Aus der Medizinischen Klinik mit Schwerpunkt Rheumatologie und
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DISSERTATION

Die Sicherheit der Therapie mit Biologika bei rheumatoider Arthritis

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Abkürzungen

EMA	European Medicine Agency
bDMARD	Biologic Disease-Modifying Anti-Rheumatic Drug
BSG	Blutsenkungsgeschwindigkeit
CRP	C-reaktives Protein
csDMARD	Conventional synthetic Disease-Modifying Anti-Rheumatic Drug
DAS28	Disease-activity-score basierend auf 28 Gelenken
DMARD	Disease-Modifying Anti-Rheumatic Drug
GI	Gastrointestinal
HR	Hazard ratio
IR	Inzidenzrate
KHK	koronare Herzerkrankungen
KI	Konfidenzintervall
MedDRA	Medical Dictionary for Regulatory Activities
NSAR	Nicht-steroidales Antirheumatikum
OR	Odds ratio
PJ	Patientenjahre
RA	Rheumatoide Arthritis
RABBIT	Rheumatoide Arthritis: Beobachtung der Biologika Therapie
RCT	Randomised controlled trial
SUE	Schwerwiegendes unerwünschtes Ereignis
TIA	Transitorische ischämische Attacke
TNF	Tumornekrosefaktor alpha
TNFi	Tumornekrosefaktor alpha Inhibitor
UE	Unerwünschtes Ereignis

Zusammenfassung / Abstract

Einleitung: Für die Abschätzung von Arzneimittelrisiken im klinischen Alltag bedarf es Langzeitbeobachtungsstudien, die Patienten in der ärztlichen Routineversorgung einschließen und regelmäßig beobachten. Im Rahmen der Untersuchung der Langzeitsicherheit von Biologika bei Patienten mit rheumatoider Arthritis (RA) wurden (1) selten auftretende Ereignisse am Beispiel von unteren Darmperforationen sowie das Risiko für Ereignisse mit einer langen Latenzzeit am Beispiel von (2) Myokardinfarkt und (3) nicht-hämorrhagischem Schlaganfall untersucht. **Methodik:** Die Analysen basieren auf Daten des deutschen Biologika-Registers RABBIT, das seit 2001 RA-Patienten mit Beginn einer neuen DMARD-Therapie einschließt. Alle Untersuchungen umfassten eingehende Fallvalidierungen und die Bestimmung von Risikofaktoren sowie die Analyse des Einflusses der medikamentösen Therapie. Zusätzlich wurden Inzidenzraten (IR) bestimmt (1+3). Die Arbeiten (2) und (3) basieren auf eingebetteten Fall-Kontroll-Studien: Zu jedem Fallpatienten mit einem Ereignis wurde(n) eine (Arbeit 2) bzw. zwei (Arbeit 3) Kontrolle(n) gematcht, die in Geschlecht, Alter und Komorbiditäten sowie dem Raucherstatus (nur 3) übereinstimmten. **Ergebnisse:** (1) Bei 13.310 Patienten traten insgesamt 37 untere Darmperforationen auf. Mit 2,7/1.000 Patientenjahre (PJ) lag die rohe IR bei Patienten unter Tocilizumab-Therapie höher als unter allen anderen Therapien (0,2-0,6/1.000 PJ). Als Risikofaktoren für Perforation des unteren Darmtraktes stellten sich höheres Alter sowie die Therapie mit Glukokortikoiden, nicht-steroidalen Antirheumatika und Tocilizumab heraus. (2) Von 11.285 RA-Patienten entwickelten 112 einen Myokardinfarkt während der Beobachtungszeit, 105 davon konnten zu einer Kontrolle gematcht werden. Höhere CRP-Werte und Rauchen wurden als Risikofaktoren für Myokardinfarkt identifiziert. (3) In der Beobachtungszeit erlitten 166 Patienten einen Schlaganfall. Die IR lag bei 3,2/1.000 PJ. Andere schwerwiegende Ereignisse (SUE) im Vorfeld des Schlaganfalls erhöhten die IR auf 9,0/1.000 PJ, insbesondere in den ersten 30 Tagen nach dem Ereignis (IR 94,9/1.000 PJ). 163 Schlaganfall-Patienten wurden zu jeweils zwei Kontrollen gematcht. Hier zeigten sich unbehandelte kardiovaskuläre Begleiterkrankungen und schwerwiegende Infektionen bzw. andere SUEs als Risikofaktoren. Für die DMARD-Therapien konnte kein Einfluss auf die Outcomes in den Arbeiten (2) und (3) gezeigt werden. **Schlussfolgerung:** (1) Perforationen des unteren Darmtraktes treten bei RA-Patienten unter Tocilizumab häufiger auf als unter anderen Therapien. Ein besonderes Augenmerk sollte auf die mögliche untypische Symptomatik beim Auftreten der Perforation unter Tocilizumab gelegt werden. (2+3) Nicht therapierte kardiovaskuläre Begleiterkrankungen erhöhen das Risiko für Myokardinfarkt und Schlaganfall. Die Art der DMARD-Therapie scheint dagegen keinen

