superior

hemostatic effectiveness (64% vs 52%) was accompanied by other patient-important outcomes: statistically non-significant higher 30-day mortality (Andexanet alfa: 27.8% vs. usual care 25.5%, P>0.05) and significantly higher 30-day thrombotic complications (ischemic stroke and myocardial infarction: Andexanet alfa 10.3% vs. usual care 5.6%; *P*=0.048). Modelling the lifetime cost in both arms in different countries will illustrate and inform package decisions in the interim.

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