UNIVERSITÄT BERN

Kantonsspital Aarau

MASTER THESIS

Awarding the academic title of

Master of Science in Pharmacy (M Sc Pharm)

University of Bern

Evaluation of a drug therapy safety algorithm for the detection of Triple Whammy prescriptions in inpatients at risk of acute kidney injury

Master Thesis submitted by

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Immatriculation Nr.: 17-100-215

Handed in on the 3rd of July 2022

For the degree of

Master of Science in Pharmacy (M Sc Pharm)

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I. ACKNOWLEDGEMENTS

My most sincere gratitude goes toward Hendrike Dahmke for always supporting me and giving me a helping hand. Her programming knowledge was especially beneficial and inspiring to me. Thanks for always being honest about research and giving me an insight into the KPHARM project. I wish her the best of luck with her PhD, and I am happy to be a small part of it!

Thanks to Claudia Zaugg and Dr. med. Rico Fiumefreddo from the KPHARM project for hearing my ideas and their constructive feedback. Their work is crucial for patient safety, and I look up to them for putting so much effort into it — also, warm gratitude to all people from the hospital pharmacy team at the KSA for having me. The diploma thesis of Lee Flückiger guided me a lot in the beginning and reassured me about my working process.

I am thankful to Prof. Dr. med. Philip Schütz, for reading and discussing my master thesis with me; I appreciate his time and valuable input for my project.

Special praise goes to Alan Haynes from the Clinical Trial Unit of the Faculty of Medicine of the University of Bern for taking so much interest in my thesis and helping me with my statistical work.

Dr. Marc von Gernler and Ursina Wernli helped me immensely with my literature research, and I profoundly appreciate their input.

Thanks to PD Dr. med. et phil. Felix Hammann for having an exciting exchange about clinical decision support systems and algorithms.

I am so grateful to Kathrin Baumann, Jan Adelmann and Dana Kissling for proofreading my master thesis and for their everlasting support.

I want to express my appreciation to my family and friends, who support me in every life situation and keep being proud of me.

Last but not least, thanks to Prof. Dr. phil. II Carla Meyer-Massetti for supporting my master thesis and taking me under her wing. She encouraged me to pursue my interest in hospital pharmacy. She is a role model to any woman in science.

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III. GLOSSARY

ACEI ANGIOTENSIN-CONVERTING ENZYME INHIBITOR

AKI ACUTE KIDNEY INJURY

API ACTIVE PHARMACEUTICAL INGREDIENT

ARA ANGIOTENSIN RECEPTOR ANTAGONIST

CDSS CLINICAL DECISION SUPPORT SYSTEM

CHF SWISS FRANCS

CKD(-EPI) CHRONIC KIDNEY DISEASE (EPIDEMIOLOGY COLLABORATION)

COX CYCLOOXYGENASE

(E)GFR (ESTIMATED) GLOMERULAR FILTRATION RATE

FDC FIXED-DOSE COMBINATIONS

KDIGO KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES

KISIM KLINIKINFORMATIONSSYSTEM INNERE MEDIZIN

KSA KANTONSSPITAL AARAU

MAS MULTI-AGENT SYSTEM

NSAID NON-STEROIDAL ANTI-INFLAMMATORY DRUG

PPI PROTON PUMP INHIBITOR

RAAS-(I) RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITOR

IV. ABSTRACT

BACKGROUND: The term “Triple Whammy” refers to the concomitant use of a non-steroidal anti-inflammatory drug, a diuretic and an angiotensin-converting enzyme inhibitor or an angiotensin receptor antagonist. This triple combination significantly increases the risk for acute kidney injury and should thus be avoided in hospitalised patients. For this purpose, an electronic algorithm was developed and implemented in a tertiary hospital's clinical decision support system that screens medication use in patients for early detection of Triple Whammy prescriptions, among others.

OBJECTIVES: The aim of this study was to investigate the usability and performance of an electronic algorithm designed to detect patients with Triple Whammy prescriptions prone to develop an acute kidney injury.

METHODS: Performance by calculating sensitivity and specificity, determining compliance rate among clinicians and assessing renal function in patients triggering an alert was studied. The usability through a semi-structured interview among clinicians who recently received a Triple Whammy alert via the clinical decision support system was evaluated.

RESULTS: Among 21’326 patients, 216 had a Triple Whammy alert corresponding to a sensitivity of 88.3% and a specificity of 99.7%. Seventy-three of 94 clinicians changed their medication prescriptions or ordered renal monitoring, corresponding to a compliance rate of 77.7%. Acute kidney injury was not prevented in all patients triggering a Triple Whammy alert. Most clinicians (75%) were previously unaware of the Triple Whammy risk, and they unanimously approved the clinical decision support system.

DISCUSSION: This analysis suggested that a Triple Whammy alert communicated through a clinical decision support system to clinicians was highly sensitive and specific in detecting patients at risk for acute kidney injury, with high compliance rates among clinicians. There is a need for prospective studies to understand the clinical benefits of such tools in preventing kidney injury.

CONCLUSION: This master's thesis credits the Triple Whammy alert's effective performance and convenient usability in preventing acute kidney injury.

V. ZUSAMMENFASSUNG

HINTERGRUND: Der Begriff «Triple Whammy» bezeichnet die gleichzeitige Einnahme eines nichtsteroidalen Entzündungshemmers, eines Diuretikums und eines Angiotensin-Converting-Enzym-Hemmers oder eines Angiotensin-Rezeptor-Antagonisten. Diese Dreierkombination kann akute Nierenschäden verursachen. In einem Krankenhaus wurde ein Triple-Whammy-Agent in ein Clinical Decision Support System eingeführt, um Patient*innen mit einem erhöhten Risiko für eine akute Nierenschädigung zu erkennen.

ZIELE: Wir untersuchten die Leistungsfähigkeit und Anwendbarkeit eines Triple-Whammy-Agenten, der Patient*innen mit Triple-Whammy-Verordnungen erkennt, bei denen ein erhöhtes Risiko für eine akute Nierenschädigung besteht.

METHODEN: Wir untersuchten die Leistungsfähigkeit anhand der Berechnung von Sensitivität und Spezifität, der Bestimmung der Umsetzungsrate unter Ärzt*innen und der Bewertung der Nierenfunktion bei Patient*innen. Wir bewerteten die Benutzerfreundlichkeit durch eine halbstrukturierte Befragung von Assistenzärzt*innen, die kürzlich eine Triple-Whammy-Mitteilung, ausgelöst durch den Triple-Whammy-Agenten, erhalten haben.

ERGEBNISSE: Von 21'326 stationären Patient*innen wurden 216 durch den Triple-Whammy-Agenten entdeckt, was einer Sensitivität von 88,3 % und einer Spezifität von 99,7 % entspricht. 73 von 94 Ärzt*innen passten die Medikation an oder verordneten eine Nierenüberwachung nach einer Triple-Whammy-Meldung, was einer Umsetzungsrate von 77,7 % entspricht. Eine akute Nierenschädigung wurde nicht bei allen Patient*innen verhindert, die eine Triple-Wammy-Meldung auslösten. Die meisten Ärzt*innen (75 %) waren sich des Triple-Whammy-Risikos vorgängig nicht bewusst. Das Clinical Decision Support System wurde von allen befragten Assistenzärzt*innen als hilfreich empfunden.

DISKUSSION: Diese Analyse legt nahe, dass der Triple-Whammy-Agent eine hohe Sensitivität und Spezifität bei der Erkennung von Patient*innen mit einem erhöhten Risiko für eine akute Nierenschädigung aufweist. Eine hohe Umsetzungsrate wurde erreicht. Es braucht weitere Studien, um den klinischen Nutzen solcher Instrumente bei der Prävention von akuten Nierenschäden zu verstehen.

SCHLUSSFOLGERUNG: Diese Masterarbeit bescheinigt dem Triple-Whammy-Agenten eine angemessene Leistungsfähigkeit und eine gute Anwendbarkeit bei der Prävention akuter Nierenschäden.

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1 INTRODUCTION

Unexpected adverse events following unsuitable medication are common in Swiss hospitals (1,2). No nationwide strategy to avoid adverse drug events is established in Switzerland (3); therefore, the responsibility of medication safety remains with the hospitals. This master thesis addresses the potentially inadequate therapy with Triple Whammy and the approach of a tertiary care hospital to avoid Triple Whammy side effects.

1.1 TRIPLE WHAMMY

Triple Whammy is the therapeutic triple combination of a non-steroidal anti-inflammatory drug (NSAID), a diuretic and an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor antagonist (ARA). The term 'Triple Whammy' was first introduced in 2000 (4) and refers to the adverse effects of this simultaneous triple medical therapy, particularly in the elderly (5). Triple Whammy prescriptions increase the risk of prerenal acute kidney injury (AKI), which is highest at the beginning of treatment (6).

The underlying pathomechanism is explained best by addressing the physiological effects of each drug class involved in the Triple Whammy and shown in *Figure 1*:

- Non-steroidal anti-inflammatory drugs are essential analgesic drugs with antipyretic and anti-inflammatory properties. Their mode of action hinders cyclooxygenase (COX) isomers from synthesising prostaglandins, which has minimal effect on renal haemodynamics and glomerular filtration rate (GFR) under normal conditions. However, if a patient taking NSAIDs suffers from hypovolaemia, the preservation of renal function is at risk. NSAIDs disturb the crucial role of prostaglandin E_2 and I_2 in counteracting vasoconstriction of the afferent arterioles in a hypovolaemic crisis. This eventually leads to severe adverse renal effects (7), such as acute interstitial nephritis or nephrotic range proteinuria from glomerular injury (8).
- Diuretics are a heterogeneous class of drugs used to treat several illnesses such as cardiac insufficiency, edema and hypertension. Diuretics lower blood pressure by decreasing extracellular fluid volume since volemia is the leading chronic regulator of blood pressure. Several response mechanisms, such as activation of the renin-angiotensin-aldosterone system (RAAS), counteract the antihypertensive diuretic effects maintaining normative blood pressure and GFR (7). Loop diuretics and spironolactone seem to have an unfavourable impact on the kidney (9) in a Triple Whammy combination.
- Angiotensin-converting enzyme inhibitors and ARAs are first-line medications to treat hypertension. Angiotensin-converting enzyme inhibitors and ARAs reduce the effects of Angiotensin II, a potent vasoconstrictor and stimulator of aldosterone secretion,

which leads to a decrease in blood pressure and reduced water retention. Also, they cancel the RAAS as a compensatory mechanism needed to sustain an appropriate GFR under challenging circumstances (7). Under an ACEI or ARA therapy, a reduction of 25% from the initial GFR is acceptable according to The National Institute for Health and Care Excellence recommendations (10). These antihypertensives are crucial to decelerate renal insufficiency progression because uncontrolled hypertension is a leading cause of chronic kidney disease (CKD) (9) and therefore benefit patients with CKD (11).

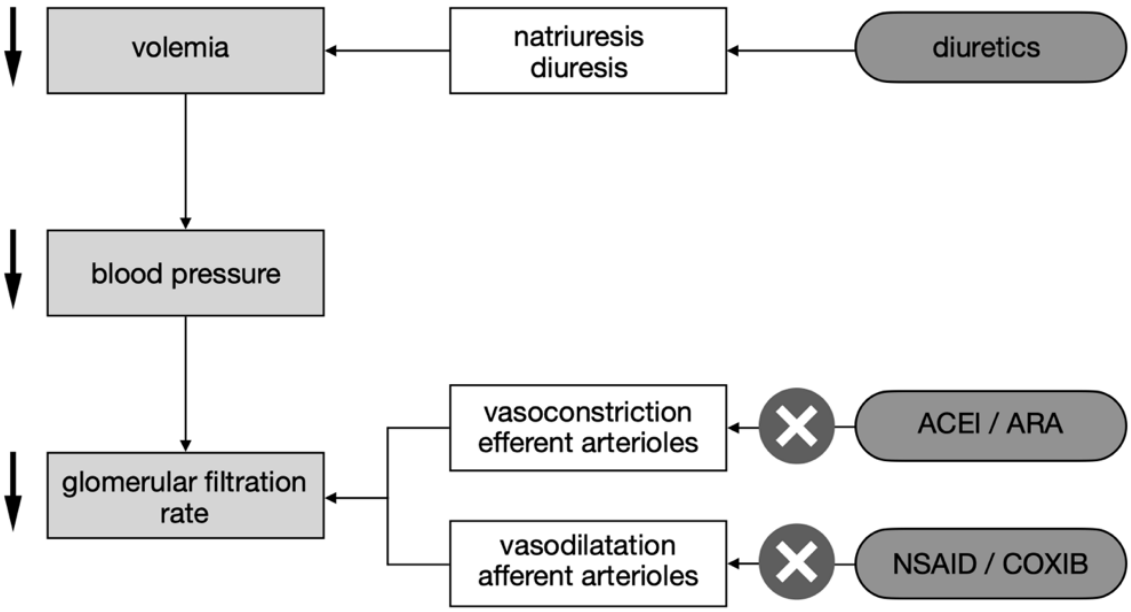

Figure 1 Simplified Triple Whammy pathomechanism

The Triple Whammy combination can lead to various renal side effects. If all three drug classes are administered simultaneously in an individual, regulatory mechanisms of blood pressure and GFR are mitigated. According to a case-control study from Lapi et al. conducted in 2013, Triple Whammy increases AKI risk by 31% (6). Newer studies suspect an even higher risk for AKI under Triple Whammy therapy. Lapi et al. relied on hospital discharge data which may underestimate the risk because AKI is often underreported (9,12). Further, other studies expressed concerns about Lapi et al., who found no significant risk for dual combination – it seems almost evident that NSAIDs with either a diuretic or a RAAS-inhibitor (RAAS-I) can trigger AKI; however, with a lower probability. Another apprehension is lasting renal dysfunction after long-term administration of Triple Whammy (13). Even a slight but consistent rise in creatinine seems linked to chronic and end-stage kidney disease (14).

The Triple Whammy must be considered as a critical drug-drug interaction. However, each drug class can exert harmful effects by itself. In particular, NSAIDs should rarely be

chosen as first-line therapeutics in older patients. Also, NSAIDs are formally contraindicated if the estimated GFR is below 30 ml/min/1.73m^2 and should generally be avoided in patients with CKD (10). According to Beers criteria, NSAIDs with a long half-life, such as naproxen, should be avoided in patients older than 65 years if given long-term and without adjusted dosing (15). The PRISCUS list also states several NSAIDs as potentially inadequate medication in geriatric patients (16), especially indomethacin is unsuitable due to its extensive side effects on the central nervous system. Non-steroidal anti-inflammatory drugs should be stopped in patients with eGFR below 50 ml/min/1.73m^2. At the same time, ACEI therapy should be initiated in diabetic patients with renal involvement according to START / STOPP criteria (17). Apart from renal side effects, NSAID can reduce the antihypertensive effects of ACEI and is therefore considered a clinically relevant drug-drug interaction (18). The use of other medications such as paracetamol, tramadol, or short-term narcotic analgesics is preferred by the Swiss Society Of Nephrology over NSAIDs or COX-II inhibitors because their usage may be safer and equally effective in individuals with hypertension, heart failure and CKD (19).

Triple Whammy drug classes are among the most frequently prescribed medications in Switzerland. Orally administered ibuprofen and diclofenac, both NSAIDs, ranked 5th and 18th as the best-selling medication in the Helsana-Arzneimittelreport in 2020. Torsemide, a diuretic, was the 15th most bought drug in Switzerland in the same year. Cardiovascular medicines use, such as antihypertensive drugs, grew by 10% between 2017 and 2020 (20).

If a Triple Whammy is prescribed, the following recommendations (21) should be considered:

- deprescribe NSAIDs or, if necessary, administer the minimal effective dose of NSAIDs for the shortest amount of time possible
- deprescribe additional non-essential nephrotoxic medication
- monitor serum creatinine levels, mainly if the dosage regimen is changed (4)
- sustain a sufficient hydration
- educate patients on NSAIDs available over the counter (22).

1.2 ACUTE KIDNEY INJURY

Acute kidney injury is a severe and underestimated disease. Prerenal AKI is caused by depleted perfusion altering renal hemodynamics and decreasing glomerular filtration. Triggering factors for prerenal AKI include dehydration (23), hemorrhagic shock, sepsis or administering certain drugs like ACEIs or NSAIDs (24). Triple Whammy medications, individually or in combination, are involved in over half of iatrogenic AKIs (4).

The independent non-profit organisation 'Kidney Disease: Improving Global Outcomes' (KDIGO) (25) defines AKI as follows:

- increase in serum creatinine to ≥ 1.5 times baseline within seven days or
- increase in serum creatinine by ≥ 0.3 mg/dl within 48 hours or
- urine volume < 0.5 ml/kg/h for 6 hours

A total AKI incidence rate of 21.4% was estimated in a German tertiary hospital between 2014 and 2017 in adult patients with at least two measured creatinine levels (26). Acute kidney injury cases were associated with prolonged hospitalisation, renal morbidity (27,28) and mortality.

Acute kidney injury incidence increases even further if multiple risk factors are present in a patient. Acute kidney injury risk is highest in older patients with pre-existing renal impairment (9) or volume deficit (10). This is because, in humans, renal function naturally declines over the course of a lifetime (29). Contributing comorbidities seem to be diabetes mellitus, hypertension and other cardiovascular diseases, adiposity and even coronavirus disease 2019 (27,30,31). Female sex appears to be an additional risk factor for AKI (32). Acute kidney injury is a growing threat for patients, especially in Western countries like Switzerland. Our demographics show a persistently ageing population and a massive rise in the morbidities mentioned above (33).

ESTIMATED GLOMERULAR FILTRATION RATE

The GFR is essential for assessing kidney performance. The GFR is a valid parameter to detect renal diseases and a necessary criterion during treatment to adapt therapy or decide about illness progression. Since the GFR cannot be measured directly, it is calculated using a variety of biomarkers, including inulin, creatinine or cystatin C (34). Inulin is the gold standard, but its measurement is costly. Hence, creatinine is the most used biomarker. Once creatinine is measured, various formulas are available to calculate the estimated GFR (eGFR); the most popular for adults are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the Modification of Diet in Renal Disease Study equation, and the Cockcroft-Gault equation.

The laboratory at the Kantonsspital Aarau (KSA) automatically provides an eGFR according to CKD-EPI with each creatinine measurement; therefore, this formula is the one that KSA physicians will usually use as guidance when assessing their patients' renal function. The following patient information is needed to calculate the eGFR via CKD-EPI: ethnicity[1], sex, age, and serum creatinine. Several sources of error are known when

[1] ethnicity is not systematically collected at KSA and is set to 'caucasian and others' by default - may cause an overestimation of GFR in people of colour

estimating GFR: extreme body morphology anomalies (e.g. bodybuilding, obesity, limb amputations), non-European or non-African origin, a diet rich in protein, muscle diseases or palsy (10). Also, an overestimation of GFR can be caused by drugs with a known influence on creatinine secretion, such as trimethoprim or several human immunodeficiency virus medications. To estimate GFR in patients above 70 years of age, CKD-EPI is not a favourable choice, while newer equations are considered to be more suitable (35).

1.3 CLINICAL DECISION SUPPORT SYSTEMS

A clinical decision support system (CDSS) is a 'health information technology, providing clinicians […] with knowledge and person-specific information to help health […]. CDS encompasses a variety of tools to enhance decision-making in the clinical workflow. These tools include computerised alerts […]. Clinical decision support systems constitute an essential topic in artificial intelligence in medicine'[2]. Clinical decision support systems are widely used in hospitals and pharmacies to ensure patient safety. Clinical decision support systems alert clinicians or pharmacists about adverse effects and medication errors (36). Since medication errors occur in almost 6% of drug administrations, implementing CDSSs seems crucial to decreasing problems associated with pharmacotherapy (37).

Several reviews or meta-analyses doubted the clinical advantage of CDSS in reducing adverse drug events (38,39), or results were mixed or non-significant (40), especially with interruptive alerts. These inadvertent findings could be due to lacking appropriateness of the alerts (e.g. low specificity) and missing evaluation prior to implementing the CDSS into day-to-day business.

Triple Whammy depicts a pharmacodynamic drug-drug interaction among three drug classes and exerts a higher risk for kidney injury than a dual interaction. Drug-drug interactions account for approximately 17% of adverse drug events (37). According to various studies, medications especially prone to cause drug-drug interactions are ACE inhibitors, diuretics and NSAIDs (41–43). Most studies about CDSS revealing drug-drug interactions reported no benefit in patient outcomes (44). Also, most CDSSs only detect dual drug-drug interactions (45). However, most patients are treated with more than just two active pharmaceutical ingredients (API) or even experience polypharmacy. Fixed-dose combinations (FDC) include multiple individual APIs and are often not detected as such by CDSS. Multiple combined drugs augment the risk of adverse effects (46). A Swiss study makes it apparent that 18-25% of people over 65 regularly take five or more

[2] https://en.wikipedia.org/wiki/Clinical_decision_support_system (accessed 11.5.2022)

medications, and consequently, polypharmacy is a widespread phenomenon in the elderly (3).

Sensitivity and specificity calculations are among the most relevant parameters for assessing the performance of CDSSs (47). Sensitivity is a tool's ability to identify patients with a clinically critical combination precisely. Specificity is the software's capability to disregard clinically insignificant drug combinations (48).