Einfluss auf das Ereignis zu haben, solange die Krankheitsaktivität der Patienten ausreichend kontrolliert ist. Mit diesen Arbeiten wurde gezeigt, dass Langzeitkohorten einen anderen Fokus haben als klinische Studien und für die detaillierte Bestimmung von Arzneimittelrisiken im täglichen Gebrauch unabdingbar sind.

Introduction: Long-term observational studies that enrol patients in daily medical care are important for the evaluation of the safety of authorized medicines. To estimate the long-term safety of bDMARDs in patients with rheumatoid arthritis (RA) this work analysed (1) a rare outcome using the example of lower intestinal perforations (LIP), and outcomes with a long latency, especially (2) myocardial infarction (MI) and (3) non-haemorrhagic stroke. **Methods:** Data of the German biologics register RABBIT were used. Since 2001 the observa-tional cohort enrols patients at the time of treatment start with a new DMARD. For all analyses, case reports were thoroughly validated, and risk factors as well as the influence of drug treatment evaluated. Additionally, incidence rates (IR) were calculated (1+3). In parts (2) and (3), risk factors were investigated using a nested case-control study. Each case with an event was matched to one (part 2) or two (part 3) control(s) with identical baseline risk profile defined by gender, age, selected comorbidities and smoking habits (only 3). **Results:** (1) In total, 37 LIPs were observed in 13,310 patients. Crude IR was substantially increased in tocilizumab treated patients (2.7/1,000 PYs) compared to all other treatments (0.2-0.6/1,000 PYs). The adjusted model showed a significant association of tocilizumab with the risk for LIPs. Other risk factors were increased age and co-medication with glucocorticoids and non-steroidal anti-inflammatory drugs. (2) 112 MIs were reported in 11,285 patients. Of those, 105 were 1:1 matched to control patients. As risk factors for MI, elevated CRP levels and smoking were identified. (3) During follow-up, 166 strokes were reported. The overall IR was 3.2/1,000 PY. The IR was higher after a serious adverse event (9.0/1,000), particularly within 30 days after the event (94.9/1,000). 163 patients with stroke were 1:2 matched to controls. Major risk factors were untreated cardiovascular comorbidity and serious infections or other serious events. DMARD treatment did not have an influence on the outcome in (2) and (3). **Conclusions:** (1) LIPs were more often reported under tocilizumab treatment than under all other observed treatments. Physicians and patients should be aware that LIP may occur with mild symptoms only and without CRP elevation. (2+3) Untreated cardiovascular comorbidities increased the risk for MI and stroke in patients with RA. It seems irrelevant with which class of DMARD effective control of disease activity is achieved. This work showed that long-term observational studies focus on other issues than clinical trials. They are essentially important to determine drug safety in daily medical care.

1. Einführung

Zum Zeitpunkt der Zulassung eines Arzneimittels ist das Wissen über sein Sicherheitsprofil nicht vollständig. Im Rahmen klinischer Studien (randomised controlled trial, RCT) werden unerwünschte Ereignisse (UEs) zwar erfasst und ausgewertet. Jedoch sind Aussagen zur Langzeitsicherheit, zur Inzidenz seltener Ereignisse oder zu Wechselwirkungen kaum möglich. Dies ist der spezifischen Patientenselektion, der begrenzten Anzahl der Probanden und der relativ kurzen Laufzeit solcher Studien geschuldet. Um diese Lücke zu schließen, bedarf es der Pharmakovigilanz, also der Überwachung von Arzneimitteln auch nach deren Zulassung und Markteinführung. Im Spontanmeldesystem werden aufgetretene UEs durch Heilberufler erfasst und gemeldet. Eine zentrale Sammlung aller UEs ermöglicht die Erkennung von Sicherheitssignalen für einzelne Arzneimittel auf Basis einer großen Population. Zusammenhänge mit Krankheitsfaktoren, Komorbiditäten oder Komedikationen können jedoch nicht oder nur bedingt erkannt werden. Hierfür dienen Studien, die Patienten in der Routineversorgung einschließen und in Alltagsbedingungen über lange Zeiträume beobachten. Diese Langzeitkohorten sind wichtig, um das Nutzen-Risiko-Verhältnis neu zugelassener Arzneimittel in der klinischen Praxis zu bestimmen. Ein wesentlicher Vorteil dieser Studien ist die Möglichkeit, seltene Risiken, Outcomes mit langer Latenzzeit und Risikogruppen wie Schwangere und ältere oder multimorbide Patienten untersuchen zu können. Zudem können Krankheitscharakteristika beziehungsweise sich zeitlich verändernde Risiken bei der Analyse berücksichtigt werden.

Eine solche Langzeitbeobachtungskohorte ist das deutsche Biologika-Register RABBIT (***R**heumatoide **A**rthritis – **B**eobachtung der **Bi**ologika-**T**herapie*), gestartet im Jahr 2001 mit der Markteinführung der ersten Biologika (biologic disease modifying drug (bDMARD)) zur Therapie der rheumatoiden Arthritis (RA). RABBIT hat zum Ziel, die Langzeitwirksamkeit und –sicherheit von Biologika im Vergleich zu konventionellen synthetischen (cs)DMARDs zu untersuchen. Biologika sind biotechnologisch hergestellte Substanzen, die gezielt in das Immunsystem eingreifen. Dort binden und hemmen sie beispielsweise das Zytokin Tumornekrosefaktor alpha (TNF), das eine wichtige Rolle im Entzündungsprozess der RA spielt. Weitere Wirkprinzipien der Biologika für die RA-Therapie umfassen die Inhibition von Interleukin-6 Rezeptoren, die Depletion CD20-positiver B-Zellen und die Suppression der T-Zell-Costimulation.

Die vorliegende Zusammenfassung basiert auf Daten der RABBIT-Kohorte. In der ersten Arbeit wurde ein sehr seltenes Ereignis untersucht. Die anderen beiden Arbeiten befassten sich mit Endpunkten, die eine lange Latenzzeit haben können.

1.1 Risiko für Perforationen des unteren Darmtraktes

Perforationen des unteren gastrointestinalen (GI) Traktes sind selten. Veränderungen der Darmwandstruktur, ausgelöst durch Entzündungen oder Divertikulosen, aber auch durch Arzneimittel wie Glukokortikoide und nicht-steroidale Antirheumatika (NSAR), können Perforationen zur Folge haben (1-3). Zudem erhöhen Glukokortikoide und NSARs das Perforationsrisiko bestehender Divertikulosen (4, 5). Patienten mit RA erleiden häufiger Darmperforationen im Vergleich zur Allgemeinbevölkerung (6). Vor der Markteinführung der Biologika zählten Perforationen des oberen Darmtraktes zu den häufigsten Todesursachen, vor allem im Zusammenhang mit der Einnahme von Glukokortikoiden und NSAR (7-9). Methotrexat und TNF-Inhibitoren (TNFi) scheinen das Risiko nicht zu erhöhen (7). Durch die vor der Zulassung durchgeführten RCTs des Interleukin-6-Inhibitors Tocilizumab gab es dagegen Hinweise, dass das Risiko für Perforationen des unteren Darmtraktes unter dem Medikament erhöht sein könnte, da in den mit dem Biologikum behandelten Gruppen Perforationen beobachtet wurden, während in den mit csDMARDs behandelten Patientengruppen keine Perforation aufgetreten war (10). Durch die mangelhafte Datenlage zum Auftreten von Darmperforationen bei RA-Patienten unter verschiedenen Therapien war es schwierig, das Risiko der in den RCTs aufgetretenen Ereignisse zu beurteilen.