Once a CDSS detects a critical prescription, the prescribing clinician must be informed with an appropriate alert. Medication-related alerts are often shown as a pop-up window, interrupting the workflow. These interruptive alerts are overridden frequently if presented with insufficient specificity to the prescriber (49). Overuse of pop-up alerts can cause alert fatigue among clinicians and pharmacists. Alert fatigue can lead to fatal events if a potential life-threatening contraindication alert in drug-drug interactions is overridden (50). Studies have shown high inappropriate override rates in geriatric and renal alerts (51).

INTERNALLY DEVELOPED CLINICAL DECISION SUPPORT SYSTEM AT KSA

The KSA developed a multi-agent system (MAS) to target medication errors and different risk constellations with an increased probability of adverse effects. The MAS is developed internally in the KSA, programmed by CISTEC AG[3] and directly implemented into the clinical information system used in KSA, called KISIM. The MAS was initiated in 2015 as a joint project between the hospital pharmacy and the medical clinic[4]. The MAS is used to detect inappropriate medication prescriptions such as duplication of anticoagulants, wrongly dosed drugs or circumstances with high risk for adverse drug events such as digoxin intoxication or cefepime neurotoxicity, but also detects missing medications according to specific protocols like lacking proton pump inhibitor (PPI) when treated with NSAIDs. Until June 2022, the MAS consisted of 20 active agents capable of generating over 200 alerts. The MAS hourly evaluates all inpatients in the KSA and an affiliated hospital, Spital Zofingen. The MAS checks several parameters, and the corresponding alert is created in real-time if all are present, as seen in *Figure 2*.

A pharmacist processes the automatically produced individual alerts based on their clinical relevance before sending an intervention to the prescribing physician. The responsible clinical pharmacist becomes familiar with the affected patient by thoroughly looking into their case history and deciding whether an alert is relevant. If applicable, the clinician in charge of the affected patient is informed by calling or sending a ready-made but customisable intervention message via KISIM consisting of a recommendation. Another

[3] https://www.cistec.com
[4] General Internal Medicine & Emergency Medicine

Swiss study suggests that this intermediate step through clinical pharmacists generates high specificity to avoid alert fatigue in clinicians (52).

TRIPLE WHAMMY AGENT

The Triple Whammy agent aids health personnel in detecting Triple Whammy prescriptions in patients at risk of developing an AKI. Triple Whammy was one of the first risk constellations defined as a target for the MAS. Even before the implementation into KISIM, the Triple Whammy tool was evaluated and improved through an external system[5]. Estimating kidney function with creatinine clearance renders it possible to implement nephrotoxic interactions into a CDSS. The goal is to identify patients at risk of renal impairment and give the responsible clinician a heads-up by suggesting therapy adjustments without causing alert fatigue. A screenshot of a Triple Whammy alert in KISIM can be seen in *Figure 10* in the appendix. There are five different alert levels within the Triple Whammy agent, as seen in *Figure 11* in the appendix:

- *alert 1*: Triple Whammy and GFR < 30 ml/min/1.73m^2
- *alert 2*: Triple Whammy and GFR between 30-60 ml/min/1.73m^2
- *alert 3*: Triple Whammy at age ≥ 75y
- *alert 4*: Triple Whammy without current creatinine value available
- *alert 5*: error in the calculation of Triple Whammy medication dosage[6]

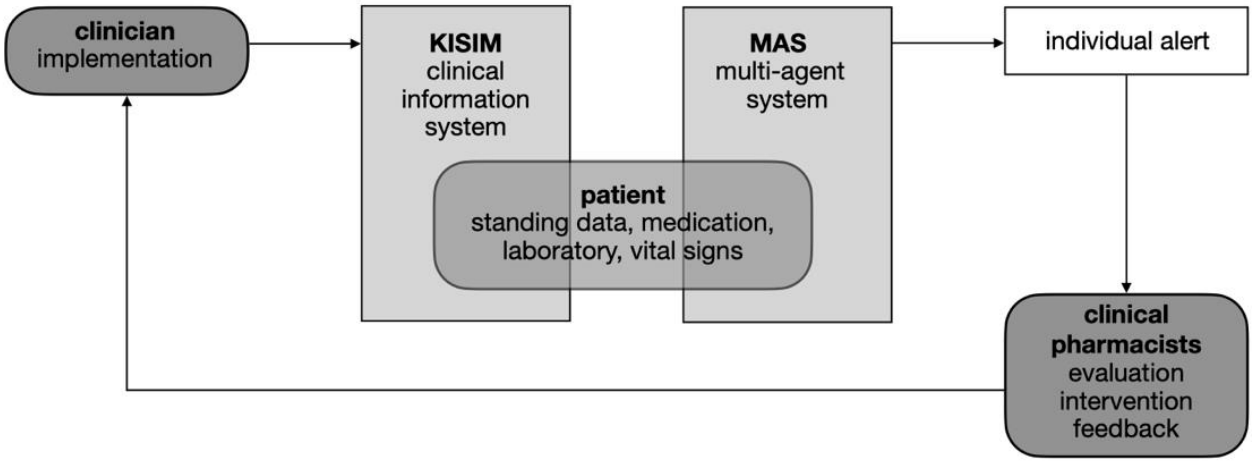

Figure 2 Clinical decision support system at Kantonsspital Aarau

Since various studies question the positive impact of CDSSs, this master thesis evaluates the appropriateness of the Triple Whammy agent.

[5] reliability of the Triple Whammy alert is guaranteed
[6] the purpose of alert 5 is to avoid missed patients due to technical misprescriptions

2 OBJECTIVE

The objective was to investigate the usability and performance of a clinical decision support system designed to detect patients with Triple Whammy prescriptions prone to suffer from acute kidney injury.

3 MATERIALS & METHODS

3.1 LITERATURE RESEARCH

A literature search was conducted to determine if any other research group published a paper on implementing CDSS to detect Triple Whammy prescriptions. The following research question was posed: 'What is the potential effect of a clinical decision support system on hospitalised patients with a Triple Whammy prescription?'.

The research question was split according to the PICO framework:

- **P**opulation: hospitalised adult patients with a Triple Whammy prescription
- **I**ntervention: implementation of a CDSS
- **C**omparison: n/a
- **O**utcome: prevention of AKI, including decreased mortality and burden of treatment

The literature research in PubMed® was first formed around the two PICO concepts 'population' and 'intervention'. The initial trial was unsuccessful since Triple Whammy itself is a particular and small research topic. Furthermore, it was challenging to gather all synonyms and equivalent terms for CDSS without missing any important papers. Consequently, the decision was to focus on 'population' as a single concept and screen through all articles about Triple Whammy without concentrating on a specific 'intervention'.

The databases PubMed®[7], Elsevier B.V.®[8], Web of Science™ by Clarivate®[9], Scopus® by Elsevier[10] and Dimensions© by Digital Science & Research Solutions[11] were consulted on 2.5.2022, and papers published since 1981 were considered. The search string was constructed in PubMed® and then translated (53) into Elsevier B.V.®. and Web of Science™. Since CDSS using algorithms is a recent topic, the database Scopus® by Elsevier, which features technological research, was consulted additionally through a quick hand search. The same method was applied in Dimensions© by Digital Science & Research Solutions.

To find all relevant publications about Triple Whammy, all three drug classes (ACEI/ARA + diuretic + NSAID) were handled as separate concepts and synonyms of each class were sought with medical subject headings (MeSH), the most common trade names of drugs

[7] https://pubmed.ncbi.nlm.nih.gov
[8] https://www.elsevier.com
[9] https://www.webofscience.com/wos/woscc/basic-search
[10] https://www.scopus.com/search/form.uri?display=basic#basic
[11] https://www.dimensions.ai

via Access Pharmacy®[12], author keywords in core papers via PubReMiner (Version 1.31)[13] and Yale MeSH Analyzer[14].

Using the Boolean operator 'AND', all three drug classes were connected to form the Triple Whammy concept. Angiotensin-converting enzyme inhibitor and ARA were combined with the Boolean operator 'OR' since they are equivalent in a Triple Whammy combination. Additionally, the term 'Triple Whammy' introduced by Thomas et al. (4) for the concomitant use of ACE/ARA, diuretic drug and NSAID was added and combined with 'OR' to our search string.

EndNote™ (Version 20.3) by Clarivate™ was used to reduplicate repeated papers (54).

To facilitate screening, each publication was ranked from one to five stars ★. Only five-star rated publications were considered to answer the research question potentially. Still, four-star texts could be used to deepen the knowledge about Triple Whammy prescriptions, including publications about risk factors.

3.2 DATA ANALYSIS

3.2.1 STUDY DESCRIPTION

STUDY DESIGN

A retrospective, cross-sectional study was performed. A time span of one year was analysed.

The northwestern and central Switzerland ethics committee[15] approved the study (Project-ID: 2021-01379), as seen in *Figure 12* in the appendix.

SETTING & STUDY POPULATION

The study was conducted at the KSA between 1.1.2021 and 30.6.2022. The KSA is a tertiary care hospital group with 669 beds in Switzerland. Routinely collected data of patients hospitalised during 2021 were used for quantitative analysis. Patients in inpatient treatment were included, and patients who rejected general consent, aged < 18 years on 1.1.2021 and hospitalised in Spital Zofingen were excluded.

SOFTWARE

Jupyter® Notebook (Version 6.1.5) with Python™ (Version 3.9.2) was used for data aggregation and cleaning.

Microsoft® Excel for Mac (Version 16.75) and IBM® SPSS Statistics (Version 27.0) were used for statistical evaluations.

[12] https://accesspharmacy.mhmedical.com
[13] https://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi
[14] https://mesh.med.yale.edu
[15] Ethikkommission Nordwest- und Zentralschweiz

3.2.2 CHARACTERISTICS OF PATIENTS WITH A TRIPLE WHAMMY ALERT

Descriptive statistics were performed to characterise and explore the patients whom the Triple Whammy agent detected between 1.1.2021 and 31.12.2021. If a patient triggered multiple Triple Whammy alerts, we reported data obtained from their first created warning as a default.

Age was reported by calculating the median with 0.25 and 0.75 interquartile range values, respectively, and the mean with standard deviation, minimum and maximum. The patients were classified into age groups (18-34, 35-54, 55-74, 75-84, ≥85 years of age).

Sex was reported as a binary variable, either male or female. Frequencies were calculated.

Several explorative analyses were formed around the medication prescribed or administered to the patients. Different APIs are available for each Triple Whammy drug class, and we reported each drug's prescription frequencies. Diuretics and ACEIs/ARAs are often prescribed together in an FDC[16] instead of separate pills. The number of prescribed medications, including as-needed prescriptions, was recorded to contextualise polypharmacy. We screened each patient for additional systemic nephrotoxic or renally excreted drugs apart from Triple Whammy, as seen in *Table 5* in the appendix (8,55–58). We screened each patient for creatinine falsifiers (*Table 6*, appendix) to avoid an overestimation of eGFR in these patients.

Duration of hospitalisation was calculated with each patient's corresponding admission and discharge date. The duration of hospitalisation was rounded to full days. We calculated the mean with standard deviation, minimum and maximum.

The hospital ward each patient stayed in was reported. We summarised them into six groups in *Table 7* in the appendix: internal medicine, surgery, neurology, orthopaedics, gynaecology and emergency.

Only comorbidities directly linked to renal function or known to influence the kidneys were collected. Active comorbidities at discharge were collected and reported via their ICD-10: glomerular kidney diseases (N00-N08), tubulointerstitial kidney disease (N10-N16), chronic renal failure (N18-N19), AKI (N17), other kidney diseases (N25-N29), diabetes mellitus (E10-E14), hypertensive kidney disease (I12-I13), heart failure (I50) and malignant neoplasm of the urinary organs (C64-C65).

The renal function of each patient before their Triple Whammy alert was reported, and the mean value with standard deviation was calculated.

[16] ATC-Codes: C09BA*, C09DA*, C09BX01 and C09DX*

3.2.3 COMPLIANCE RATE

ALERTS

Frequencies of each alert level 1 through 5 and their corresponding statuses were reported as absolute numbers and percentages. Several status types are possible (reported in *Table 8* in the appendix), depending on the editing progress of the alert. Suppose specific parameters do not apply after the hourly re-evaluation; an alert is terminated by the MAS ('termination by system'). Clinical pharmacists process all other alerts. The following actions are possible:

- send an intervention message based on the MAS alert ('intervention') – an intervention can, later on, be assessed as accepted, as not accepted or as not assessable
- pause the MAS alert for an arbitrary amount of days ('paused')
- mark alert as irrelevant or wrong ('irrelevant')
- no assessment is necessary because the patient left the hospital ('patient dismissed')

COMPLIANCE RATE

We reported the intervention rate among clinical pharmacists. The intervention rate among clinical pharmacists was calculated by noting the total intervention messages sent divided by all processable alerts. An alert terminated by the MAS or if the patient was already discharged from the hospital was not processable.

Equation 1 Intervention rate pharmacists

$$intervention\ rate\ among\ pharmacists = \frac{n\ (total\ interventions)}{n\ (processable\ alerts)}$$

We calculated the compliance rate of interventions advised to the clinicians. The compliance rate includes all Triple Whammy agent alerts with the status type 'intervention' and known progression. An intervention was defined as 'accepted' if the responsible physician partially complied with the suggested recommendation. The term 'total interventions with known progression' in *Equation 2* consists of 'accepted and implemented' and 'not accepted' interventions but excludes interventions with an unknown progression, such as 'intervention: not assessable' and 'intervention: progression unknown'. The overall compliance rate was calculated, meaning all five alert levels were included. The compliance rate was also individually determined for each alert level.

Equation 2 Compliance rate clinicians

$$compliance\ rate\ among\ clinicians = \frac{n\ (accepted\ interventions)}{n\ (total\ interventions\ with\ known\ progression)}$$

3.2.4 SENSITIVITY AND SPECIFICITY

We aimed for high specificity while sensitivity was kept at an acceptable rate. Sensitivity and specificity were calculated by allocating each patient to either:

- true positive
- false positive
- true negative
- false negative

All patients hospitalised during 2021 were considered. Also, the total incidence of Triple Whammy administrations was calculated within the same population.

POSITIVE: ASSESSMENT OF PATIENTS WITH TRIPLE WHAMMY ALERT

Patients who triggered at least one Triple Whammy alert were classified as either 'true positive' or 'false positive'. They were grouped into the contingency table by checking their alerts' status. If the situation was 'patient dismissed', a re-evaluation was conducted by thoroughly looking at the patient's medical file and consulting a pharmacist.

Each patient was matched once into the contingency table independent of the number of alerts generated. If a patient triggered several MAS alerts, each alert was assessed individually. If no coherent decision was obtained, the first alert created was used and reported in the contingency table. An exception was posed for patients with at least one alert following an 'intervention'; these were reported as 'true positive' independently of any other alerts created.

Patients with alert level 5 were excluded from sensitivity and specificity calculations since it was impossible to classify a status based on an error message with no clinical relevance.

NEGATIVE: ASSESSMENT OF PATIENTS WITHOUT TRIPLE WHAMMY ALERT

Patients who did not receive a Triple Whammy alert were ranked as either 'true negative' or 'false negative'. We mimicked all relevant aspects of the Triple Whammy agent to discover false-negative patients.

The sum of each subgroup was reported in *Table 1*:

Table 1 Theoretical contingency table

	detection necessary	**detection not necessary**	
alert created	true positive	false positive	
no alert created	false negative	true negative	

The following *Equations 3 and 4* were used to calculate sensitivity and specificity once the corresponding values were obtained:

Equation 3 Sensitivity

$$sensitivity = \frac{n\,(true\ positive)}{n\,(true\ positive) + n\,(false\ negative)}$$

Equation 4 Specificity

$$specificity = \frac{n\,(true\ negative)}{n\,(true\ negative) + n\,(false\ positive)}$$

To visualise the matching of each patient into either true positive, false positive, true negative or false negative, a decision path, as seen in *Figure 3,* was used:

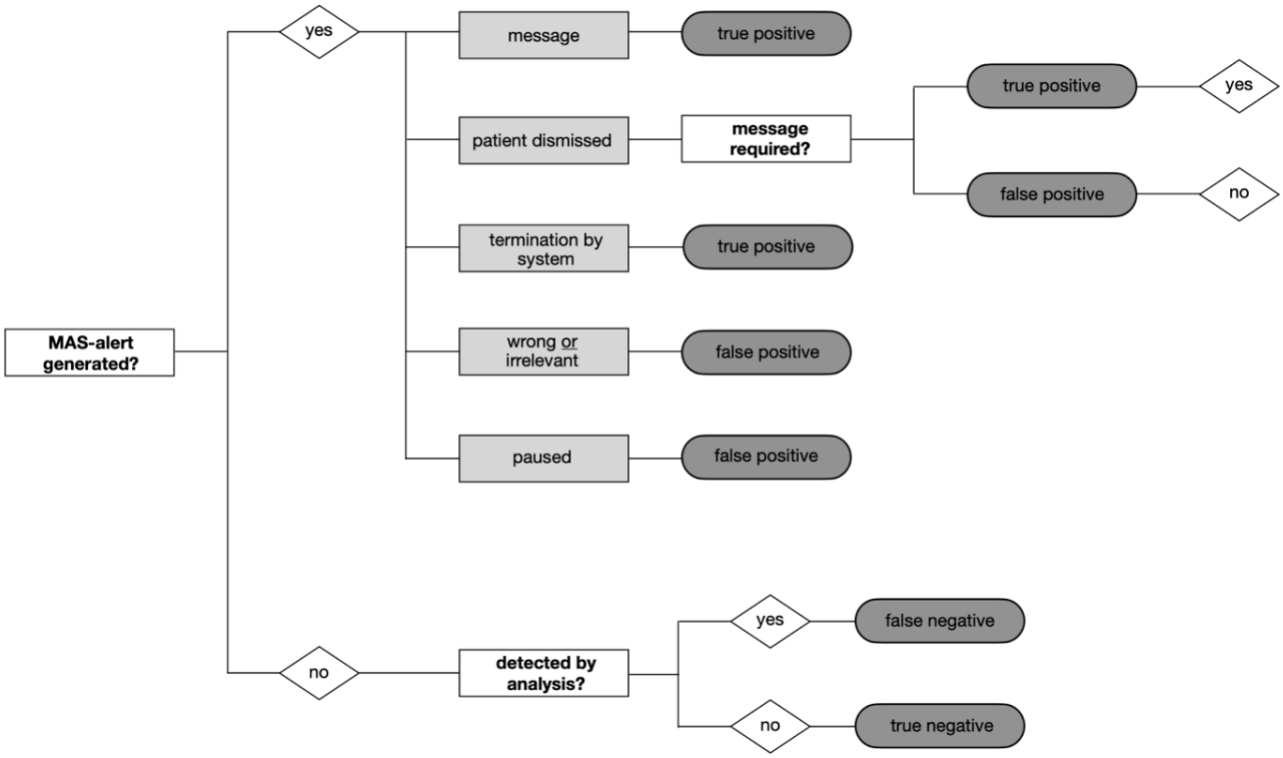

Figure 3 Sensitivity & specificity decision path

3.2.5 RENAL FUNCTION

Three separate investigations were performed to assess the CDSS's effect on renal function:

DEVELOPMENT OF RENAL FUNCTION AFTER INTERVENTION

We observed the development of renal function in patients with an accepted intervention compared to patients with a denied intervention. Each patient's last measured eGFR before the alert was compared to their GFR nadir after the alert[17]. Only patients with at least two measured creatinine values could be assessed. The significance level was standardised to 0.05.

[17] before discharge within the same inpatient stay

OCCURRENCE OF ACUTE KIDNEY INJURY DESPITE ALERT

We checked for patients who suffered from AKI despite being detected by the Triple Whammy alert. We examined the etiopathology and demographics of these individuals. We also checked the patients' diagnoses to see if AKI or other renal insufficiencies were reported. A particular focus was paid to patients with paused alerts. Clinical pharmacists disclosed their concerns about critical outcomes if an alert for a patient was paused wrongfully by them.

OCCURRENCE OF ACUTE KIDNEY INJURY UNDER TRIPLE WHAMMY

Patients who experienced an AKI under a Triple Whammy administration were detected if they did not trigger an alert. Furthermore, their case history was studied, and their age and eGFR before AKI were reported.

A literature search was conducted to find reports about risk factors contributing to the probability of experiencing an AKI under Triple Whammy, mainly focusing on age and baseline eGFR. Literature research was conducted as described in *Chapter 3.1,* and papers with a four-star rating were consulted.

3.3 QUALITATIVE ANALYSIS

A semi-structured interview with clinicians was initiated at the KSA and the Spital Zofingen, an emergency hospital and a residential care home for the elderly in the KSA group. The survey among clinical pharmacists was performed in the KSA. The semi-structured interview and the survey were conducted between 4.4.2022 and 4.5.2022.

3.3.1 SURVEY WITH PHARMACISTS

A written survey was launched among clinical pharmacists who assessed Triple Whammy alerts. The clinical pharmacists were asked to note their action (e.g., paused, an intervention message written) and justify their decision, as seen in *Figure 13* in the appendix. Currently, an internal document guides through the five different alert levels. The decision-making process is not fully standardised and depends on each pharmacist’s clinical knowledge and experience. The intention was to gather thinking processes and develop new internal guidelines for future assessments.