Die Hauptfragestellungen dieser Arbeit (11) bestanden daher in Folgendem:

(I) *Vergleich der Inzidenz von Perforationen des unteren Darmtraktes unter verschiedenen Therapien: csDMARDs, TNFi, Abatacept, Rituximab und Tocilizumab*

(II) *Bestimmung von Risikofaktoren für Perforationen des unteren Darmtraktes unter spezieller Berücksichtigung der Exposition gegenüber Glukokortikoiden und NSAR*

(III) *Klinische Symptome beim Auftreten einer Perforation des unteren Darmtraktes*

Zudem wurden weitere Punkte betrachtet:

(IV) *Häufigkeit von Divertikulitiden*

(V) *Ausgang der Perforationen definiert durch 30-Tages Mortalität*

1.2 Risiko für Myokardinfarkt

Patienten mit RA haben im Vergleich zur Allgemeinbevölkerung ein um 68% erhöhtes Myokardinfarktrisiko und ein um 59% erhöhtes Risiko, an einer ischämischen Herzerkrankung zu versterben (12, 13). Traditionelle Risikofaktoren erklären diese Risikoerhöhung nicht zur Genüge, und andere Parameter wie Entzündung, pro-inflammatorische Zytokine und C-reaktives Protein (CRP) wurden identifiziert (14). Die Komedikation mit Glukokortikoiden und NSAR

erhöht das Risiko zusätzlich (15). Zum Einfluss der Biologika gibt es widersprüchliche Studienergebnisse, die entweder von einer Risikoreduktion (15) oder aber von keinem Einfluss (16) ausgehen. Diese Unterschiede können im Studiendesign, in der Definition des Outcomes oder in der betrachteten Patientenpopulation begründet liegen. Vergleiche von RA-Patienten mit einem Myokardinfarkt und solchen ohne sind mitunter schwierig, da sich die Patienten in wesentlichen Merkmalen wie Alter, Geschlecht und kardiovaskulären Begleiterkrankungen unterscheiden (17, 18). Ein adäquates Studiendesign im Sinn einer Fall-Kontroll-Studie kann für solche Störfaktoren kontrollieren. In der vorliegenden Arbeit wurde jedem RA-Patienten mit einem Myokardinfarkt im Beobachtungszeitraum (=Fall) eine Kontrolle zugeordnet, die sowohl in Alter und Geschlecht übereinstimmt als auch in kardiovaskulären Komorbiditäten. Somit hatte jedes Fall-Kontroll-Paar ein zu Baseline vergleichbares Risiko, einen Myokardinfarkt zu erleiden. Die Hauptfragestellungen dieser Arbeit (19) waren Folgende:

(I) *Bestimmung von Risikofaktoren für Myokardinfarkt bei RA unter Berücksichtigung bekannter traditioneller Risikofaktoren durch das Fall-Kontroll-Design*

(II) *Einfluss der RA-Therapien und von kardiovaskulären Komorbiditäten auf das Myokardinfarktrisiko*

(III) *Einfluss von Entzündung und Krankheitsaktivität auf die Entstehung von Myokardinfarkten, und zwar zu verschiedenen Zeitpunkten der Beobachtung*

In einer Subanalyse wurden Patienten mit einer koronaren Herzerkrankung (KHK) zu Studienbeginn ausgeschlossen und

(IV) *der Einfluss von Entzündung und Krankheitsaktivität sowie das Risiko für inzidente Myokardinfarkte bei RA-Patienten* analysiert.

1.3 Risiko für zerebrovaskuläre Ereignisse

Patienten mit RA haben im Vergleich zur Allgemeinbevölkerung nicht nur ein erhöhtes Myokardinfarktrisiko, sondern auch ein größeres Risiko, einen ischämischen oder hämorrhagischen Schlaganfall zu erleiden (20). Die wenigen Studien, die speziell RA-Populationen untersuchten, identifizierten Komorbiditäten, den RA-Schweregrad und Entzündungsmarker als Risikofaktoren (21, 22). Neuere Studien in der Allgemeinbevölkerung diskutieren neben traditionellen Risikofaktoren auch den Einfluss erhöhter Konzentrationen von TNF alpha und hochsensitivem CRP (23) sowie von im Vorfeld des Schlaganfalls aufgetretenen Ereignissen wie Infektionen, Krebserkrankungen und Hospitalisierungen (23-25). In einem Patientenkollektiv mit Autoimmunerkrankungen wurde ein erhöhtes Schlaganfallrisiko gezeigt,