3.3.2 INTERVIEW WITH CLINICIANS

A semi-structured interview was conducted amongst clinicians who got an intervention message via KISIM. We gathered their current knowledge about Triple Whammy prescriptions and their opinion about the multi-agent alerts. The interview was conducted over the phone and guided by *Figure 14* in the appendix.

4 RESULTS

4.1 LITERATURE RESEARCH

The literature review identified 640 papers, as seen in *Figure 4*. All were screened based on their title or abstract, and four were included after the full-text screening. We found 22 texts that were thought to possibly answer the research question 'What is the potential effect of a clinical decision support system on hospitalised patients with a Triple Whammy prescription?'. There were several reasons why publications with an initial 5-star rating were excluded after the full-text screening such as differing population[18] or intervention like concentrating on shared-decision making. Three studies conducted before 2000 were not available and were most likely not using technically advanced algorithms. One paper was written in Spanish.

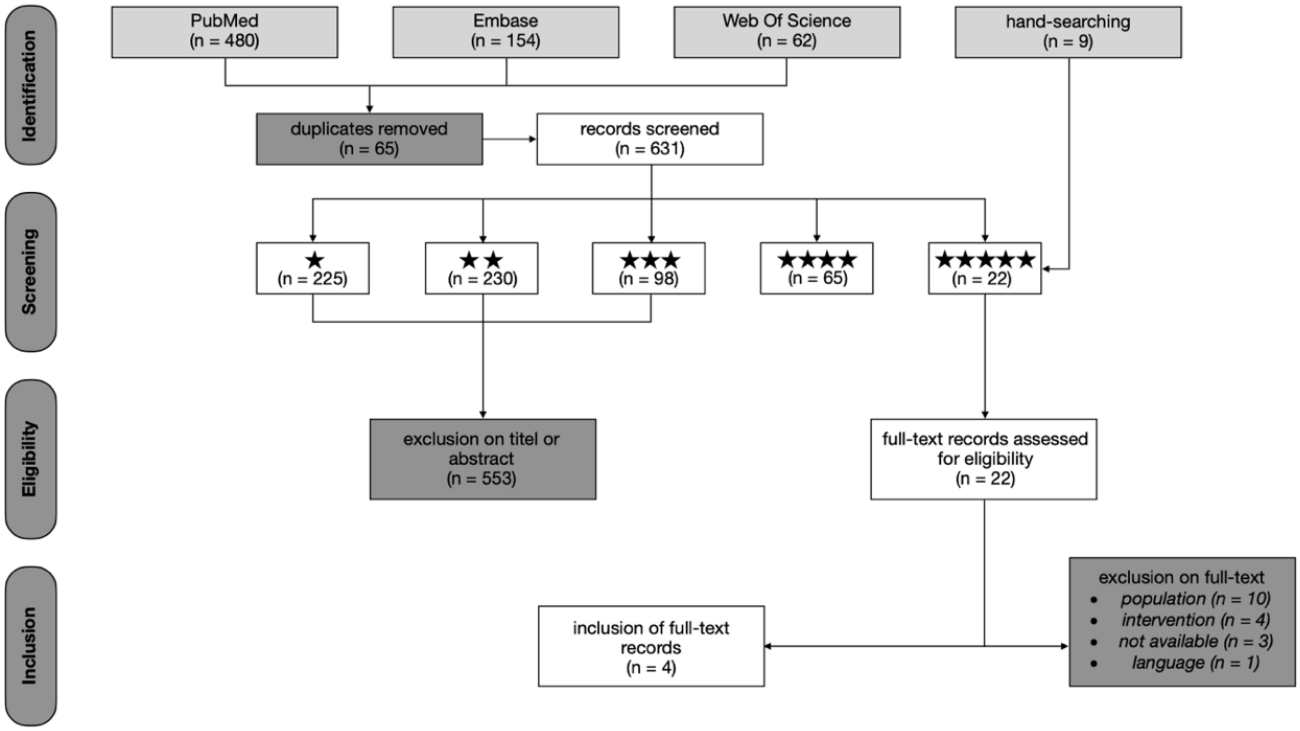

Figure 4 Literature research method and results

Four research groups examined a similar research question and gathered information about a CDSS detecting Triple Whammy prescriptions to prevent adverse outcomes (*Table 9*, appendix):

- Pons-Mesquida et al. (59,60) implemented a clinical decision-making tool in primary care that provides information about medication-related problems such as Triple Whammy prescription in patients over 75 years old or undergoing diabetes treatment. Pons-Mesquida et al. reported a decline in Triple Whammy alerts between 2016 and

[18] primarily focusing on single or the double prescription of Triple Whammy drug classes

2018 due to increased specificity. The compliance rate of the Triple Whammy alerts ranged from 22% (2018) to 30% (2016), thereby observing a decreased implementation rate even though specificity was improved. They found that in 65% of their Triple Whammy cases, the NSAIDs ibuprofen and naproxen were involved.

- Alzueta et al. (61) tried to detect high-risk patients treated with Triple Whammy via their in-house software. They published preliminary results suggesting a high compliance rate among general practitioners who were advised to withdraw NSAID administration or, if not possible, monitor renal function. Their compliance rate was 82%. Alzueta et al. stated that 'intervention through electronic clinical records optimises pharmacotherapy and may reduce adverse events and improve patients' safety'.
- Guthrie et al. (62) worked with indicators within their existing IT system in primary care. Their intervention included Triple Whammy high-risk prescribing feedback from clinical and technical support teams. They found a significant reduction in Triple Whammy prescribing when general practitioners had individual feedback provided on their overall prescribing pattern (63). Their findings suggest a considerable decrease in Triple Whammy high-risk administration is also possible with a less expensive population approach rather than having relatively intensive pharmacist-led intervention.
- Rogero-Blanco et al. (64) dealt with geriatric, multimorbid patients (aged 64 to 75) treated with polypharmacy in primary care. Their computer-assisted prescription system is supposed to detect drug-drug interactions, including Triple Whammy. Within their study population, 2.5% had a Triple Whammy alert, one of their system's most commonly found drug-drug interactions. Triple Whammy is considered a 'type D' interaction, which means it is clinically relevant, and a therapy adjustment should be considered.

4.2 DATA ANALYSIS

Data aggregation and cleaning can be seen and retraced in *Figure 15* in the appendix.

4.2.1 CHARACTERISTICS OF PATIENTS WITH A TRIPLE WHAMMY ALERT

Triple Whammy alerts were generated for 216 patients between 1.1.2021 and 31.12.2021. Their features are reported in *Table 2.*

The median age was 77 years, while 25% were younger than 67 and 25% were older than 83. The mean age was 74 ± 12 years. The youngest patient triggering a Triple Whammy alert was 31, and the oldest was 96. Almost 60% (n = 129 out of 216) of patients were 75 years of age or older.

Table 2 Summary of descriptive data

Age	
median [years]	77
.25 quartile [years]	67
.75 quartile [years]	83
18-34 years [number of patients]	**0.5%** (1)
35-54 years [number of patients]	**8.3%** (18)
55-74 years [number of patients]	**31.5%** (68)
75-84 years [number of patients]	**40.3%** (87)
>85 years [number of patients]	**19.4%** (42)
Sex [number of patients]	
female	**51.9%** (112)
male	**48.1%** (104)
Medication	
prescribed drugs [number of drugs]	21 ± 8
nephrotoxic medication [number of patients]	**14.8%** (32)
creatinine falsifiers [number of patients]	**3.2%** (7)
Duration Of Hospitalisation	
mean ± standard deviation [d]	7.1 ± 6.5
Hospital Ward [number of patients]	
surgery	**35.6%** (77)
orthopaedics	**25.9%** (56)
neurology	**22.7%** (49)
gynaecology	**7.4%** (16)
internal medicine	**6.5%** (14)
emergency	**0.9%** (2)
others	**0.9%** (2)
Amount Of Alerts [number of patients]	
1	**66.20%** (143)
2	**20.37%** (44)
3	**6.94%** (15)
4	**3.24%** (7)
5	**1.85%** (4)
6	**0.93%** (2)
7	**0.46%** (1)
eGFR Before Alert	
mean ± standard deviation [ml/min/1.73m²]	52 ± 22

The distribution of sex was almost equal with 104 male patients (48.1%) and 112 females (51.9%). The youngest and oldest patients triggering a Triple Whammy alert were females.

The number of medications prescribed was 21 ± 8, including as-needed prescriptions. The maximum number of prescribed drugs was 46; one patient had only three medications. Affected by polypharmacy were 91.0% (n = 193 out of 212) of patients.

The most commonly prescribed NSAID was ibuprofen, with 53.2% (n = 184 out of 346). More than half of all prescribed diuretics were torsemide, which was prescribed in 55.7% of cases (n = 157 out of 282). The most frequently prescribed ACEI was perindopril with 23.8% (n = 91 out of 382). All other frequencies can be seen in *Table 10,* 'Triple Whammy drug frequencies' in the appendix.

Fixed-dose combinations with ACEI/ARA and a diuretic are prescribed to 43.5% (n = 94 out of 216) of patients with a Triple Whammy alert.

At least one additional nephrotoxic or renally excreted medication was prescribed to 14.8% of patients (n = 32 out of 216). Vancomycin, acyclovir and alendronate were prescribed to one patient, respectively. Two patients were given digoxin on the day of their MAS alert. Metformin or an FDC containing metformin was administered to 28 patients, and five received methotrexate.

The potential creatinine falsifier Bactrim® forte[19] was prescribed therapeutically[20] to seven patients. No precise estimation of GFR was possible because cystatin C was not measured in these patients. We identified no other creatinine-falsifying drug in patients with a Triple Whammy alert.

The mean duration of hospitalisation was 7.1 days with a standard deviation of 6.5 days. The most extended inpatient period was 51 days.

Most patients with a Triple Whammy MAS alert were hospitalised on a surgical ward. Urological procedures were most common among the surgery group (n = 19 out of 76). The internal medicine wards, cardiology, nephrology and gastroenterology, had one patient, respectively. Category ‘others’ consisted of one patient from nuclear medicine and one from radiology.

More than half of patients (71.6%, n = 155 out of 216) had at least one comorbidity which could negatively influence their renal function. Most patients had a reported diabetes mellitus (n = 85) or chronic renal failure (n = 56). Other kidney diseases such as AKI (n = 50), tubulointerstitial kidney disease (n = 16), hypertensive kidney disease (n = 13) or glomerular kidney disease (n = 1) were common. Heart failure was reported in 25 patients, and malignant neoplasm in two.

Several patients triggered multiple warnings. The majority of the 216 patients triggered only one Triple Whammy alert. One patient triggered a maximum of seven Triple Whammy alerts during 2021.

4.2.2 COMPLIANCE RATE

ALERTS

The MAS generated 343 Triple Whammy alerts during 2021. There was no Triple Whammy alert generated by the MAS on 162 days of the year. Five warnings were produced in one day at most. Alerts 1 to 5[21] were produced with differing frequencies. Alert level 2 accounts for 32.4% (n = 111 out of 343) and is the most frequently delivered alert. Alert 5 was the least frequently produced alert with 2.9% (n = 10).

[19] an antibiotic containing trimethoprim and sulfamethoxazole
[20] prophylactic administration is not expected to alter creatinine levels
[21] alert 1 = eGFR < 30 ml/min/1.73m^2; alert 2 = eGFR < 60 ml/min/1.73m^2; alert 3 = age ≥ 75 years; alert 4 = no baseline eGFR available; alert 5 = error

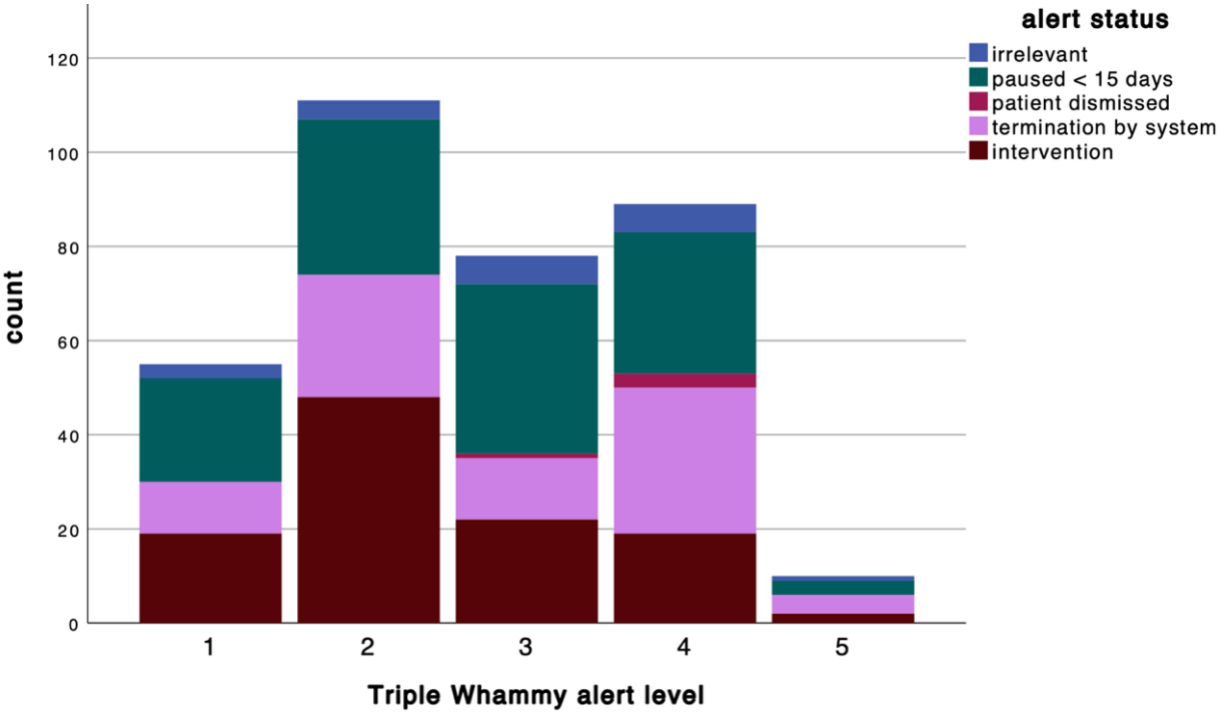

Figure 5 Alert level and status

Figure 5 shows the absolute frequencies of the five different alerts, categorised based on the assessment of the clinical pharmacists. Alert level 3 was found to be 'irrelevant'[22] in 7.7% times (n = 6 out of 78) and was also the most frequently paused alert with 46.2% (n = 36 out of 78). Most patients with the status 'patient dismissed' triggered an alert level 4 (n = 3 out of 4). Alert level 2 had the highest intervention rate with 43.6% (n = 48 out of 110). The highest 'termination by system' rate with 34.8% was in alert level 4 (n = 31 out of 89).

Five different status types[23] were set with varying frequencies, as seen in *Figure 6*. Pausing for less than 15 days was the most chosen action by clinical pharmacists with 36.2% (n = 124 out of 343). An intervention message was written in 109 events or, in one case, the clinician was directly called about the risky Triple Whammy (32.1%). Most interventions (n = 73 out of 110) were accepted and implemented by the clinician - less than a quarter of interventions were not accepted (19.1%). The MAS terminated almost a quarter (24.8%) of all alerts created (n = 85 out of 343). Only a few Triple Whammy alerts, 5.8%, were marked as irrelevant (n = 20).

[22] 'irrelevant' is equal to 'paused for 15 days' according to internal guidelines
[23] 'irrelevant'; 'paused'; 'patient dismissed'; 'termination by system'; 'intervention'

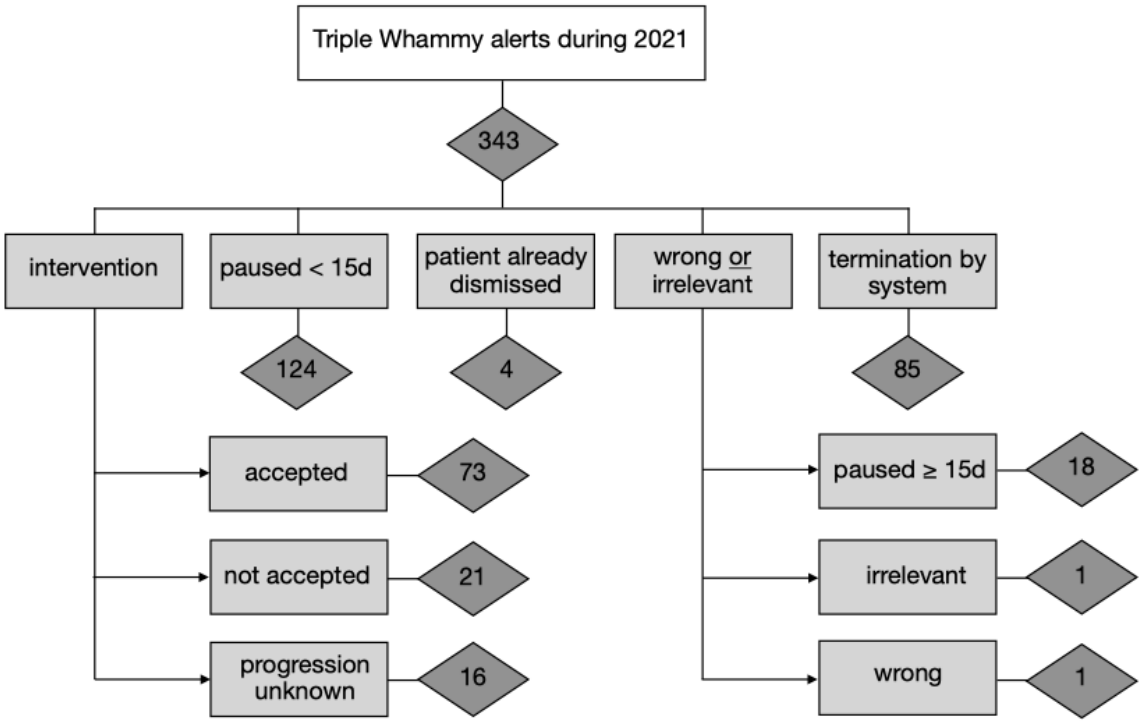

Figure 6 Flowchart status

COMPLIANCE RATE

Clinical pharmacists ranked 43.3% of alerts (n = 110 out of 254) as relevant and recommended interventions for the resident physicians.

The physician implemented 73 interventions, and 21 interventions were not accepted, resulting in a compliance rate of 77.7%. The progression of 16 interventions stayed unknown.

The compliance rate was not the same for each alert level, as seen in *Figure 7*. Alert level 1 had the highest implementation rate with 93.8% (n = 15 out of 16). Alert 2 had a compliance rate of 82.9% (n = 34 out of 41), followed by alert level 3 with a compliance rate of 70.0% (n = 14 out of 20). The intervention proposed via alert level 4 was implemented 53.3% of the time (n = 8 out of 15). Both interventions about missing dosing regimes were resolved, resulting in a compliance rate of 100% for alert level 5, as seen in *Figure 7*. The highest rate of unknown progression interventions was alert level 4 with 21.1% (n = 4 out of 19).

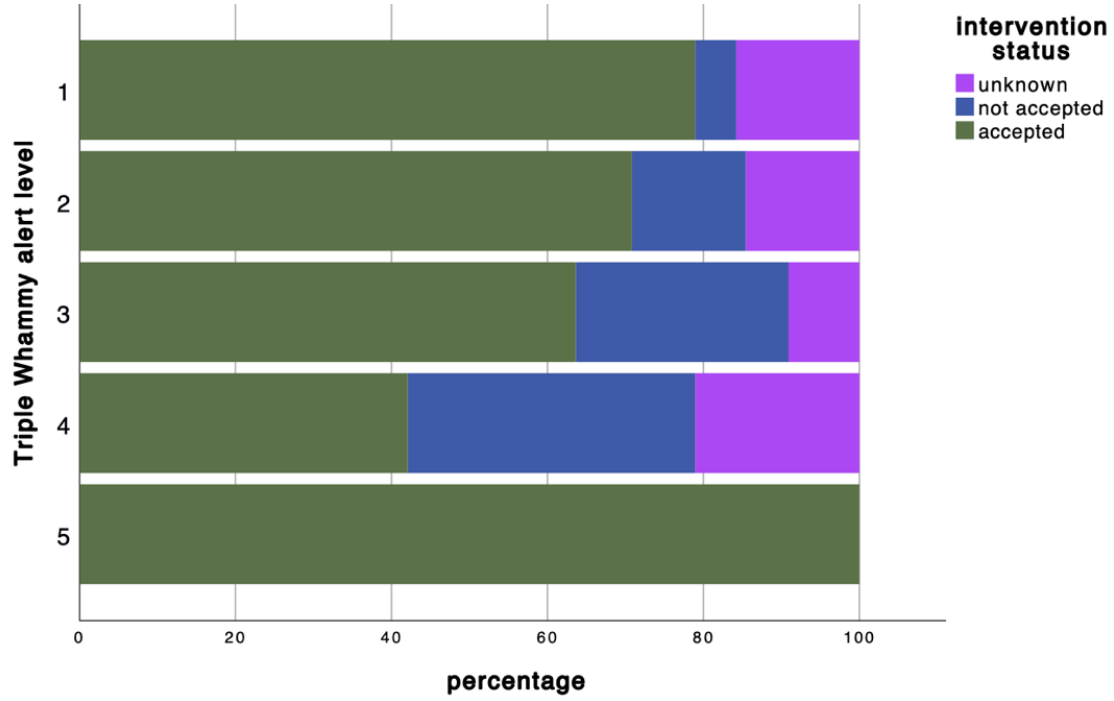

Figure 7 Intervention progression

4.2.3 SENSITIVITY & SPECIFICITY

The Triple Whammy administration incidence was 1.4% (n = 290 out of 21'326) at the KSA in 2021.

Table 3 includes all necessary numbers to calculate sensitivity and specificity according to Equations *3* and *4*.

Table 3 Contingency table

	detection necessary	**detection not necessary**	
alert created	true positive = 144	false positive = 66	210
no alert created	false negative = 19	true negative = 21'097	21'116
total	163	21'163	21'326

POSITIVE: ASSESSMENT OF PATIENTS WITH TRIPLE WHAMMY ALERT

A total of 210 patients were evaluated and classified according to the decision path depicted in *Figure 3*. Patients with only alert level 5 were excluded from calculations (n = 6) and subtracted from the total number of patients, as seen in *Table 3*. A pharmacist assessed both alerts with the status 'patient dismissed' as 'true positive'. Most patients were 'true positive' since at least one of their alerts resulted in a message or the MAS terminated their alert. Sixty-six patients were categorised as 'false positive' since none of their alerts resulted in an intervention. They can be considered to have triggered an unnecessary Triple Whammy alert.

NEGATIVE: ASSESSMENT OF PATIENTS WITHOUT TRIPLE WHAMMY ALERT

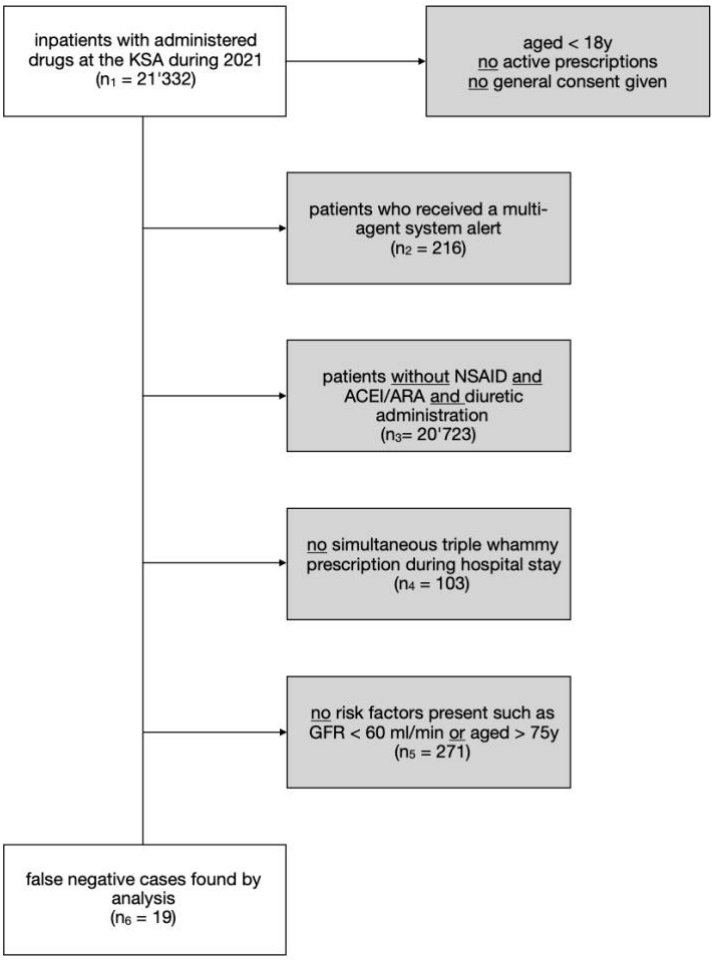

Figure 8 Flowchart false negative cases

The analysis detected 19 patients as 'false negative', whereas 21'097 inpatients were ranked as 'true negative'. 'True negative' was obtained by adding all excluded patients from n_3, n_4 and n_5, as seen in *Figure 8*. These 'true negative' patients have never triggered a Triple Whammy alert. Most of these patients had no Triple Whammy administered. If they did, no additional risk factor was present, and it was assumed unnecessary for them to receive a Triple Whammy alert. The remaining 19 patients were considered 'false negative' cases because they had a Triple Whammy administered and at least one risk factor present. Fifteen false-negative patients should have triggered an alert level 2, three were more than 75 years old but did not generate a Triple Whammy alert, and one should get an alert level 4.

4.2.4 RENAL FUNCTION

DEVELOPMENT OF RENAL FUNCTION AFTER INTERVENTION

Kidney function was known in 45 patients with an accepted intervention and another six with an unaccepted intervention message. A boxplot of their eGFRs is depicted in *Figure 9*. On average, patients with an accepted intervention had an eGFR of 49.76 ± 22.14 ml/min/1.73m^2 before triggering a Triple Whammy alert. After the alert, their nadir eGFR was 48.31 ± 22.58 ml/min/1.73m^2. Six patients with an unaccepted intervention had a mean eGFR of 54.83 ± 30.38 ml/min/1.73m^2 before their alert. After the Triple Whammy alert, their eGFR was 53.50 ± 27.09 ml/min/1.73m^2. A paired samples test showed no significant change in renal function, neither in patients with an accepted intervention nor in those with unaccepted interventions. Accepted interventions had a mean paired difference of 1.356 ± 11.983 ml/min/1.73m^2 (-2.245, 4.956; p=0.452), while unaccepted intervention showed a mean difference of 1.333 ± 9.416 (-8.548, 11.215; p=0.743).

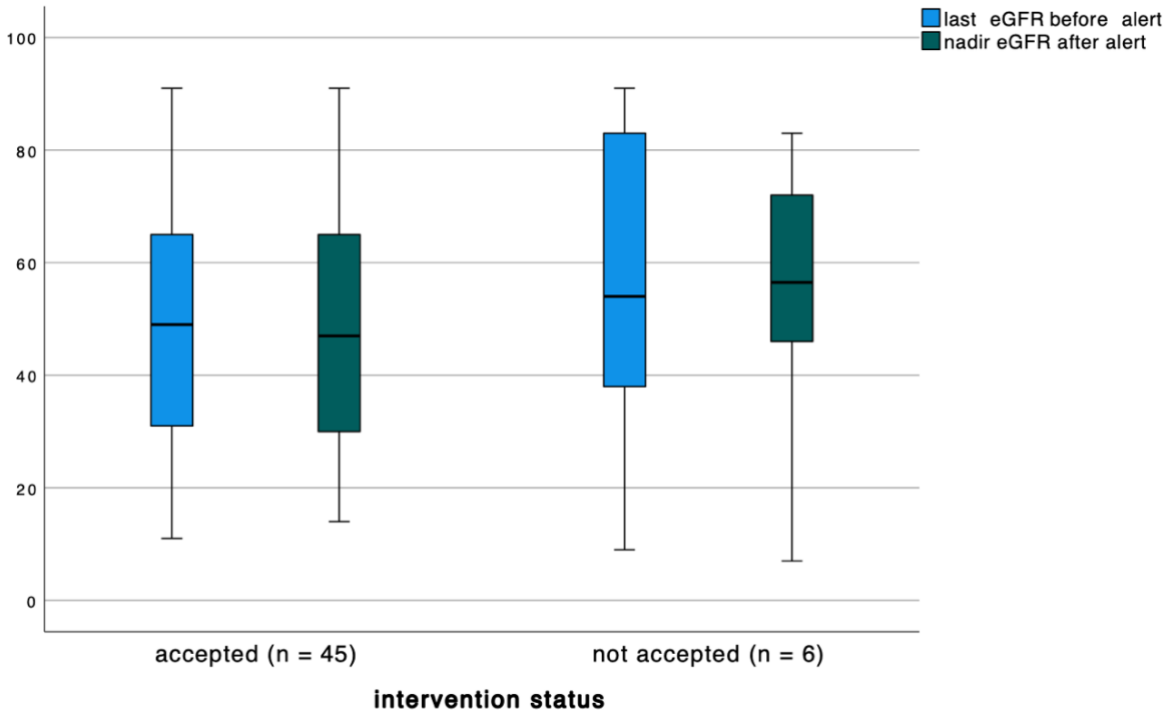

Figure 9 Renal development before and after intervention

OCCURRENCE OF ACUTE KIDNEY INJURY DESPITE ALERT

Despite being detected by the Triple Whammy agent, 15 patients are assumed to have experienced an AKI under the Triple Whammy administration. Their median age was 76 years. Patients' mean eGFR before Triple Whammy administration was 70.4 ± 24.6 ml/min/1.73m^2. Triple Whammy administration was not noted as a possible AKI cause in their case files, but NSAID prescription was mentioned twice as a differential diagnosis.

Clinical pharmacists paused 33.3% (n = 5 out of 15) alerts in patients who subsequently suffered from AKI. An intervention message was written in eight cases, whereas one patient was dismissed before their alert was assessed by a clinical pharmacist, and the system terminated one alert.

OCCURRENCE OF ACUTE KIDNEY INJURY UNDER TRIPLE WHAMMY

Patients who had not triggered an alert suffered less (n = 2) from AKI under Triple Whammy administration than those detected by the MAS (n = 15). Their characteristics are shown in *Table 4*. On average, these patients were 12.5 years younger than the minimum age, considered a risk factor by CDSS. Also, in both patients, their renal functions were >91 ml/min/1.73m^2 and therefore not depleted before Triple Whammy administration.

Table 4 Descriptive data of patients with AKI without alert

patient ID	age [y]	eGFR before Triple Whammy [ml/min/1.73m²]
1	60	>90
2	65	>90
average	62.5	>90

4.3 QUALITATIVE ANALYSIS

4.3.1 SURVEY WITH PHARMACISTS

The clinical pharmacists evaluated 22 Triple Whammy alerts during the one-month observational phase. Intervention messages were sent to the clinician in 15 cases. Clinical pharmacists make varying considerations before sending an intervention to the responsible clinician. Decreasing renal function was considered the most frequent reason to initiate an intervention (n = 7 out of 15). Four intervention messages were sent due to inappropriate NSAID prescriptions: In two cases, alternatives to NSAIDs were not exhausted as analgesics. The two other cases reported unnecessary high NSAID dosing regimens. One intervention was launched since it was not evident in the patients' anamnesis as to why they have prescribed these medications.

Pharmacists paused for one day (n = 1 out of 5), for two days (n = 3), for three days (n = 1). According to the internal policy, one alert was paused for 15 days, equivalent to 'not relevant'. An alert level 5 was marked as 'not relevant'. There were several different reasons mentioned as to why no intervention was sent:

- alert reappeared after a non-compliant intervention (n = 2)
- the patient was only recently admitted to the hospital (n = 2) in alerts level 4, and subsequent creatinine measurement was expected
- the patient was likely to be released the same day (n = 1) in an alert level 4
- no creatinine measurement was scheduled to be initiated over the Easter holidays (n = 1) in an alert level 4
- the as-needed prescription was administered once only, and further supervision from the clinical pharmacy team was assumed to be sufficient (n = 1) in an alert level 4.

4.3.2 INTERVIEW WITH CLINICIANS

A total of 15 intervention messages were sent during the one-month observational phase. A resident physician got two messages concerning different patients and was contacted once. We conducted eleven semi-structured interviews over the phone. We contacted three resident physicians via e-mail, only one associate physician returned his answers in writing. An overall return rate of 85.7% (n = 12 out of 14) was accomplished.

Most resident physicians (75%; n = 9 out of 12) reported they had never heard about Triple Whammy as a hazardous triple prescription before. A single physician, who knew about Triple Whammy risk before triggering the alert, noticed the unfavourable medications in their patient independently of the pharmacists' intervention.

All resident physicians found the Triple Whammy alert meaningful (n = 11 out of 11). Wordings such as 'exonerating', 'reassuring' and 'helpful' were used to describe the MAS implemented at the KSA. The MAS was perceived as a good support tool since there was a lack of time and knowledge around pharmacology and drugs. Especially surgical wards did not seem to prioritise drug therapy and felt unburdened by the clinical pharmacists (n = 2). Some were educated and sensitised by the MAS about Triple Whammy prescriptions and were curious to learn more (n = 3). The interprofessional teamwork at the KSA between clinical pharmacists and the medical team was complimented (n = 1).

Sometimes clinicians do not notice the intervention message from the clinical pharmacy team in KISIM (n = 4). Early discharge from the inpatient treatment is why one physician did not see intervention. Nurses pointed out the Triple Whammy intervention to one resident physician since they also have access to KISIM.

Prescriptions ordered by a general practitioner in primary care before the hospitalisation was mentioned to justify why patients were treated with risky Triple Whammy prescription (n = 5). Concerns about changing medications were expressed if it was prescribed by the general practitioner, especially in drugs to control hypertension (n = 2).

Most resident physicians shared the clinical pharmacists' recommended intervention to remove NSAIDs if asked about their opinion on adapting Triple Whammy medication (n = 5). They stopped NSAID administration or removed it from the as-needed prescriptions list. One resident physician was hesitant to stop NSAID administration because he believed pain control to be crucial and, consequently, stopped diuretic therapy alternatively. In one patient with an alert level 1, all Triple Whammy medications were immediately stopped after the MAS intervention. RAAS-I was later reintroduced.

Most resident physicians will try to avoid Triple Whammy prescriptions in the future (n = 8 out of 10). The remaining resident physicians will decide situation-dependent if a Triple Whammy prescription might be suitable for a patient.

Two points of criticism about the MAS were expressed: MAS warnings might be missed because the intervention is not sent to the responsible clinician directly. The emergency ward does not work with KISIM as a clinical information system. Therefore, they do not receive alerts from the MAS, which could be a reason for delays in changing inappropriate medication combinations.

5 DISCUSSION

5.1 MAIN FINDINGS

We evaluated the performance and the usability of a CDSS detecting Triple Whammy treatments in patients with a high probability of developing an AKI.

5.1.1 PERFORMANCE

Good CDSS performance is obtained if a high compliance rate and sensitivity are reached. An acceptable specificity is favourable. An increase or at least no worsening in renal function should be observed in patients with an accepted intervention, and AKIs should be averted.

COMPLIANCE RATE

The compliance rate of the Triple Whammy agent at the KSA is superior compared to similar CDSS. A general compliance rate of more than 60% is suggested for action-oriented interventions (65). Our Triple Whammy agent had a compliance rate of 77.7% and thus conformed with this recommendation. In Triple Whammy clinical decision-making tools used in primary care, the compliance rates were 30% (59,60) and 82% (61), respectively. The latter high compliance rate must be cautiously interpreted because general practitioners evaluated only 15% of proposals (61). Our superior compliance rate could be due to direct communication of drug-related problems via a clinical pharmacist (66). Even if compared to the overall compliance rate among all MAS agents in the same tertiary hospital (72.2%[24]), our Triple Whammy compliance rate is slightly higher.

SENSITIVITY & SPECIFICITY

Sensitivity and specificity aligned with requirements for a sophisticated CDSS (67) and fulfilled our internally set goal. We reached a high specificity and an acceptable sensitivity in our Triple Whammy agent. A comparison to other Triple Whammy CDSS is impossible because no other publication provided a sensitivity or specificity analysis.

Our high specificity of 99.7% is essential to avoid alert fatigue (49). A comparable specificity of 92% was found in a previous master thesis evaluating the appropriate dosage of direct oral anticoagulants at the same tertiary hospital (67). The PPI alert at the KSA had a specificity of 97.1% for deprescribing PPI without indication (68).

Our overall sensitivity of 88.3% aligns with the recommendation that a CDSS should maximise specificity while sensitivity is kept at a value above 75% (47). A scoping review checked the clinical validation of several CDSS and found a sensitivity for drug-related problems

[24] these results will be published soon

ranging from 28 to 85% (69). A lower sensitivity can be justified by arguing that a high compliance rate among clinicians is more meaningful in reducing harm than catching all error-prone prescriptions (70). Also, a CDSS adds a supplementary safety net and does not have to be flawless in terms of sensitivity.

Still, the heterogeneity of methods makes it difficult to compare these results to our sensitivity and specificity analysis. The method utilised in this master's thesis was selected because we wanted to identify patients who are at high risk of having an AKI rather than selecting every patient with a prescribed Triple Whammy.

RENAL FUNCTION

The overarching goal of the Triple Whammy alert is to prevent kidney injury. Even though there was no significant improvement in the renal function of patients with an accepted intervention, their eGFR had not worsened either. The same applies to patients with an unaccepted intervention. It can be argued that these patients were overall less morbid, and their attending physician's decision to continue Triple Whammy administration had no negative influence on renal function. Our findings are based on a small study population and must be interpreted cautiously. In another study, pharmacists' intervention has shown substantial improvement of renal function in Triple Whammy prescriptions if NSAIDs are deprescribed and stable eGFR was reached when monitored (71). These contradicting findings by Koeck et al. could be explained by their differing study design: they only considered surgical patients and reported eGFR at discharge instead of eGFR nadir. Additionally, in our study, we are uncertain if an accepted intervention meant deprescribing NSAIDs or merely intensified monitoring of renal function.

Acute kidney injury occurred in patients despite being detected by the Triple Whammy agent. The cause of AKIs remains unknown, but we provide two possible explanations:

- Our patient collective had elevated AKI risk independently of Triple Whammy administration. Patients of advanced age have the highest susceptibility to experiencing an AKI (25). Polypharmacy in patients increases the risk of adverse effects on the kidney (72,73). Surgery, especially cardiac, exerts an extra strain on renal health (25). Chronic kidney diseases and diabetes are essential risk factors for AKI (21,74–76). Our patients triggering a Triple Whammy alert were mostly geriatric, affected by polypharmacy, inpatients in a surgical ward, and already suffering from kidney diseases.
- Acute kidney injury might have been caused by the overuse of pausing Triple Whammy alerts. Pharmacists paused one-third of alerts in patients who later suffered from AKI. This could suggest that the initiation of an intervention is too conservative. The

appropriateness of pausing behaviour should be re-evaluated internally. Encouragement of pharmacists to send interventions to clinicians more frequently could be one area for improvement.

Nevertheless, the MAS can attest to the ability to detect patients at risk for AKI. Fifty patients triggering a Triple Whammy alert experienced an AKI during their inpatient stay, whereas 15 patients had a direct time correlation to their Triple Whammy administration.

Acute kidney injury occurred in two patients with a Triple Whammy, not detected by the CDSS. We investigated a possible need to adjust the thresholds for eGFR (alert 2) and age (alert level 3) in our CDSS:

However, an eGFR threshold of < 60 ml/min/1.73m^2 is reasonable and should not be changed. Our patient's initial eGFRs were considered healthy[25] (≥ 90 ml/min/1.73m^2), implicating a drastic change in the eGFR threshold. Yu et al. (76) reported an odds ratio of 4.69 (2.88-7.64) for baseline eGFR < 60 ml/min/1.73m^2 when comparing cases with drug-induced AKI with controls. Dreischulte et al. (9) showed that cases compared with controls had lower baseline renal function, meaning an eGFR between 30 – 59 ml/min/1.73m^2. No elevation of the eGFR threshold can be justified by current data availability.

The age threshold of ≥ 75 years could be lowered to improve sensitivity. Both patients with an AKI episode were younger than 75 years. Dreischulte et al. (9) conducted a case-control study and found highest risk for AKI in Triple Whammy patients over 75 years. Camin et al. (5) published that 78% of Triple Whammy patients with a hospitalisation episode due to AKI were older than 70 years. The case-control study of Yu et al. (76) did not announce age as an independent risk factor for drug-induced AKI. Nevertheless, they reported a significant correlation between age ≥ 60 and drug-induced AKI. A lower age threshold could be favourable, but impacts on alert burden and resources due to reduced specificity must be considered first.

5.1.2 USABILITY

Good usability of the CDSS is obtained if clinicians benefit from the generated alerts and alerts are noticed on time. The alert burden should be kept low for clinical pharmacists and clinicians.

QUALITATIVE ANALYSIS

An astounding approval rate of 100% was achieved for the Triple Whammy alert among the resident physicians. Another study found comparable results, where physicians

[25] https://next.amboss.com/de/article/lg0vv2?q=GFR#Z9b64c222c41232ab914b726d36f985de (accessed 14.6.22)

collectively agree on the usefulness of receiving drug-related alerts (77). Most resident physicians said they would not have spotted the Triple Whammy prescription on their own; the MAS made them aware of their patients' Triple Whammy prescription.

Usability in terms of timely intervention and presentation in KISIM could be improved. Even though the MAS does an hourly evaluation and generates alerts in real-time, the intermediate step via clinical pharmacists can delay the presentation of important information to the responsible clinician. Pharmacists paused alerts because patients would likely be discharged from the hospital soon, and intervention seemed redundant. Some clinicians overlooked Triple Whammy intervention in KISIM and asked for a more straightforward way of alert presentation, e.g., via e-mail. An interruptive CDSS was proven to promote timely discontinuation of nephrotoxic medication during AKI (78).