wenn vor dem Infarkt ein Herpes zoster diagnostiziert worden ist (26). Dieses Risiko war zeitabhängig mit größeren Inzidenzraten (IR) für Schlaganfall innerhalb von 90 Tagen nach der Herpes zoster Diagnose. Auf Grund der Studienlage bestanden die beiden Hauptfragestellungen der vorliegenden Arbeit (27) in Folgendem:

(I) *Inzidenz nicht-hämorrhagischer Schlaganfälle, inklusive transitorischer ischämischer Attacken (TIA), bei RA-Patienten unter Berücksichtigung von im Vorfeld aufgetretenen schwerwiegenden unerwünschten Ereignissen (SUE)*

(II) *Bestimmung von Risikofaktoren nicht-hämorrhagischer Schlaganfälle innerhalb von zwei Studiendesigns: in der gesamten RABBIT-Kohorte und in einer eingebetteten Fall-Kontroll-Studie, inklusive der Berechnung von Cause-specific Hazard Ratios (HR)*

Des Weiteren wurden

(III) *Krankheitscharakteristika im Verlaufszeitraum* sowie

(IV) *die Verteilung der Subgruppen mit unterschiedlichen zerebrovaskulären Ereignissen und deren Patientencharakteristika* untersucht.

2. Methodik

RABBIT ist eine fortlaufende prospektive Langzeitkohorte, die seit 2001 Patienten mit RA in der Routineversorgung bei Neubeginn einer DMARD-Therapie nach mindestens einem csDMARD-Versagen rekrutiert (28). Der behandelnde Rheumatologe dokumentiert auf standardisierten Fragebögen in regelmäßigen Zeitabständen (zu Studieneinschluss/Baseline, nach 3 und 6 Monaten und danach halbjährlich) unter anderem die laufende RA-Therapie sowie den aktuellen Krankheitszustand des Patienten. Patientenberichtete Outcomes umfassen unter anderem Funktionsfähigkeit, Lebensqualität und Gesundheitszustand. Patienten werden über mindestens fünf bis maximal zehn Jahre beobachtet. Es liegt ein positives Votum der Ethikkommission der Charité Universitätsmedizin Berlin vor. Vor Beobachtungsbeginn muss jeder Patient seine schriftliche Einwilligungserklärung abgeben.

Ein besonderes Augenmerk von RABBIT liegt in der Dokumentation von UEs. Der Rheumatologe berichtet zu jedem Messzeitpunkt alle im Follow-up aufgetretenen UEs und klassifiziert diese in schwerwiegend und nicht schwerwiegend. Alle UEs werden mit Hilfe der MedDRA Terminologie (Medical Dictionary for Regulatory Activities) kodiert. Bei SUEs von besonderem Interesse (28) wird der Rheumatologe gebeten, anhand spezifischer Nachfragen

Details zum Ereignis zu berichten und, falls vorhanden, einen Facharzt- oder Krankenhausbericht zu übersenden.

Ein übergeordnetes Ziel der vorliegenden Arbeiten war, die definierten Endpunkte erneut und eingehend zu prüfen, um das Reporting durch die Rheumatologen zu validieren, die Outcomes zu kategorisieren beziehungsweise Details zum Ereignis in die Auswertungen mit einzubeziehen. Die Prüfung erfolgte entweder durch externe Experten (Arbeit 1) oder durch Sichtung der Patientenakten sowie vorhandener Facharzt- und Krankenhausberichte beim behandelnden Rheumatologen (Arbeiten 2 und 3).