The alert burden for the Triple Whammy agent was low, preventing alert fatigue among clinicians. A clinical decision support tool should flag not more than 10% of inpatient prescriptions (70). With this master thesis, we cannot conclusively discuss the alert burden for pharmacists and clinicians at the KSA since there are 19 agents active in addition to the Triple Whammy agent. In 2021, less than one Triple Whammy alert was produced per day. A significant number of alerts were automatically terminated by the MAS and, therefore, never assessed by the clinical pharmacists. Clinicians were confronted with one-third of the total alerts created during the timespan of a year.

The Triple Whammy alert indicates a little-known but relevant drug-drug interaction to resident physicians. Physicians reported lacking knowledge about preparation names and APIs, which could lead to a Triple Whammy oversight. Especially FDC can promote drug-drug interactions. Fixed-dose combinations incorporating ACEI/ARA and a diuretic into a single pill are almost as frequently prescribed as individually administered preparations. This common habit of prescribing FDC could diminish the learning effect of the Triple Whammy interaction. Often FDC, such as Co-Diovan®[26], are prescribed without having more profound insight into their interaction potential. Even though FDC have various advantages, such as strengthening therapy compliance and decreasing health costs (79), their extensive usage could promote oversight of AKI risk.

5.2 LIMITATIONS AND STRENGTHS

Our study used a mixed-methods approach, and therefore, several limitations and strengths are discussed:

LIMITATIONS

There are several limitations and biases concerning the patient collective studied:

[26] consisting of valsartan and hydrochlorothiazide

1) The coronavirus disease 2019 pandemic raged throughout 2021 and greatly influenced day-to-day business and the inpatient collective.
2) No data of patients without general consent was used. Therefore, sensitivity and specificity analysis, compliance rate and descriptive statistics only represent patients with general consent, and results may vary slightly from an encompassing patient collective.
3) A particular selection bias is possible because only patients with at least two measured creatinine values during their hospitalisation could be included in the evaluation of renal development. Closely monitored creatinine is often mandated in patients with more severe conditions, whereas it seems redundant in stable and healthier individuals.
4) To avoid confounding descriptive statistics, each patient was included once even though they triggered several alerts. We always choose the value present in the first MAS alert generated for non-statical values; for example, if a patient was an inpatient in a surgical ward in January but was re-admitted in February for a neurological incident, we only reported the one case in surgery.

There are several limitations to our study design:

1) As mentioned by McCoy et al. in their ‘framework for evaluating the appropriateness of clinical decision support alerts and responses’, a comparative or controlled trial is required to demonstrate alert contribution to process or patient outcomes (80). Our study design is not outlined according to this framework but is a cross-sectional analysis.
2) Our classification of positive cases, as seen in *Figure 3,* depends on the clinical pharmacists. Even though a general gold standard was communicated, the review of the Triple Whammy alert may differ slightly depending on the pharmacist assigned to the day shift. It may also fluctuate with the time of the day or the specific workload on this day.
3) The number of prescriptions included all pharmaceutical forms, NaCl infusions and non-recurring administrations. Therefore, the number of prescribed drugs in a hospital does not represent the daily, long-term medication and was potentially overestimated.
4) Logically, the analysis should detect the same patient collective as the MAS. The MAS works with prescriptions; our study used actual administrations. We furthermore looked at patients with an admission date after 1.1.2021, but four patients detected by the MAS arrived at the KSA in 2020 and triggered an alert in 2021.
5) A trained nephrologist did not verify the diagnosis of AKI but was strictly determined according to KDIGO guidelines (25).

6) A week before the interviews, a clinical pharmacist held a presentation on medication interaction for all clinicians working in internal medicine. This could have influenced clinicians' state of knowledge about Triple Whammy prescriptions since it was explicitly mentioned as a critical triple combination to be avoided.
7) The interview among clinicians was only conducted in a fraction of resident physicians employed at KSA, but their opinions were primarily unanimous and therefore generalisable.

STRENGTH

1) Most drug-drug interaction checking tools can only detect two APIs involved in an interaction. Thus, most commercially available tools cannot identify a Triple Whammy prescription.
2) The study was performed with real-life data and reflects the current situation in a Swiss tertiary hospital.

5.3 IMPLICATIONS

We discussed the performance and usability of our Triple Whammy agent thoroughly and tried to gather some relevant implications and continuative thoughts:

COSTS

The prevention of AKI can help reduce healthcare expenses, but the need to show the cost-efficiency of prevention measurements remains. The Federal Health Insurance Act (KVG) calls in Art. 32 for the following requirement for medicinal prevention: 'benefits […] must be effective, expedient and economical' (81). If the GFR drops below 15 ml/min/1.73 m^2, dialysis or kidney transplant become inevitable. Costs of 250,000 Swiss francs (CHF) per patient's lifespan can be saved for whom dialysis can be prevented (11). Each adverse event costs 5,000 CHF per hospital admission due to prolonged hospitalisation and direct expenses (82). An internal document from the KSA predicts a maximum saving of costs if at least 90% of clinically relevant adverse effects are detected with high specificity and the need to address the generated alerts as soon as possible.

EXCHANGE OF KNOWLEDGE

Switzerland, especially the German-speaking Northern part of Switzerland, lags behind in establishing clinical pharmacy practice (83). Recent publications insist on integrating a CDSS into Swiss healthcare (84), but e-health is not harmonised yet. Other hospitals using CDSS could benefit from implementing the Triple Whammy agent. Communication among Swiss hospital pharmacists should be encouraged, and their usage of CDSSs and algorithms should be declared publicly.

ADVANCED TRAINING

Clinical decision support systems can exert a teaching effect on clinicians (85). In our semi-structured interview, most resident physicians were not educated enough on Triple Whammy to make a well-informed prescription decision. Besides finding it helpful, clinicians credited the MAS for executing a training impact and informing them about unfamiliar drug-drug interactions. But disproportionate reliance on CDSS can be a potential disadvantage. None of the interviewed resident physicians expressed such concerns directly, but wording such as ‘improved certainty due to the assurance someone double-checks prescriptions’ could be interpreted as an exceeding trust. Nevertheless, the educational impact of a CDSS in teaching hospitals like the KSA cannot be denied and is especially important for resident physicians shortly after their state examination (86). Feedbacks also show advanced training for nursing staff.

DEPRESCRIBING

Deprescribing at least one Triple Whammy drug class is the most frequently implemented practice among interviewed physicians. Actionable interventions seem the most promising way to avoid AKI (87). Most resident physicians deprescribed an NSAID as suggested by the clinical pharmacist. Some additionally paused ACEI/ARA or diuretic administration for a short duration if stable blood pressure was warranted. Deprescribing was proven in other studies to cause no unwanted side effects or death if the available evidence is customised to each patient (88,89). Predominantly geriatric and renally impaired patients benefit from the deprescribing practice (90,91). If possible, shared decision-making should be considered whenever a deprescribing is performed.

The most straightforward measure to avoid AKI within a Triple Whammy prescription is to stop NSAID administration (21) and consider discontinuing any nephrotoxic medications, including those requiring dose adjustment in case of renal dysfunction, such as metformin (92). One resident physician reported, for example, the cessation of allopurinol as a precaution. Nevertheless, essential drug therapy should be re-introduced once the renal function has improved (74). The process of re-starting needs to be monitored, e.g. by measuring creatinine levels. If renal function recovers and improves from baseline, clinicians must consider dosing adjustment with renally excreted drugs like metformin.

Denying the deprescription of an NSAID and adhering to Triple Whammy administration is a valid clinical consideration. One resident physician did not implement the recommendation of stopping NSAIDs at the expense of insufficient pain control. The deprescription of NSAIDs is not necessarily superior because alternatives might be less potent, such as paracetamol, or exert other adverse effects, such as opioids (93). Also,

the triple combination of NSAIDs, ACEIs/ARAs and a diuretic is not a strict contraindication. Hence, there is room for flexibility regarding Triple Whammy prescriptions.

5.3.1 FUTURE RESEARCH

Another approach to increase sensitivity is a dynamic eGFR calculation. The current static eGFR calculation at KSA does not incorporate the progression of renal function. More suitable would be the calculation of a dynamic eGFR to intercept drastic declines early, especially in patients with an initially healthy eGFR[27]. A dynamic eGFR would promote early detection of renal insufficiency caused by a Triple Whammy prescription but also increase the alert burden. A change to dynamic eGFR is considered for the Triple Whammy agent and is already successfully implemented in three other agents[28] at the KSA.

5.4 CONCLUSION

This master thesis credits adequate performance and favourable usability to the Triple Whammy agent used at the Kantonsspital Aarau to prevent acute kidney injury.

Good usability was credited to the Triple Whammy agent. Resident physicians felt supported by the CDSS, mainly because only a few knew about Triple Whammy risk beforehand. The timely warning could be improved by re-evaluating the pausing behaviour of clinical pharmacists.

The performance of the Triple Whammy agent can be judged as satisfactory. The MAS successfully disregarded unproblematic Triple Whammies while still detecting most high-risk prescriptions. Even though a high intervention rate was obtained, we could not demonstrate a significant improvement in the renal function of patients. There is a need for prospective studies to understand the clinical benefits of such tools in preventing kidney injury.

[27] e.g. a patient with an estimated GFR of 61 ml/min/1.73m^2 is above the predefined threshold and will not trigger the MAS even though their renal function might have decreased from 90 ml/min/1.73m^2 within a week

[28] cefepime agent, vancomycin agent, aminoglycoside agent

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7 FIGURES AND TABLES

FIGURES

TABLES

EQUATIONS

8 APPENDIX

8.1 DEFINITIONS

ACUTE ON CHRONIC a chronic condition (e.g. CKD) develops into an acute illness (e.g. AKI)

DEPRESCRIBING supervised removal of drugs to avoid potentially problematic outcomes and to improve quality of life

GERIATRIC a person older than 65 years

KPHARM departments of clinical pharmacology and clinical pharmacy jointly striving to develop a multi-agent system in KISIM

MULTIMORBIDITY three or more chronic diseases

POLYPHARMACY simultaneous and continuous administration of five or more medications

SHARED-DECISION MAKING therapy adjustments involving patients' personal preferences

8.2 APPENDIX

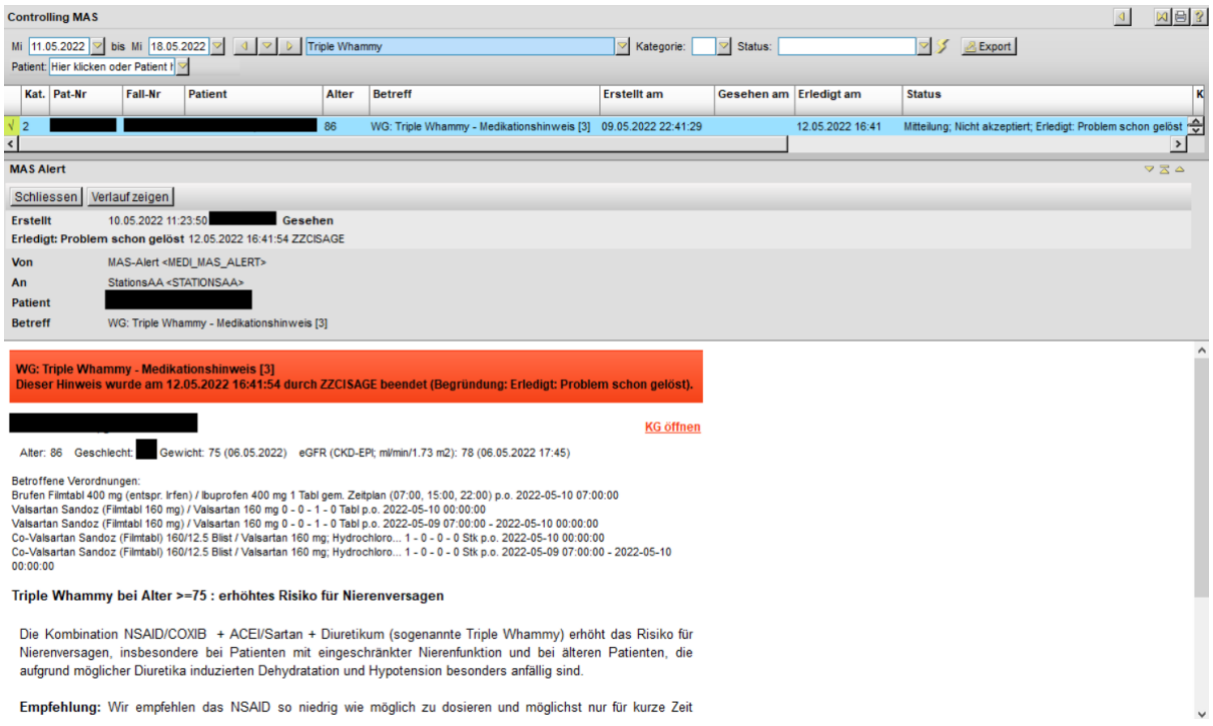

Figure 10 Screenshot Triple Whammy alert KISIM

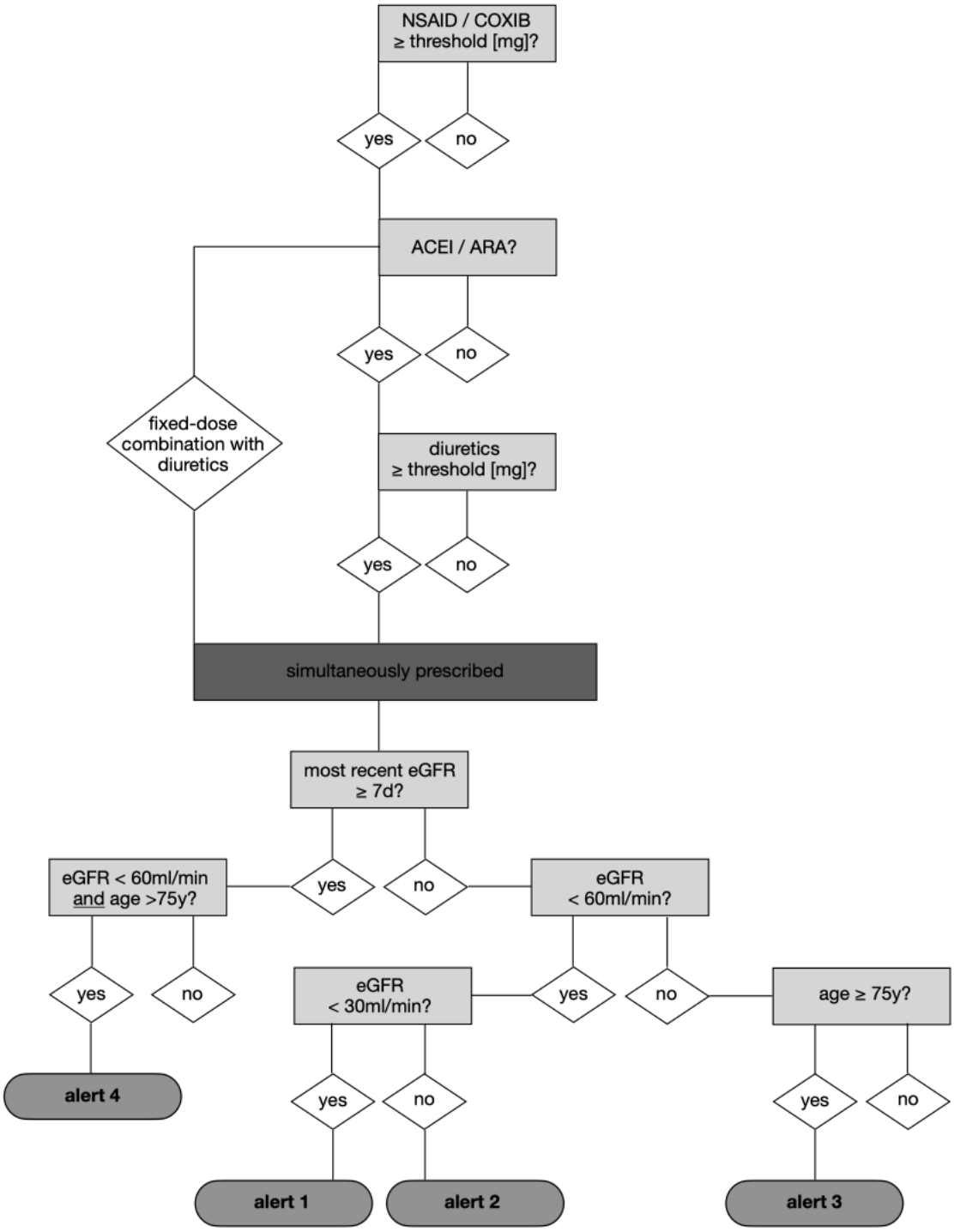

Figure 11 Flowchart Triple Whammy alert levels

EKNZ

Ethikkommission
Nordwest- und
Zentralschweiz

Prof. Dr. Philipp Schütz
Kantonsspital Aarau
Haus 7
Tellstrasse 25
5001 Aarau

Basel, 14. Juli 2021

Verfügung der Ethikkommission Nordwest- und Zentralschweiz (EKNZ)

Project-ID	2021-01379
Projekttitel	Evaluation of alerts of an algorithm-based electronic tool for detection of medication errors and reduction of potential adverse events
Master-/Doktorarbeit von	Dahmke, Hendrike
Projektleitung	Prof. Dr. med. Philipp Schütz
Sponsor	Prof. Dr. med. Philipp Schütz
Zentren	• Prof. Dr. med. Philipp Schütz, Kantonsspital Aarau, Aarau

Entscheid

- ☒ Die Bewilligung wird erteilt → die Auflagen der EKNZ vom 08. Juli 2021 wurden erfüllt.
- ☐ Die Bewilligung wird mit Auflagen erteilt
- ☐ Die Bewilligung kann noch nicht erteilt werden
- ☐ Die Bewilligung wird nicht erteilt
- ☐ Auf das Gesuch wird nicht eingetreten

Klassifizierung

☒ Forschungsprojekt gemäss HFV — Kategorie: --

- ☐ Forschung mit Personen
- ☒ Weiterverwendung des biologischen Materials oder der gesundheitsbezogenen Personendaten
- ☐ mit Verstorbenen
- ☐ mit Embryonen / Föten
- ☐ mit ionisierender Strahlung
- ☒ Das Forschungsprojekt ist eine Weiterverwendung biologischen Materials und gesundheitsbezogener Personendaten bei fehlender Einwilligung (Art. 34 HFG, Art. 37-40 HFV)

a. Zweck der Weiterverwendung:

Evaluation der Meldungen eines Multiagentensystems zur Detektion von Medikationsfehlern und Reduktion potentiell unerwünschter Arzneimittelereignisse.

b. Bezeichnung des biologischen Materials/der gesundheitsbezogenen Personendaten:

routinely collected clinical data from the clinical information system (KISIM) seit 01-01-2018 bis heute.

c. **Personen, die berechtigt sind biologisches Material und gesundheitsbezogenen Personendaten weiterzugeben:**

Alle behandelnde Ärzte des KSA

d. **Personen, die berechtigt sind biologisches Material und gesundheitsbezogene Personendaten entgegenzunehmen:**

Prof. Dr. Philipp Schütz
Kantonsspital Aarau
Haus 7
Tellstrasse 25
5001 Aarau

Entscheidverfahren

☐ ordentliches Verfahren ☐ vereinfachtes Verfahren ☒ Präsidialverfahren

Die Ethikkommission bestätigt, dass sie nach ICH-GCP arbeitet.

Gebühren

Betrag: **CHF** **Tarifcode:**

Gemäss der geltenden Gebührenordnung von swissethics.

Rechtsmittelbelehrung

1. Gegen diesen Entscheid kann innert einer nichterstreckbaren Frist von 30 Tagen seit Zustellung beim Regierungsrat des Kantons Aargau, Regierungsgebäude, 5001 Aarau, Beschwerde geführt werden. Es gelten keine Rechtsstillstandsfristen.
2. Die Beschwerdeschrift, die von der beschwerdeführenden Partei selbst oder einer von ihr bevollmächtigten Person zu verfassen ist, muss einen Antrag und eine Begründung enthalten, d.h., es ist a) anzugeben, wie der Regierungsrat entscheiden soll, und b) darzulegen, aus welchen Gründen diese andere Entscheidung verlangt wird.
3. Auf eine Beschwerde, welche den Anforderungen gemäss den Ziffern 1 und 2 nichtentspricht, wird nicht eingetreten.
4. Eine Kopie der angefochtenen Verfügung ist der unterzeichneten Beschwerdeschrift beizulegen. Allfällige Beweismittel sind zu bezeichnen und soweit möglich einzureichen.
5. Das Beschwerdeverfahren ist mit einem Kostenrisiko verbunden, d.h., die unterliegende Partei hat in der Regel die Verfahrenskosten sowie gegebenenfalls die gegnerischen Anwaltskosten zu bezahlen

Kopie an

☐ BAG

☐ Andere

Unterschrift

Prof. Dr. med. Christoph Beglinger
Präsident

Seite 2 / 4

Figure 12 Ethics approval

Table 5 ATC Nephrotoxic drugs

drug	ATC-Code
Amphotericin B	J02AA01
Ciclosporin	L04AD01
Tacrolimus	L04AD02
Vancomycin	J01XA01
Gentamicin	J01GB03
Tobramycin	J01GB01
Cidofovir	J05AB12
Aciclovir	J05AB01
Foscarnet	J05AD01
Ganciclovir	J05AB06
Adefovir	J05AF08
Quinine	M09AA* P01BC*
Bisphosphonates	M05BA* M05BB*
iodinated contrast media	V08A*
Digoxin	C01AA*
Aliskiren	C09XA02/53/52/54
Enoxaparin	B01AB05
Metformin	A10BA02, A10BD17/13/16/15/20/23/22/18/11/26/05/14/03/10/07/02/08/27/25
Lithium	N05AN01
Cisplatin	L01XA01
Carmustine	L01AD01
Semustine	L01AD03
Gemcitabine	L01BC05
Interferons	L03AB*
Methotrexate	L01BA01 L04AX03
Mitomycin	L01DC03

Table 6 ATC Creatinine falsifiers

drug	ATC-Code
Cobicistat	V03AX03 J05AR18 J05AR22 J05AR09
Trimethoprim and Sulfamethoxazole	J01EE01
Dolutegravir	J05AX12 J05AR21
Rilpivirin	J05AR08 J05AR19 J05AG05

Table 7 Hospital wards

hospital ward	included wards
internal medicine	general internal medicine, angiology, dermatology, endocrinology, gastroenterology, oncology, infectiology, cardiology, nephrology, pneumology and rheumatology
surgery	plastic surgery, vascular surgery, ophthalmic clinic, otolaryngology, neurosurgery and urology
neurology	neurology
orthopaedics	orthopaedics wards and traumatology
gynaecology	breast centre, obstetrics ward and gynaecology
emergency	emergency

Table 8 Translated statuses

grouped status	original status in German
intervention = message	• "Mitteilung: Akzeptiert und umgesetzt" • "Verlaufseintrag"
	• "Mitteilung: Nicht akzeptiert"
	• "Mitteilung: Erledigt" • "Mitteilung: Nicht bewertbar" • "Mitteilung: Verlauf unbekannt"
irrelevant	• "Pausiert für 15/30 Tage" • "Irrelevant" • "Falsch"
paused	• "Pausiert für 1/2/3/4/5/7/10 Tage"
patient dismissed	• "Schon ausgetreten"
termination by system	• "Problem schon gelöst"

The following standard improvements to the current prescription are recommended (Ger. 'Empfehlung'):

- *alert 1*: stop NSAIDs prescription
- *alert 2*: dose NSAIDs as reduced as possible and prescribe for as short as possible and/or check renal function regularly (2x weekly)
- *alert 3*: dose NSAIDs as reduced as feasible and prescribe for as short as possible and/or check renal function regularly (2x weekly)
- *alert 4*: check renal function regularly
- *alert 5*: n/a

Umfrage zum **Triple-Whammy-Agenten**

Datum	**Kürzel**	**Meldung**	**Intervention** (z.B. pausiert für _ Tage, Mitteilung)	**Begründung** (z.B. Medikament nicht verabreicht)

1

Figure 13 Survey pharmacists

INTERNAL GUIDELINE TO ASSESS TRIPLE WHAMMY ALERTS

- *alert 1*: Triple Whammy and GFR < 30 ml/min/1.73m^2
  - check the dynamic of the eGFR, necessarily check preceding laboratory data
  - check if a creatinine falsifier is newly prescribed to the patient
- *alert 2*: Triple Whammy and GFR between 30-60 ml/min/1.73m^2
  - check the dynamic of the eGFR, and necessarily check preceding laboratory data, especially if an NSAID is administered to the patient → if an apparent eGFR decline is seen, send an intervention to the physician
  - check if a creatinine falsifier is newly prescribed
- *alert 3*: Triple Whammy at age ≥ 75y
  - no advice available
- *alert 4*: no current creatinine value for Triple Whammy is available
  - no advice available
- *alert 5*: error in the calculation of dosage
  - no advice available

Interviewleitfaden

1 Einführung

Name Patient*in: _____ Geburtstdatum: _____

Patient*innen-ID: _____ Datum Meldung: _____

Name Ärzt*in: _____

Ausbildungsstand Ärzt*in: _____ Station: _____

Telefonnummer: _____

Guten Tag!
Mein Name ist Jana Schelshorn und ich schreibe aktuell im Rahmen des **KPHARM-Projektes** an meiner Masterarbeit. Meine Aufgabe ist es, den **«Triple Whammy»-Agenten** auszuwerten. Da Sie kürzlich eine 'Triple Whammy'-Meldung auf Ihrer Station hatten, würde ich Ihnen gerne einige Fragen dazu stellen. Haben Sie gerade circa 5 Minuten Zeit?

1.1. falls gerade keine Zeit

Datum + Zeitpunkt für Rückruf: _____

Telefonnummer für Rückruf: _____

2 Umfrage

Wussten Sie bereits vor der »Triple Whammy»-Stationsmitteilung im KISIM, dass mit «Triple Whammy» die Kombination aus einem NSAID, einem Diuretika und einem ACE-Inhibitor/Sartan gemeint ist?

- **ja**
- **nein**

Waren Sie sich vor der Stationsmitteilung bewusst, dass bei Frau / Herr _____ ein «Triple Whammy» verordnet war?

- **ja** → *welcher Faktor hat dazu geführt, dass Sie sich trotzdem für die «Triple Whammy»-Verordnung entschieden haben?*

_____

_____

- **nein** → *Wie schätzen Sie die «Triple Whammy»-Kombination bei Frau / Herr _____ ein?*

Erachten Sie die «Triple Whammy»-Stationsmeldung als sinnvoll?

- **ja**
- **nein** → *wären Sie an einem Austausch zur Verbesserung der Stationsmeldung interessiert?*

Werden Sie in Zukunft versuchen, eine «Triple Whammy»-Kombination zu vermeiden?

Haben Sie noch eine Bemerkung zu den KISIM-Stationsmitteilungen der klinischen Pharmazie? Gibt es z.B. einen Medikationshinweis, den Sie persönlich nützlich finden würden?

3 Schlussteil

Herzlichen Dank für Ihre Teilnahme!

4 Notizen

Figure 14 Interview clinicians

APPENDIX

SEARCH STRING PUBMED

((("angiotensin converting enzyme inhibit*"[MeSH Terms] OR ("angiotensin converting enzyme inhibit*"[Title/Abstract] OR "ace inhibit*"[Title/Abstract] OR "kininase ii inhibit*"[Title/Abstract] OR "angiotensin i converting enzyme inhibit*"[Title/Abstract] OR "dipeptidyl carboxypeptidase inhibit*"[Title/Abstract] OR "angiotensin receptor antagonist*"[Title/Abstract] OR "ACEI"[Title/Abstract] OR "renin angiotensin aldosterone system inhibit*"[Title/Abstract] OR "renin angiotensin aldosterone system antagonist*"[Title/Abstract] OR "RAASI"[Title/Abstract] OR "RAAS-I"[Title/Abstract]) OR "Perindopril"[MeSH Terms] OR "Lisinopril"[MeSH Terms] OR "Ramipril"[MeSH Terms] OR "Enalapril"[MeSH Terms] OR ("Perindopril"[Title/Abstract] OR "Lisinopril"[Title/Abstract] OR "Zestril"[Title/Abstract] OR "Prinivil"[Title/Abstract] OR "Ramipril"[Title/Abstract] OR "Enalapril"[Title/Abstract] OR "renite*"[Title/Abstract]) **OR** ("angiotensin ii type 1 receptor block*"[MeSH Terms] OR ("angiotensin ii type 1 receptor block*"[Title/Abstract] OR "angiotensin ii type 1 receptor antagonist*"[Title/Abstract] OR "angiotensin ii type i receptor block*"[Title/Abstract] OR "angiotensin ii type i receptor antagonist*"[Title/Abstract] OR "selective angiotensin ii receptor antagonist*"[Title/Abstract] OR "sartan*"[Title/Abstract] OR "at1 antagonist*"[Title/Abstract] OR "at1 block*"[Title/Abstract] OR "at1 receptor antagonist*"[Title/Abstract] OR "at1 receptor block*"[Title/Abstract] OR "ARB"[Title/Abstract] OR "ARBS"[Title/Abstract] OR "angiotensin receptor antagonist*"[Title/Abstract] OR "angiotensin receptor block*"[Title/Abstract] OR "A2A"[Title/Abstract]) OR "Valsartan"[MeSH Terms] OR "Losartan"[MeSH Terms] OR ("Valsartan"[Title/Abstract] OR "Diovan"[Title/Abstract] OR "Losartan"[Title/Abstract] OR "Cozaar"[Title/Abstract] OR "Cosaar"[Title/Abstract]))) **AND** ("anti inflammatory agents, non steroidal"[MeSH Terms] OR ("anti inflammatory agents non steroidal"[Title/Abstract] OR "nsaid*"[Title/Abstract] OR "NSAR"[Title/Abstract] OR "anti inflammatory analgesic*"[Title/Abstract] OR "antiinflammatory analgesic*"[Title/Abstract] OR "nonsteroidal antiinflammatory agent*"[Title/Abstract] OR "nonsteroidal antiinflammatory drug*"[Title/Abstract] OR "non steroidal antiinflammatory drug*"[Title/Abstract] OR "non steroidal anti inflammatory agent*"[Title/Abstract] OR "non steroidal anti inflammatory drug*"[Title/Abstract] OR "nonsteroidal anti inflammatory agent*"[Title/Abstract] OR "nonsteroidal anti inflammatory drug*"[Title/Abstract] OR "nonsteroidal anti inflammatory medication*"[Title/Abstract]) OR "Ibuprofen"[MeSH Terms] OR "Diclofenac"[MeSH Terms] OR "Indomethacin"[MeSH Terms] OR "Naproxen"[MeSH Terms] OR "cyclooxygenase inhibitor*"[MeSH Terms] OR ("Ibuprofen"[Title/Abstract] OR "Motrin"[Title/Abstract] OR "Rufen"[Title/Abstract] OR "Brufen"[Title/Abstract] OR "Advil"[Title/Abstract] OR "Diclofenac"[Title/Abstract] OR "Diclophenac"[Title/Abstract] OR "Voltarol"[Title/Abstract] OR "Voltaren"[Title/Abstract] OR "Indometacin"[Title/Abstract] OR "indomethacin*"[Title/Abstract] OR "Indocin"[Title/Abstract] OR "Naproxen"[Title/Abstract] OR "Naprosyn"[Title/Abstract] OR "cyclooxygenase inhibitor*"[Title/Abstract] OR "cyclo oxygenase inhibitor*"[Title/Abstract] OR "prostaglandin synthase inhibitor*"[Title/Abstract])) **AND** ("diuretic*"[MeSH Terms] OR "diuretic*"[Title/Abstract] OR "sodium chloride symporter inhibitor*"[MeSH Terms] OR "Chlorthalidone"[MeSH Terms] OR "Hydrochlorothiazide"[MeSH Terms] OR ("sodium chloride symporter inhibitor*"[Title/Abstract] OR "thiazide diuretic*"[Title/Abstract] OR "Chlorthalidone"[Title/Abstract] OR "Chlortalidone"[Title/Abstract] OR "Hygroton"[Title/Abstract] OR "Hydrochlorothiazide"[Title/Abstract] OR "HCTZ"[Title/Abstract] OR "Dihydrochlorothiazide"[Title/Abstract] OR "Esidrix"[Title/Abstract] OR "Esidrex"[Title/Abstract] OR "Hypothiazide"[Title/Abstract] OR "HCT"[Title/Abstract]) OR "diuretics, potassium sparing"[MeSH Terms] OR "Spironolactone"[MeSH Terms] OR "Amiloride"[MeSH Terms] OR ("diuretics potassium sparing"[Title/Abstract] OR "potassium sparing diuretic*"[Title/Abstract] OR "Spironolactone"[Title/Abstract] OR "Spirolactone"[Title/Abstract] OR "Aldactone"[Title/Abstract] OR "Amiloride"[Title/Abstract]) OR "sodium potassium chloride symporter inhibitor*"[MeSH Terms] OR "Furosemide"[MeSH Terms] OR ("sodium potassium chloride symporter inhibitor*"[Title/Abstract] OR "loop diuretic*"[Title/Abstract] OR "high ceiling diuretic*"[Title/Abstract] OR "Furosemide"[Title/Abstract] OR "Frusemide"[Title/Abstract] OR "Lasix"[Title/Abstract]))) **OR** (("triple"[All Fields] OR "triples"[All Fields]) AND "whamm*"[All Fields])

SEARCH STRING ELSEVIER

(('angiotensin converting enzyme inhibit*/exp OR ('angiotensin converting enzyme inhibit*':ti,ab OR 'ace inhibit*':ti,ab OR 'kininase ii inhibit*':ti,ab OR 'angiotensin i converting enzyme inhibit*':ti,ab OR 'dipeptidyl carboxypeptidase inhibit*':ti,ab OR 'angiotensin receptor antagonist*':ti,ab OR ACEI:ti,ab OR 'renin angiotensin aldosterone system inhibit*':ti,ab OR 'renin angiotensin aldosterone system antagonist*':ti,ab OR RAASI:ti,ab OR RAAS-I:ti,ab) OR Perindopril/exp OR Lisinopril/exp OR Ramipril/exp OR Enalapril/exp OR (Perindopril:ti,ab OR Lisinopril:ti,ab OR Zestril:ti,ab OR Prinivil:ti,ab OR Ramipril:ti,ab OR Enalapril:ti,ab OR renite*:ti,ab) OR ('angiotensin ii type 1 receptor block*/exp OR ('angiotensin ii type 1 receptor block*':ti,ab OR 'angiotensin ii type 1 receptor antagonist*':ti,ab OR 'angiotensin ii type i receptor block*':ti,ab OR 'angiotensin ii type i receptor antagonist*':ti,ab OR 'selective angiotensin ii receptor antagonist*':ti,ab OR sartan*:ti,ab OR 'at1 antagonist*':ti,ab OR 'at1 block*':ti,ab OR 'at1 receptor antagonist*':ti,ab OR 'at1 receptor block*':ti,ab OR ARB:ti,ab OR ARBS:ti,ab OR 'angiotensin receptor antagonist*':ti,ab OR 'angiotensin receptor block*':ti,ab OR A2A:ti,ab) OR Valsartan/exp OR Losartan/exp OR (Valsartan:ti,ab OR Diovan:ti,ab OR Losartan:ti,ab OR Cozaar:ti,ab OR Cosaar:ti,ab))) AND ('anti inflammatory agents, non steroidal'/exp OR ('anti inflammatory agents non steroidal':ti,ab OR nsaid*:ti,ab OR NSAR:ti,ab OR 'anti inflammatory analgesic*':ti,ab OR 'antiinflammatory analgesic*':ti,ab OR 'nonsteroidal antiinflammatory agent*':ti,ab OR 'nonsteroidal antiinflammatory drug*':ti,ab OR 'non steroidal antiinflammatory drug*':ti,ab OR 'non steroidal anti inflammatory agent*':ti,ab OR 'non steroidal anti inflammatory drug*':ti,ab OR 'nonsteroidal anti inflammatory agent*':ti,ab OR 'nonsteroidal anti inflammatory drug*':ti,ab OR 'nonsteroidal anti inflammatorymedication*':ti,ab) OR Ibuprofen/exp OR Diclofenac/exp OR Indomethacin/exp OR Naproxen/exp OR 'cyclooxygenase inhibitor*/exp OR (Ibuprofen:ti,ab OR Motrin:ti,ab OR Rufen:ti,ab OR Brufen:ti,ab OR Advil:ti,ab OR Diclofenac:ti,ab OR Diclophenac:ti,ab OR Voltarol:ti,ab OR Voltaren:ti,ab OR Indometacin:ti,ab OR indomethacin*:ti,ab OR Indocin:ti,ab OR Naproxen:ti,ab OR Naprosyn:ti,ab OR 'cyclooxygenase inhibitor*':ti,ab OR 'cyclo oxygenase inhibitor*':ti,ab OR 'prostaglandin synthase inhibitor*':ti,ab)) AND (diuretic*/exp OR diuretic*:ti,ab OR 'sodium chloride symporter inhibitor*/exp OR Chlorthalidone/exp OR Hydrochlorothiazide/exp OR ('sodium chloride symporter inhibitor*':ti,ab OR 'thiazide diuretic*':ti,ab OR Chlorthalidone:ti,ab OR Chlortalidone:ti,ab OR Hygroton:ti,ab OR Hydrochlorothiazide:ti,ab OR HCTZ:ti,ab OR Dihydrochlorothiazide:ti,ab OR Esidrix:ti,ab OR Esidrex:ti,ab OR Hypothiazide:ti,ab OR HCT:ti,ab) OR 'diuretics, potassium sparing'/exp OR Spironolactone/exp OR Amiloride/exp OR ('diuretics potassium sparing':ti,ab OR 'potassium sparing diuretic*':ti,ab OR Spironolactone:ti,ab OR Spirolactone:ti,ab OR Aldactone:ti,ab OR Amiloride:ti,ab) OR 'sodium potassium chloride symporter inhibitor*/exp OR Furosemide/exp OR ('sodium potassium chloride symporter inhibitor*':ti,ab OR 'loop diuretic*':ti,ab OR 'high ceiling diuretic*':ti,abOR Furosemide:ti,ab OR Frusemide:ti,ab OR Lasix:ti,ab))) OR ((triple OR triples) AND whamm*)

SEARCH STRING WEB OF SCIENCE

((("angiotensin converting enzyme inhibit*" OR ("angiotensin converting enzyme inhibit*" OR "ace inhibit*" OR "kininase ii inhibit*" OR "angiotensin i converting enzyme inhibit*" OR "dipeptidyl carboxypeptidase inhibit*" OR "angiotensin receptor antagonist*" OR ACEI OR "renin angiotensin aldosterone system inhibit*"OR "renin angiotensin aldosterone system antagonist*" OR RAASI OR RAAS-I) OR Perindopril OR Lisinopril OR Ramipril OR Enalapril OR (Perindopril OR LisinoprilOR Zestril OR Prinivil OR Ramipril OR Enalapril OR renite*) OR ("angiotensin ii type 1 receptor block*" OR ("angiotensin ii type 1 receptor block*" OR "angiotensin ii type 1 receptor antagonist*" OR "angiotensin ii type i receptor block*" OR "angiotensin ii type i receptor antagonist*" OR "selective angiotensin ii receptor antagonist*" OR sartan* OR "at1 antagonist*" OR "at1 block*" OR "at1 receptor antagonist*" OR "at1 receptor block*" OR ARB OR ARBS OR "angiotensin receptor antagonist*" OR "angiotensin receptor block*" OR A2A) OR Valsartan OR Losartan OR (Valsartan OR Diovan OR Losartan OR Cozaar OR Cosaar))) AND ("anti inflammatory agents, non steroidal" OR ("anti inflammatory agents non steroidal" OR nsaid* OR NSAR OR "anti inflammatory analgesic*" OR "antiinflammatory analgesic*" OR "nonsteroidal antiinflammatory agent*" OR "nonsteroidal antiinflammatory drug*" OR "non steroidal antiinflammatory drug*"OR "non steroidal anti inflammatory agent*" OR "non steroidal anti inflammatory drug*" OR "nonsteroidal anti inflammatory agent*" OR "nonsteroidal anti inflammatory drug*" OR "nonsteroidal anti inflammatory medication*") OR Ibuprofen OR Diclofenac OR Indomethacin OR Naproxen OR "cyclooxygenase inhibitor*" OR (Ibuprofen OR Motrin OR Rufen OR Brufen OR Advil OR Diclofenac OR Diclophenac OR Voltarol OR Voltaren OR Indometacin OR indomethacin* OR Indocin OR Naproxen OR Naprosyn OR "cyclooxygenase inhibitor*" OR "cyclo oxygenase inhibitor*" OR "prostaglandin synthase inhibitor*")) AND (diuretic* OR diuretic* OR "sodium chloride symporter inhibitor*" OR Chlorthalidone OR Hydrochlorothiazide OR ("sodium chloride symporter inhibitor*" OR "thiazide

diuretic*" OR Chlorthalidone OR Chlortalidone OR Hygroton OR Hydrochlorothiazide OR HCTZ OR Dihydrochlorothiazide OR Esidrix OR Esidrex OR HypothiazideOR HCT) OR "diuretics, potassium sparing" OR Spironolactone OR Amiloride OR ("diuretics potassium sparing" OR "potassium sparing diuretic*" OR Spironolactone OR Spirolactone OR Aldactone OR Amiloride) OR "sodium potassium chloride symporter inhibitor*" OR Furosemide OR ("sodium potassium chloride symporter inhibitor*" OR "loop diuretic*" OR "high ceiling diuretic*" OR Furosemide OR Frusemide OR Lasix))) OR ((triple OR triples) AND whamm*)

The following screening criteria for title/abstract screening were defined:

- *1 star*: no thematic overlap, mostly writings using 'Triple Whammy' in a different context such as economy or sewerage
- *2 stars*: different focus, meaning each Triple Whammy drug class included but focussing on another primary drug such as vancomycin, lithium or acetaminophen/paracetamol or covering another medical topic such as blood pressure, gout or Bartter-syndrome or different population such as newborns or animals
- *3 stars*: mainly reports discussing renal adverse effects but without focussing on the concomitant use of Triple Whammy or no abstract available
- *4 stars*: papers highlighting Triple Whammy prevalence, risk factors or pathomechanism
- *5 stars*: publications researching the prevention of AKI caused by Triple Whammy prescription using CDSSs or algorithms