Um den Einfluss der medikamentösen Behandlung auf das Risiko von UEs zu bestimmen, gibt es verschiedene Ansätze, die Therapieexposition festzulegen. In den vorliegenden Arbeiten wurden Risikofenster vor dem Auftreten des Ereignisses definiert (Arbeiten 1 und 2): Diese Methode ordnet das Ereignis einer bestimmten bDMARD-Therapie zu, wenn der Patient mindestens eine Dosis des Medikaments in dem festgelegten Zeitfenster erhalten hat. In der dritten Arbeit wurde der Therapieeffekt mit einer Cox-Regression analysiert, die die Therapieexposition während der gesamten Beobachtungszeit bis zum Ereignis für den jeweiligen Patienten berücksichtigt. Für die Analysen wurden alle TNFi (Adalimumab, Certolizumab, Etanercept, Golimumab und Infliximab) zusammengefasst. Biologika mit anderen Wirkmechanismen (Abatacept, Rituximab und Tocilizumab) wurden je nach Fragestellung zusammengefasst oder einzeln betrachtet. Patienten ohne bDMARD-Therapie im betrachteten Zeitraum wurden der csDMARD-Gruppe zugeordnet.

2.1 Risiko für Perforationen des unteren Darmtraktes

Die Auswertung umfasste Daten von insgesamt 13.310 RA-Patienten, die bis 31. Oktober 2015 in RABBIT eingeschlossen worden sind.

Fallvalidierung

Um alle aufgetretenen Darmperforationen zu berücksichtigen, erfolgte eine weitgefasste Ereignisselektion: Zunächst wurden alle Ereignisse, die im Zusammenhang mit Perforationen stehen könnten, aus der UE-Datenbank ausgewählt und anhand ihrer SUE-Nachfragen sowie vorliegender Krankenhausberichte validiert (n=141). Nach Ausschluss iatrogener und traumatischer Perforationsereignisse (n=97) sowie oberer Darmperforationen (n=7), erfolgte eine zusätzliche externe Validierung der Perforationen des unteren Darmtraktes (n=37) durch eine Gastroenterologin. Klinische Symptome und Laborwerte wurden anhand der Krankenhausberichte evaluiert (Fragestellung III).

Definition der Therapieexposition

Für die Analyse und den Vergleich zu csDMARDs wurden alle TNFi zusammengefasst und die Wirkstoffe Abatacept, Rituximab und Tocilizumab einzeln betrachtet. Als Risikofenster wurden drei Monate vor dem Ereignis (Rituximab: 9 Monate[*]) definiert. Der Einfluss der Komedikation wurde mit aktueller und kumulativer Dosis bestimmt, wobei die aktuelle Glukokortikoid-Dosis diejenige zum Zeitpunkt der Perforation ist. Die kumulative Dosis wurde wie folgt ermittelt: Die jeweilige Dosis der Messzeitpunkte wurde für die Folgemonate fortgeschrieben. Jeder Monat im Follow-up-Zeitraum (von Einschluss bis Ereignis) wurde gewichtet, und zwar für Dosierungen von ≤5 mg/d mit 0, von >5–10 mg/d mit 0,5 und von >10 mg/d mit 1. Die Division der summierten gewichteten Monate durch die Anzahl der Follow-up-Monate ergibt Werte im Intervall von 0 bis 1. Für die kumulative NSAR-Variable wurde die Anzahl der Messzeitpunkte mit begleitender NSAR-Therapie durch die Gesamtzahl der Messzeitpunkte dividiert (Intervall 0-1).

Statistische Methoden

Für die einzelnen DMARD-Gruppen wurden IR und Konfidenzintervalle (KI) nach Poisson berechnet (Fragestellung I). Die Bestimmung von Risikofaktoren (Fragestellung II) erfolgte durch multiple Cox-Regression unter Berücksichtigung der aktuellen (Modell A) und kumulativen (Modell B) Komedikation. Für die Fragestellungen IV und V wurden Anteile sowie Clopper-Pearson-KI ermittelt.

2.2 Risiko für Myokardinfarkte

Daten der bis einschließlich 31. Oktober 2013 rekrutierten 11.285 RA-Patienten wurden in die Analyse einbezogen. Für die eingebettete Fall-Kontroll-Studie wurden alle Patienten mit dem ersten berichteten Myokardinfarkt im Follow-up-Zeitraum als Fälle definiert. Diese wurden nach den folgenden Kriterien zu einer Kontrolle exakt gematcht (1:1): Geschlecht, Baseline-Alter (±3 Jahre), Einschlussjahr (±2 Jahre) sowie Baseline-Komorbiditäten (Hypertonie, KHK, Herzinsuffizienz, frühere zerebrovaskuläre Ereignisse und Hyperlipoproteinämie). Insgesamt konnten 105 Patienten mit Myokardinfarkt einer entsprechenden Kontrolle zugeordnet werden. Das Datum des Myokardinfarkts wurde als Indexdatum definiert.