Table 9 Included publications literature research

titel	author	population	intervention	comparison	outcome	notes
Safer prescription of drugs: impact of the PREFASEG system to aid clinical decision-making in primary care in Catalonia	**Pons-Mesquida**	primary care patients with Triple Whammy ≥ 75 years of age or undergoing treatment for diabetes (n = 46'020 in 2016; 73.860 in 2018)	prescription decision support system in an electronical clinical workstation	different time points (2016-2018)	acceptance rate among clinicians ranged from 22% (2018) to 30% (2016)	an alert is considered 'accepted' if medication is deprescribed
TRIPLE WHAMMY INTERACTION: IMPROVING PATIENTS' SAFETY	**Alzueta**	primary care patients with Triple Whammy (n = 1'699 patients)	deprescription proposal for candidates via clinical pharmacists directly to general practitioners	n/a	15% of proposals were evaluated by general pracitioners with an acceptance rate of 82%	candidates for intervention were found through an in-house developed software integrated in electronic clinical records
Data feedback and behavioural change intervention to improve primary care prescribing safety (EFIPPS): multicentre, three arm, cluster randomised controlled trial	**Guthrie**	primary care patients with Triple Whammy ≥ 65 years of age (n ≈ 15'500 patients per arm)	three different interventions: e-mailed educational material (arm 1), feedback on individual prescribing habit (arm 2) or feedback with behavioural change component (arm 3)	three-armed, randomised controlled trial	arm 1 is ineffective at changing practice arm 2 and 3 were both effective	patients with high risk prescriptions were found via datasets from electronic prescribing or electronic medical record data
Drug interactions detected by a computer-assisted prescription system in primary care patients in Spain: MULTIPAP study	**Rogero-Blanco**	primary care, multimorbid patients aged 65 to 74 years old (n = 593)	computer-assisted prescription system to identifiy drug interactions	n/a	Triple Whammy prescription is a prevalent drug-drug interaction (n = 15; 2.5%)	/

Table 10 Triple Whammy drug frequencies

Drug	ATC-Codes	amount	percentage
Non-Steroidal Anti-Inflammatory Drugs (total = 346)			
Ibuprofen	M01AE01	184	53.2%
Diclofenac	M01AB05	98	28.3%
Acemetacin	M01AB11	19	5.5%
Etodolac	M01AB08	11	3.2%
Celecoxib	M01AH01	11	3.2%
Naproxen	M01AE02/52	11	3.2%
Etoricoxib	M01AH05	8	2.3%
Mefenamic Acid	M01AG01	2	0.6%
Ketorolac	M01AB15	1	0.3%
Nimesulide	M01AX17	1	0.3%
Diuretics (total = 282)			
Torasemide	C03CA04	157	55.7%
Hydrochlorothiazide	C03AA03/EA01	46	16.3%
Furosemide	C03CA01	44	15.6%
Spironolactone	C03DA01	21	7.4%
Indapamide	C03BA11	9	3.2%
Metolazone	C03BA08	3	1.1%
Chlortalidone	C03BA04	2	0.7%
Angiotensin-Converting Enzyme Inhibitor or **Sartan** (total = 382)			
Perindopril	C09AA04/BA04/BX01	91	23.8%
Lisinopril	C09AA03/BA03	85	22.3%
Valsartan	C09DA03/DB01/CA03/DX01/DX04	64	16.8%
Candesartan	C09DA06/CA06	53	13.9%
Olmesartan	C09DA08/CA08/DB02/DX03	30	7.9%
Irbesartan	C09DA04/CA04	19	5%
Losartan	C09DA01/CA01	17	4.5%
Telmisartan	C09DA07/DB04	9	2.4%
Ramipril	C09AA05	9	2.4%
Azilsartan	C09CA09	3	0.8%
Enalapril	C09AA02/BB02	2	0.6%

Import

Libraries

In [1]:
```
import pandas as pd
import numpy as np
import os

import re
from datetime import datetime, timedelta

import matplotlib.pyplot as plt
import seaborn as sns
```

Load Data

General Consent

In [66]:
```
df_consent_original = pd.read_excel('U:/Ksamedarzt/KPHARM/Publications/Triple Whammy/Rohdaten/Generalkonsent 2020-2021.xlsx')
```

In [69]:
```
df_consent = df_consent_original.copy()
```

Verordnungen KISIM

In [4]:
```
path_verordnungen = 'U:/Ksamedarzt/KPHARM/Publications/Triple Whammy/Rohdaten/2021/Verordnungen'
```

In [5]:
```
files_verordnungen = os.listdir(path_verordnungen)
```

In [6]:
```
df_V_original = pd.concat((pd.read_csv((path_verordnungen + '/' + v), sep = ';') for v in files_verordnungen))
```

```
<ipython-input-6-a3e8de2f31b4>:1: DtypeWarning: Columns (0) have mixed types.Specify dtype option on import or set low_memory=F
alse.
  df_V_original = pd.concat((pd.read_csv((path_verordnungen + '/' + v), sep = ';') for v in files_verordnungen))
```

In [7]:
```
df_V = df_V_original.copy()
```

MAS-Meldungen

In [8]:
```
path_mas = 'U:/Ksamedarzt/KPHARM/Publications/Triple Whammy/Rohdaten/2021/MAS-Meldung'
files_mas = os.listdir(path_mas)
```

In [9]:
```
df_MAS_original = pd.concat((pd.read_csv((path_mas + '/' +m), sep = ';') for m in files_mas))
```

In [10]:
```
df_MAS = df_MAS_original.copy()
```

eGFR

In [11]:
```
path_gfr = 'U:/Ksamedarzt/KPHARM/Publications/Triple Whammy/Rohdaten/2021/GFR'
files_gfr = os.listdir(path_gfr)
```

In [12]:
```
df_gfr_original = pd.concat((pd.read_csv((path_gfr + '/' +f), sep = ';') for f in files_gfr))
```

In [13]:
```
df_gfr = df_gfr_original.copy()
```

Massnahmen

In [53]:
```
path_massnahmen = 'U:/Ksamedarzt/KPHARM/Publications/Triple Whammy/Rohdaten/2021/Massnahmen'
files_massnahmen = os.listdir(path_massnahmen)
```

In [54]:
```
df_mass_original = pd.concat((pd.read_csv((path_massnahmen + '/' + v), sep = ';') for v in files_massnahmen))
```

In [75]:
```
```

```
df_mass = df_mass_original.copy()
```

Clean Data

General Consent

In [71]:
```
# Entferne überflüssige Spalte
df_consent = df_consent.drop('Unnamed: 0', axis = 1)
```

In [72]:
```
# Formatiere Eintrittsdatum
df_consent.Eintrittsdatum = pd.to_datetime(df_consent.Eintrittsdatum, format='%d.%m.%Y', errors='raise')
```

In [73]:
```
# Formatiere Fallnummer
df_consent.Fallnummer = df_consent.Fallnummer.str.rstrip('FZ')
df_consent.Fallnummer = df_consent.Fallnummer.astype(int)
```

Entferne Pat ohne GC

In [20]:
```
# Funktion, die Patienten mit abgelehntem Generalkonsent ausschliesst
def general_consent(data):
    data2 = data.merge(df_consent, how = 'left', left_on = 'FALLNR', right_on = 'Fallnummer').drop_duplicates()
    data2 = data2[data2.Generalkonsent != 'Abgelehnt']
    return data2
```

Verordnungen KISIM

In [21]:
```
# Entferne Patienten mit abgelehntem Generalkonsent
df_V = general_consent(df_V)
```

In [22]:
```
# Entferne Duplikate
df_V = df_V.drop_duplicates()
```

In [23]:
```
# Entferne Testpatienten
df_V = df_V[df_V.PATNR.str.startswith('T', na= False) == False]
```

In [24]:
```
# Stelle sicher, dass Patnr und Fallnr Integere sind
df_V.PATNR = df_V.PATNR.astype(int)
df_V.FALLNR = df_V.FALLNR.astype(int)
```

In [25]:
```
# Entferne Verordnungen mit fehlenden ATCs
df_V = df_V[df_V.ATC.isnull() == False]
```

In [27]:
```
# Change to datetime
df_V['P_GEBDAT'] = pd.to_datetime(df_V['P_GEBDAT'], format='%Y-%m-%d %H:%M:%S', errors='coerce')
df_V['EINTRITT'] = pd.to_datetime(df_V['EINTRITT'], format='%Y-%m-%d %H:%M:%S', errors='coerce')
df_V['AUSTRITT'] = pd.to_datetime(df_V['AUSTRITT'], format='%Y-%m-%d %H:%M:%S', errors='coerce')
df_V['START_Verordnung'] = pd.to_datetime(df_V['START_Verordnung'], format='%Y-%m-%d %H:%M:%S', errors='coerce')
df_V['STOP_Verordnung'] = pd.to_datetime(df_V['STOP_Verordnung'], format='%Y-%m-%d %H:%M:%S', errors='coerce')
```

In [28]:
```
# Nur Patienten, die am 01.01.2021 über 18 waren
df_V = df_V[df_V.P_GEBDAT < pd.to_datetime('01.01.2003')]
```

In [29]:
```
# Ersetze immernoch fehlende Austrittsdaten mit 31.12.2021
df_V.AUSTRITT = df_V.AUSTRITT.fillna(pd.to_datetime('31.12.2021 23:59:59'))

# Entferne alle Austrittsdaten vor 01.01.2021
df_V = df_V[df_V['AUSTRITT'] > pd.to_datetime('31.12.2020')]

# Fehlendes Austrittsdatum
len(df_V[df_V.STOP_Verordnung.isnull()].PATNR.unique())

# Ersetze fehlende Stoppdaten von Verordnungen durch das Austrittsdatum für diese Fallnummer
df_V.STOP_Verordnung = df_V.STOP_Verordnung.fillna(df_V.AUSTRITT)
```

In [30]:
```
# Behalte nur relevante Spalten
df_V = df_V[['PATNR', 'FALLNR', 'P_GEBDAT', 'P_SEX', 'EINTRITT', 'AUSTRITT', 'KLINIK', 'ATC', 'Product',
             'O_ORDERTXT', 'UNIT','ApplCode', 'COMM', 'PRIORITY', 'START_Verordnung', 'STOP_Verordnung']]
```

MAS-Meldungen

In [32]:
```
# Entferne Patienten mit abgelehntem Generalkonsent
df_MAS = general_consent(df_MAS)
```

In [33]:
```
# Formatiere Datums-Angaben
df_MAS['Startdat'] = pd.to_datetime(df_MAS['Startdat'], format='%d.%m.%Y %H:%M:%S', errors='coerce')
df_MAS['SEENDAT'] = pd.to_datetime(df_MAS['SEENDAT'], format='%d.%m.%Y %H:%M:%S', errors='coerce')
df_MAS['DONEDAT'] = pd.to_datetime(df_MAS['DONEDAT'], format='%d.%m.%Y %H:%M', errors='coerce')
df_MAS['FallEinDat'] = pd.to_datetime(df_MAS['FallEinDat'], format='%d.%m.%Y %H:%M:%S', errors='coerce')
df_MAS['FallAusDat'] = pd.to_datetime(df_MAS['FallAusDat'], format='%d.%m.%Y %H:%M:%S', errors='coerce')
```

In [34]:
```
# Entferne überflüssige Spalten
df_MAS = df_MAS.drop(['STATUS', 'PATNAME', 'TIME'], axis = 1)
```

In [35]:
```
# Nimm nur Meldungen, die im Jahr 2021 generiert wurden
df_MAS = df_MAS[df_MAS.Startdat.dt.year == 2021]
```

eGFR

In [36]:
```
# Formatiere Datumsangaben
df_gfr['EINDAT'] = pd.to_datetime(df_gfr['EINDAT'], format='%d.%m.%Y %H:%M', errors='raise')
df_gfr['RESDAT'] = pd.to_datetime(df_gfr['RESDAT'], format='%d.%m.%Y %H:%M', errors='raise')
df_gfr['EINDAT_GFR'] = pd.to_datetime(df_gfr['EINDAT_GFR'], format='%d.%m.%Y %H:%M', errors='raise')
df_gfr['RESDAT_GFR'] = pd.to_datetime(df_gfr['RESDAT_GFR'], format='%d.%m.%Y %H:%M', errors='raise')
```

Clean GFR

In [37]:
```
# Ersetze nicht numerische String-values, so dass die Resultate in Floats umgewandelt werden können
# CAVE = >90 wurde durch 91 ersetzt
df_gfr.loc[df_gfr.RES_GFR == 'n.berechenb', 'RES_GFR'] = np.NaN
df_gfr.loc[df_gfr.RES_GFR == 'Infusion?', 'RES_GFR'] = np.NaN
df_gfr.loc[df_gfr.RES_GFR == 's.Text', 'RES_GFR'] = np.NaN
df_gfr.loc[df_gfr.RES_GFR == 's.u.', 'RES_GFR'] = np.NaN
df_gfr.loc[df_gfr.RES_GFR == 'z.w.Mat.', 'RES_GFR'] = np.NaN
df_gfr.loc[df_gfr.RES_GFR == 'folgt', 'RES_GFR'] = np.NaN
df_gfr.loc[df_gfr.RES_GFR == 'falsches Mat.', 'RES_GFR'] = np.NaN
df_gfr.loc[df_gfr.RES_GFR == 'kein Mat', 'RES_GFR'] = np.NaN
df_gfr.loc[df_gfr.RES_GFR == 'h□m.', 'RES_GFR'] = np.NaN

df_gfr.loc[df_gfr.RES_GFR == '>90', 'RES_GFR'] = 91
```

In [38]:
```
# Konvertiere GFR-Werte zu Float
df_gfr.RES_GFR = df_gfr.RES_GFR.astype(float)
```

Clean Kreatinin

In [39]:
```
# Remove missing values
df_gfr = df_gfr[df_gfr.RES_GFR.notna()]
```

In [40]:
```
# Ersetze das Sonderzeichen
df_gfr.RES = df_gfr.RES.str.replace("□","")
```

In [41]:
```
# Ersetze nicht numerische String-values, so dass die Resultate in Floats umgewandelt werden können
df_gfr.loc[df_gfr.RES == 'kein Mat', 'RES'] = np.NaN
df_gfr.loc[df_gfr.RES == 'z.w.Mat.', 'RES'] = np.NaN
df_gfr.loc[df_gfr.RES == 'Infusion?', 'RES'] = np.NaN
df_gfr.loc[df_gfr.RES == 'folgt', 'RES'] = np.NaN
df_gfr.loc[df_gfr.RES == 's.Text', 'RES'] = np.NaN
df_gfr.loc[df_gfr.RES == 's.u.', 'RES'] = np.NaN
df_gfr.loc[df_gfr.RES == 'hm.', 'RES'] = np.NaN
df_gfr.loc[df_gfr.RES == 'ikterisch', 'RES'] = np.NaN
df_gfr.loc[df_gfr.RES == 'falsches Mat.', 'RES'] = np.NaN

df_gfr.loc[df_gfr.RES == '<10', 'RES'] = 9
df_gfr.loc[df_gfr.RES == '<13', 'RES'] = 12
df_gfr.loc[df_gfr.RES == '<26', 'RES'] = 25
```

In [42]:
```
# Konvertiere Kreatinin-Werte zu Float
df_gfr.RES = df_gfr.RES.astype(float)
```

Massnahmen

In [77]:
```
# Entferne Patienten mit abgelehntem Generalkonsent
```

```
df_mass = general_consent(df_mass)
```

In [78]:
```
# Entferne Testpatienten
df_mass = df_mass[df_mass.PATNR.str.startswith('T', na= False) == False]
```

In [79]:
```
# Stelle sicher, dass Patnr und Fallnr Integere sind
df_mass.PATNR = df_mass.PATNR.astype(int)
df_mass.FALLNR = df_mass.FALLNR.astype(int)
```

In [80]:
```
# Nur stationäre Massnahmen
df_mass = df_mass[df_mass.FALLART == 'S']
```

In [81]:
```
# Entferne Massnahmen ohne ATC
df_mass = df_mass[df_mass.ATC.notna()]
```

In [82]:
```
# Formatiere Datumsangaben
df_mass['P_GEBDAT'] = pd.to_datetime(df_mass['P_GEBDAT'], format='%Y-%m-%d %H:%M:%S', errors='raise')
df_mass['START_Massnahme'] = pd.to_datetime(df_mass['START_Massnahme'], format='%Y-%m-%d %H:%M:%S', errors='raise')
df_mass['STOP_Massnahme'] = pd.to_datetime(df_mass['STOP_Massnahme'], format='%Y-%m-%d %H:%M:%S', errors='raise')
```

In [83]:
```
# Kürze das Geburtsdatum auf den Tag (ohne Uhrzeit)
df_mass.P_GEBDAT = df_mass.P_GEBDAT.apply(lambda x: x.date())
```

In [84]:
```
# Anzahl individueller Patienten mit Massnahmen in 2021
len(df_mass.PATNR.unique())
```

Out[84]: 21332

Auswertung MAS-Meldungen

Das finale Datenset des MAS soll neben den Informationen des Original-Datensets folgende weitere Angaben enthalten:

- Geschlecht
- Anzahl der Verordnungen, die zum Zeitpunkt der Meldung gültig waren
- letzte eGFR vor der Meldung (nicht älter als 7 Tage)
- letzte GFR vor Austritt

In [ ]:
```
# Macht eine Extraspalte, in der die Alertnr steht
alert = [re.search('(?<=\[).*?(?=\])', df_MAS.SUBJECT.iloc[x]).group() for x in range(len(df_MAS))]
df_MAS['Alert'] = alert
```

In [ ]:
```
# Kategorisiere die Statusmeldungen gemäss Janas Vorgaben
df_MAS.loc[df_MAS.Status.str.startswith('Mitteilung; Akzeptiert'), 'Status2'] = 11
df_MAS.loc[df_MAS.Status.str.startswith('Verlaufseintrag'), 'Status2'] = 11
df_MAS.loc[df_MAS.Status.str.startswith('Mitteilung; Nicht akzeptiert'), 'Status2'] = 12
df_MAS.loc[df_MAS.Status.str.startswith('Mitteilung; Nicht bewertbar'), 'Status2'] = 14
df_MAS.loc[df_MAS.Status.str.startswith('Mitteilung; Verlauf unbekannt'), 'Status2'] = 15
df_MAS.loc[(df_MAS.Status.str.startswith('Pausiert')) & (df_MAS.Status.str.contains('15')), 'Status2'] = 2
df_MAS.loc[df_MAS.Status.str.startswith('Falsch'), 'Status2'] = 2
df_MAS.loc[(df_MAS.Status.str.startswith('Pausiert')) & ~(df_MAS.Status.str.contains('15')), 'Status2'] = 3
df_MAS.loc[df_MAS.Status.str.startswith('Nicht relevant'), 'Status2'] = 2
df_MAS.loc[(df_MAS.Status.str.contains('Problem schon') & ~(df_MAS.Status.str.contains('Mitteilung'))), 'Status2'] = 5
df_MAS.loc[df_MAS.Status.str.startswith('Schon ausgetreten'), 'Status2'] = 4
```

Geschlecht

In [ ]:
```
# Füge Variable 'Geschlecht' hinzu
df_MAS = df_MAS.merge(df_V[['PATNR', 'P_SEX']], left_on='PATNR', right_on='PATNR', how='left').drop_duplicates()
```

Anzahl Verordnungen

Datenset mit allen Medis pro Meldung

In [ ]:
```
# Kombiniere Medis mit Vorordnungen
df_MAS_medi = df_MAS.merge(df_V, left_on='PATNR', right_on='PATNR', how='inner')

# Behalte nur relevante Spalten
df_MAS_medi = df_MAS_medi[['PATNR', 'FALLNR_x', 'SUBJECT', 'PRIORITY',
       'Startdat', 'ATC', 'Product', 'START_Verordnung', 'STOP_Verordnung']]

# Behalte nur Verordnungen, die zum Zeitpunkt des Alerts gültig waren
```

```
df_MAS_medi = df_MAS_medi.loc[(df_MAS_medi.Startdat >= df_MAS_medi.START_Verordnung) &
              (df_MAS_medi.Startdat <= df_MAS_medi.STOP_Verordnung)]
```

Wenn benötigt: Export to excel df_MAS_medi.to_excel("MAS_mit_medi2.xlsx")

Datenset mit Anzahl der Medis pro Meldung

In [ ]:
```
def anzahl_VO(mas, VO):
    '''Fügt dem MAS-Datenset eine Spalte hinzu, in der die Anzahl der gültigen Verordnungen
    zum Zeitpunkt der Meldung enthalten ist'''
    # Berücksichtige keine Reserve-Verordnungen
    VO = VO[VO.PRIORITY.isnull()]

    # Merge MAS-Meldungen und Verordnungen
    df_MAS_medi = mas.merge(VO, left_on='PATNR', right_on='PATNR', how='inner')

    # Selektiere nur Vorordnungen, die zum Zeitpunkt der Meldung gültig waren
    df_MAS_medi = df_MAS_medi.loc[(df_MAS_medi.Startdat >= df_MAS_medi.START_Verordnung) &
              (df_MAS_medi.Startdat <= df_MAS_medi.STOP_Verordnung)]

    # Zähle Anzahl Verordnungen pro Patient
    Anzahl_VO = pd.DataFrame(df_MAS_medi.groupby(['PATNR', 'Startdat']).size(), columns = ['Anzahl VO'])

    # Füge dies als Spalte dem Ausgangsdatenset hinzu
    df_MAS = mas.merge(Anzahl_VO, left_on=['PATNR', 'Startdat'], right_index=True,  how= 'left')

    return df_MAS
```

In [ ]:
```
def anzahl_VO2(mas, VO):
    '''Fügt dem MAS-Datenset eine Spalte hinzu, in der die Anzahl der gültigen Verordnungen
    zum Zeitpunkt der Meldung enthalten ist'''
    ## Mit Reserveverordnungen

    # Merge MAS-Meldungen und Verordnungen
    df_MAS_medi = mas.merge(VO, left_on='PATNR', right_on='PATNR', how='inner')

    # Selektiere nur Vorordnungen, die zum Zeitpunkt der Meldung gültig waren
    df_MAS_medi = df_MAS_medi.loc[(df_MAS_medi.Startdat >= df_MAS_medi.START_Verordnung) &
              (df_MAS_medi.Startdat <= df_MAS_medi.STOP_Verordnung)]

    # Zähle Anzahl Verordnungen pro Patient
    Anzahl_VO_Reserve = pd.DataFrame(df_MAS_medi.groupby(['PATNR', 'Startdat']).size(), columns = ['Anzahl VO Reserve'])

    # Füge dies als Spalte dem Ausgangsdatenset hinzu
    df_MAS = mas.merge(Anzahl_VO_Reserve, left_on=['PATNR', 'Startdat'], right_index=True,  how= 'left')

    return df_MAS
```

In [ ]:
```
# Anwendung der Formeln
df_MAS = anzahl_VO(df_MAS, df_V)
df_MAS = anzahl_VO2(df_MAS, df_V)
```

#df_MAS.to_excel("MAS_mit_alter.xlsx")

Nierenfunktion

eGFR vor Meldung

In [ ]:
```
def gfr_vor_Meldung(df_MAS, df_gfr):
    '''Fügt dem MAS-Datenset drei Spalten hinzu: Ergebnis und Datum der letzten Kreatinin/eGFR Messung vor der Meldung'''
    df_MAS_gfr = df_MAS.merge(df_gfr[['P_PATNR', 'RES', 'RES_GFR', 'EINDAT']],
                              how = 'left', left_on='PATNR', right_on='P_PATNR')
    df_MAS_gfr = df_MAS_gfr[['PATNR', 'Startdat', 'RES', 'RES_GFR', 'EINDAT']]

    index_meldung = df_MAS_gfr[df_MAS_gfr.Startdat > df_MAS_gfr.EINDAT].groupby(['PATNR', 'Startdat']).EINDAT.idxmax()
    df_MAS_gfr = df_MAS_gfr[df_MAS_gfr.index.isin(index_meldung)]

    df_MAS_gfr = df_MAS_gfr.rename(columns = {'RES' : 'Kreatinin_vor Meldung',
                                              'RES_GFR' : 'GFR_vor Meldung',
                                              'EINDAT' : 'EINDAT_Messung_vor Meldung'})
    df_MAS = df_MAS.merge(df_MAS_gfr, left_on=['PATNR', 'Startdat'], right_on= ['PATNR', 'Startdat'],  how= 'left')

    return df_MAS
```

In [ ]:
```
df_MAS2 = gfr_vor_Meldung(df_MAS, df_gfr)
```

eGFR Nadir

In [ ]:
```
def gfr_Nadir(df_MAS, df_gfr):
    '''Fügt dem MAS-Datenset dre Spalten hinzu: Ergebnis und Datum der tiefsten Kreatinin/eGFR Messung nach Meldung'''
    df_MAS_gfr = df_MAS.merge(df_gfr[['P_PATNR', 'RES', 'RES_GFR', 'EINDAT_GFR']],
                              how = 'left', left_on='PATNR', right_on='P_PATNR')
    df_MAS_gfr = df_MAS_gfr[['PATNR', 'Startdat', 'RES', 'RES_GFR', 'EINDAT_GFR', 'FallAusDat']]
```

```
    index_austritt = df_MAS_gfr[(df_MAS_gfr.FallAusDat > df_MAS_gfr.EINDAT_GFR) &
                                (df_MAS_gfr.Startdat < df_MAS_gfr.EINDAT_GFR)].groupby(['PATNR', 'Startdat']).RES_GFR.idxmin()
    df_MAS_gfr = df_MAS_gfr[df_MAS_gfr.index.isin(index_austritt)]

    df_MAS_gfr = df_MAS_gfr.rename(columns = {'RES' : 'Kreatinin_Nadir',
                                              'RES_GFR' : 'GFR_Nadir',
                                              'EINDAT_GFR' : 'EINDAT_Nadir'})
    df_MAS = df_MAS.merge(df_MAS_gfr, left_on=['PATNR', 'Startdat'], right_on= ['PATNR', 'Startdat'],  how= 'left')

    df_MAS = df_MAS.drop(['FallAusDat_y'], axis = 1)
    df_MAS = df_MAS.rename(columns = {'FallAusDat_x' : 'FallAusDat'})

    return df_MAS
```

In [ ]:
```
df_MAS3 = gfr_Nadir(df_MAS2, df_gfr)
```

AKI

In [ ]:
```
# Finde Zeitabstand zwischen beiden Kreatininwerten
df_MAS3['timediff'] = df_MAS3['EINDAT_Nadir'] - df_MAS3['EINDAT_Messung_vor Meldung']
```

In [ ]:
```
# Definiere AKI: Erhöhung des Kreatininwertes um Faktor 1.5 innert 7 Tagen
df_MAS3['AKI'] = ((df_MAS3['Kreatinin_Nadir'] > (df_MAS3['Kreatinin_vor Meldung'] * 1.5))
                  & (df_MAS3.timediff < timedelta(days = 7)))
```

Gesamt

In [ ]:
```
# Anzahl MAS Alerts in 2021
df_MAS.shape[0]
```

In [ ]:
```
# Anzahl individueller Patienten, welche 2021 mind. einen MAS-Alert erhielten
len(df_MAS3.PATNR.unique())
```

In [ ]:
```
# Datenset mit Alerts, bei denen anschliessend ein AKI auftrat
df_MAS4 = df_MAS3[df_MAS3.AKI == True]
```

#df_MAS3.to_excel("MAS_ergänzt2.xlsx") #df_MAS4.to_excel("MAS_ergänzt_AKI.xlsx")

Auswertung KISIM-Daten

Patienten, welche 2021 einen Triple Whammy erhielten

Schritt 1: Nur Patienten, welche NSAID, RASI und Diuretika erhielten (unabhängig vom Zeitpunkt)

Patienten mit NSAID

ATC-Codes: M01*, exclusive M01AX25, M01AX99

In [ ]:
```
def pat_with_nsaid(df):
    df_V_nsaid = df[df.ATC.str.startswith('M01')]
    df_V_nsaid = df_V_nsaid[df_V_nsaid.ATC.isin(['M01AX25', 'M01AX99']) == False]

    pat_nsaid = df_V_nsaid.PATNR.unique()

    df = df[df.PATNR.isin(pat_nsaid)]
    return df
```

In [ ]:
```
df_tw = pat_with_nsaid(df_mass)
```

Patienten mit ACEI/Sartan

In [ ]:
```
def pat_with_ras(df):
    df_V_ras = df[df.ATC.str.startswith('C09')]

    pat_ras = df_V_ras.PATNR.unique()

    df = df[df.PATNR.isin(pat_ras)]
    return df
```

In [ ]:
```
df_tw = pat_with_ras(df_tw)
```

Patienten mit Diuretikum

In [ ]:
```python
def pat_with_diu(df):
    df_V_diu = df[df.ATC.str.startswith(('C03','C09BA', 'C09DA', 'C09BX01', 'C09DX'))]

    pat_diu = df_V_diu.PATNR.unique()

    df = df[df.PATNR.isin(pat_diu)]
    return df
```

In [ ]:
```python
df_tw = pat_with_diu(df_tw)
```

In [ ]:
```python
# Anzahl Patienten, welche NSAID, RAS-Inhibitoren und Diuretika erhalten haben (ohne zeitlichen Zusammenhang)
len(df_tw.PATNR.unique())
```

Schritt 2: Patienten, welche NSAID/RASI und Diuretika am gleichen Tag erhielten (= Triple Whammy)

Neues Datenset mit Tag als Spalte

In [ ]:
```python
year2021 = pd.date_range(start="2021-01-01",end="2021-12-31").to_pydatetime()

df_tw2 = pd.DataFrame(np.repeat(df_tw.PATNR.unique(), 365), np.tile(year2021, len(df_tw.PATNR.unique())))
df_tw2 = df_tw2.reset_index()
df_tw2.columns = ['Day', 'PATNR']
```

Wurden an diesem Tag NSAID/RAS/Diuretika gegeben?

In [ ]:
```python
def medi_daybyday(tw_test, tw_test2):
    '''Definiere Spalten: gültige VO an diesem Tag'''
    # NSAID
    nsaid_by_day = []
    nsaid = tw_test[tw_test.ATC.str.startswith('M01')]
    nsaid = nsaid[nsaid.ATC.isin(['M01AX25', 'M01AX99']) == False]
    for n in range(tw_test2.shape[0]):
        nsaid_day = nsaid.loc[(nsaid.START_Massnahme.apply(lambda x: x.date()) <= tw_test2['Day'][n])
                              & (nsaid.STOP_Massnahme.apply(lambda x: x.date()) >= tw_test2['Day'][n])]
        nsaid_by_day.append((nsaid_day.shape[0] > 0))

    nsaid_by_day = pd.DataFrame(nsaid_by_day)
    nsaid_by_day.columns = ['NSAID']

    tw_test2 = tw_test2.join(nsaid_by_day)

    # ACE/Sartane
    ras_by_day = []
    ras = tw_test[tw_test.ATC.str.startswith('C09')]
    for n in range(tw_test2.shape[0]):
        ras_day = ras.loc[(ras.START_Massnahme.apply(lambda x: x.date()) <= tw_test2['Day'][n])
                              & (ras.STOP_Massnahme.apply(lambda x: x.date()) >= tw_test2['Day'][n])]
        ras_by_day.append((ras_day.shape[0] > 0))

    ras_by_day = pd.DataFrame(ras_by_day)
    ras_by_day.columns = ['RAS']

    tw_test2 = tw_test2.join(ras_by_day)

     # Diuretika
    diu_by_day = []
    diu = tw_test[tw_test.ATC.str.startswith(('C03','C09BA', 'C09DA', 'C09BX01', 'C09DX'))]
    for n in range(tw_test2.shape[0]):
        diu_day = diu.loc[(diu.START_Massnahme.apply(lambda x: x.date()) <= tw_test2['Day'][n])
                              & (diu.STOP_Massnahme.apply(lambda x: x.date()) >= tw_test2['Day'][n])]
        diu_by_day.append((diu_day.shape[0] > 0))

    diu_by_day = pd.DataFrame(diu_by_day)
    diu_by_day.columns = ['Diuretika']

    tw_test2 = tw_test2.join(diu_by_day)

    return tw_test2
```

In [ ]:
```python
# For-Loop für jede PATNR

df_tw3 = pd.DataFrame()

for P in df_tw2.PATNR.unique():
    tw_test = df_tw[df_tw.PATNR == P].reset_index(drop=True)
    tw_test2 = df_tw2[df_tw2.PATNR == P].reset_index(drop=True)

    df_tw3 = df_tw3.append(medi_daybyday(tw_test, tw_test2))
```

In [ ]:
```python
# reset if necessary
df_nach_loop = df_tw3.copy()
#df_tw3 = df_nach_loop
```

In [ ]:
```
# Finde Triple Whammy
df_tw3['Triple Whammy'] = (df_tw3[['NSAID', 'RAS', 'Diuretika']].sum(axis = 1) == 3)

# Entferne Columns zu besseren Übersichtlichkeit: NSAID, RAS, Diuretika
df_tw3 = df_tw3.drop(['NSAID', 'RAS', 'Diuretika'], axis = 1)

# Behalte nur Triple Whammy
df_tw3 = df_tw3[df_tw3['Triple Whammy'] == True]
```

In [ ]:
```
# Anzahl individueller Patienten mit Triple Whammy
len(df_tw3.PATNR.unique())
```

Weitere Parameter

Alter

In [ ]:
```
def calculate_age(Day, P_GEBDAT):
    age = ((Day.year - P_GEBDAT.year) - ((Day.month, Day.day) < (P_GEBDAT.month, P_GEBDAT.day)))
    return age
```

In [ ]:
```
def age_daybyday(tw_final2):
    test_age = tw_final2.merge(df_V[['PATNR', 'P_GEBDAT']], how = 'left').drop_duplicates()
    test_age['Day'] = pd.to_datetime(test_age['Day'], format='%Y-%m-%d', errors='raise')

    test_age['Alter'] = test_age.apply(lambda x: calculate_age(x['Day'],x['P_GEBDAT']),axis=1)

    test_age = test_age.drop('P_GEBDAT', axis = 1)
    return test_age
```

In [ ]:
```
# Berechne das Alter zum Zeitpunkt der Massnahme
df_tw3 = age_daybyday(df_tw3)
```

Nierenfunktion

In [ ]:
```
# Neues Datenset, um Nierenfunktion zu ergänzen
df_krea = df_tw3.copy()
```

In [ ]:
```
def krea_daybyday_pre(data):
    '''Fügt die Spalten RES zum Dataframe hinzu: Zeigt Wert des letzten Kreatinin-Wertes an,
    wenn leer, gab es keinen Wert in den letzten 7 Tagen'''
    test_gfr = data.merge(df_gfr[['P_PATNR', 'RES', 'RES_GFR', 'EINDAT_GFR']],
                          how = 'left', left_on='PATNR', right_on='P_PATNR').drop_duplicates()
    test_gfr = test_gfr[(test_gfr.Day >= test_gfr.EINDAT_GFR.dt.date)
                        & ((test_gfr.Day - timedelta(days = 7)) < test_gfr.EINDAT_GFR.dt.date)]

    test_gfr = test_gfr.loc[test_gfr.groupby(['PATNR', 'Day'])['EINDAT_GFR'].idxmax()]
    test_gfr = test_gfr.rename(columns = {'RES' : 'Krea_pre_TW',
                                          'RES_GFR' : 'GFR_pre_TW',
                                          'EINDAT_GFR' : 'Blutentnahme_pre_TW'})
    test_gfr = test_gfr.drop('P_PATNR', axis = 1)
    return test_gfr
```

In [ ]:
```
def krea_daybyday_post(data):
    '''Fügt die Spalte RES_GFR zum Dataframe hinzu: Zeigt Wert der letzten eGFR an,
    wenn leer, gab es keinen Wert in den letzten 7 Tagen'''
    test_gfr = data.merge(df_gfr[['P_PATNR', 'RES', 'RES_GFR', 'EINDAT_GFR']],
                          how = 'left', left_on='PATNR', right_on='P_PATNR').drop_duplicates()
    test_gfr = test_gfr[(test_gfr.Day < test_gfr.EINDAT_GFR.dt.date)
                        & ((test_gfr.Day + timedelta(days = 15)) > test_gfr.EINDAT_GFR.dt.date)]

    test_gfr = test_gfr.loc[test_gfr.groupby(['PATNR', 'Day'])['RES'].idxmax()]
    test_gfr = test_gfr.rename(columns = {'RES' : 'Krea_nadir',
                                          'RES_GFR' : 'GFR_nadir',
                                          'EINDAT_GFR' : 'Blutentnahme_nadir'})
    test_gfr = test_gfr.drop('P_PATNR', axis = 1)
    return test_gfr
```

In [ ]:
```
# Anwendung der Funktionen und Merge
tw_krea2 = df_krea.merge(krea_daybyday_pre(df_krea), how = 'left')

tw_krea3 = krea_daybyday_post(tw_krea2)

tw_krea4 = tw_krea2.merge(tw_krea3[['Day', 'PATNR', 'Krea_nadir', 'GFR_nadir', 'Blutentnahme_nadir']],
                          how = 'left', left_on=['PATNR', 'Day'], right_on=['PATNR', 'Day'])
```

AKI

In [ ]:
```
# Finde Zeitabstand zwischen beiden Kreatininwerten
tw_krea4['Zeitdiff'] = tw_krea4['Blutentnahme_nadir'] - tw_krea4['Blutentnahme_pre_TW']
```

In [ ]:
```
# Definiere AKI: Erhöhung des Kreatininwertes um Faktor 1.5 innert 7 Tagen
tw_krea4['AKI'] = (tw_krea4['Krea_nadir'] >= (tw_krea4['Krea_pre_TW'] * 1.5)) & (tw_krea4.Zeitdiff < timedelta(days = 7))
```

MAS

In [ ]:
```
# Gab es für den Patienten eine MAS-Meldung?
# CAVE: Die zeitliche Abhängigkeit wird nicht berücksichtigt.
tw_krea4['MAS'] = tw_krea4.PATNR.isin(df_MAS3.PATNR)
```

Simuliere MAS-Meldungen

In [ ]:
```
tw_final = tw_krea4.copy()
```

Meldung 1: Triple Whammy und eGFR < 30

In [ ]:
```
tw_final['Meldung 1'] = (tw_final['GFR_pre_TW'] < 30)
```

Meldung 2: Triple Whammy und eGFR 30-60

In [ ]:
```
tw_final['Meldung 2'] = ((tw_final['GFR_pre_TW'] >= 30) & (tw_final['GFR_pre_TW'] < 61))
```

Meldung 3: Triple Whammy und Alter > 75

In [ ]:
```
tw_final['Meldung 3'] = (tw_final['Alter'] > 75) & (tw_final['GFR_pre_TW'] > 60)
```

Meldung 4: Kein aktueller Kreatininwert bei Triple Whammy

In [ ]:
```
tw_final['Meldung 4'] = ((tw_final['GFR_pre_TW'].isnull() & (tw_final['Alter'] > 75))
                         | (tw_final['GFR_pre_TW'].isnull() & (tw_final['GFR_pre_TW'] < 61)))
```

Gesamt

Es gibt 3 Finale Datensätze:

tw_final = Alle Patiententage mit Triple Whammy
tw_final2 = Jeweils der erste Tag mit Triple Whammy pro Patient
tw_final3 = Nur Patienten mit Risikofaktoren

Alle Patiententage mit Triple Whammy

In [ ]:
```
# Anzahl Patiententage
tw_final.shape[0]
```

In [ ]:
```
# Anzahl individueller Patienten
len(tw_final.PATNR.unique())
```

Jeweils der erste Tag mit Triple Whammy pro Patient

In [ ]:
```
# Select only first occurance of Triple Whammy
tw_final2 = tw_final.loc[tw_final.groupby("PATNR")["Day"].idxmin()]
```

In [ ]:
```
# Sind alle MAS-Patienten auch im KISIM-Datenset?
# --> Nein, 79 der 216 Patienten sind nicht im TW-Datenset (Grund können Verordnungen sein, die nicht ausgeführt wurden)
len(df_MAS3[df_MAS3.PATNR.isin(tw_final2.PATNR.unique()) == False].PATNR.unique())
```

Nur Patienten mit Risikofaktoren

In [ ]:
```
# Nur Patienten mit Risikofaktoren gemäss Simulation MAS-Agent
tw_final3 = tw_final2[tw_final2[['Meldung 1', 'Meldung 2', 'Meldung 3', 'Meldung 4']].sum(axis = 1) >= 1]
```

In [ ]:
```
# Anzahl Patienten, die einen Triple Whammy erhielten und Risikofaktoren hatten
len(tw_final3.PATNR.unique())
```

In [ ]:
```
# Wie viele Patienten, die gemäss Algorithmus einen Alert bekommen hätten, haben auch tatsächlich einen bekommen?
# 101 von 120 --> möglicher Grund: Dosis von NSAID wird im Python Algorithmus nicht berücksichtigt
tw_final3.MAS.value_counts()
```

In [ ]:
```
# Potentielle Meldungen, die das MAS verpasst hat (falsch negativ)
tw_final3[tw_final3.MAS == False][['Meldung 1', 'Meldung 2', 'Meldung 3', 'Meldung 4']].sum()
```

In [ ]:
```
# Export to excel
save_file = 'Analyse_Massnahmen2021_TW_final_16062022.xlsx'

with pd.ExcelWriter(save_file) as writer:
    tw_final.to_excel(writer, sheet_name='Alle Patiententage')
    tw_final2.to_excel(writer, sheet_name='Erster Tag mit Triple Whammy')
    tw_final3.to_excel(writer, sheet_name='Nur Pat mit Risikofaktoren')
```

Figure 15 Python script

Erklärung

gemäss Art. 30 RSL Phil.-nat. 18

Name/Vorname:	Schelshorn, Jana Sophie
Matrikelnummer:	17-100-215
Studiengang:	Pharmazie
	Bachelor ☐ Master ☑ Dissertation ☐
Titel der Arbeit:	Evaluation of a drug therapy safety algorithm for the detection of Triple Whammy prescriptions in inpatients at risk of acute kidney injury
LeiterIn der Arbeit:	Dr. phil. II Carla Meyer-Massetti

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24. Juni. 2022, Aarau

Ort/Datum

Unterschrift