[*] Auf Grund des Wirkmechanismus von Rituximab (Depletion der B-Zellen) wird von einer längeren Halbwertzeit des Medikamentes im Vergleich zu anderen bDMARDs ausgegangen.

Fallvalidierung

Alle Myokardinfarkt-Fälle wurden durch die Studienärztin anhand von SUE-Nachfragen und vorhandenen Epikrisen validiert. In einer Subgruppe von bis Oktober 2011 gemeldeten Myokardinfarkten wurde der Fallstatus und der von dazugehörigen Kontrollen (n=150) durch Sichtung der Patientenakten beim behandelnden Rheumatologen durch die Autorin verifiziert.

Definition der Therapieexposition

Die DMARD-Exposition wurde in TNFi, sonstige Biologika und csDMARDs eingeteilt. Die DMARD-Expositionsgruppen sowie Glukokortikoid-Dosierung und NSAR-Therapie gingen mit einem Risikofenster von 6 Monaten in das statistische Modell ein. Alle Patienten mit Hypertonie, KHK, Herzinsuffizienz oder Hyperlipoproteinämie zu Baseline, aber ohne Angabe zur medikamentösen Therapie dieser Komorbiditäten wurden als ‚nicht kardiovaskulär therapiert' definiert.

Statistische Methoden

Die Bestimmung von Risikofaktoren für Myokardinfarkt im Fall-Kontroll-Design (Fragestellung I) erfolgte durch bedingte logistische Regression. Logarithmierte CRP-Werte wurden innerhalb der letzten sechs Monate vor dem Indexdatum (Modell A) und im gesamten Beobachtungszeitraum (von Baseline bis Indexdatum, Modell B) berücksichtigt. Die Untersuchung des Therapieeinflusses (Fragestellung II) erfolgte durch die Berechnung der kumulativen Anzahl sowie der Dauer von DMARD-Episoden anhand eines generalisierten linearen gemischten Modells. Die Fragestellung III wurde durch zwei unterschiedliche Ansätze und unter Berücksichtigung variierender Zeitfenster beantwortet: (a) die mittleren Werte von Blutsenkungsgeschwindigkeit (BSG), CRP und der Krankheitsaktivität gemessen anhand des DAS28 wurden innerhalb der ersten sechs Monate nach Einschluss (für Fälle, Kontrollen und Kohorte) sowie in den letzten 18 Monaten vor dem Indexdatum (nur für Fälle und Kontrollen) geplottet und (b) die mittleren Werte von BSG, CRP und DAS28 in der Fall-, Kontroll- und Kohortengruppe wurden zu Studieneinschluss, nach drei und sechs Monaten stratifiziert nach Baseline-Therapie dargestellt. Um das Risiko für inzidente Myokardinfarkte zu bestimmen, wurden Daten von 77 Fall-Kontroll-Paaren ohne eine KHK zu Baseline ausgewertet (Fragestellung IV).

2.3 Risiko für zerebrovaskuläre Ereignisse

Daten von 13.310 Patienten und alle bis einschließlich 31. Oktober 2015 berichteten zerebrovaskulären Ereignisse wurden in der Analyse berücksichtigt. Die Bestimmung von Inzidenzen und Risikofaktoren erfolgte innerhalb der gesamten Kohorte. Confounding durch bekannte Risikofaktoren wurde durch ein eingebettetes Fall-Kontroll-Design ausgeschlossen. Hierfür wurden zu jedem Fall nach folgenden Parametern zwei Kontrollen exakt gematcht (1:2): Geschlecht, Alter (±5 Jahre), Baseline-Komorbiditäten (Hypertonie, KHK, Herzinsuffizienz, Diabetes) sowie Nikotinkonsum (niemals vs. jemals) und Einschlussepisode (2001-2006 vs. 2007-2015). Der Zeitpunkt des Schlaganfalls wurde als Indexdatum definiert.

Fallvalidierung und Outcome-Definition

Alle Fälle wurden durch die Studienärztin mit Hilfe von SUE-Nachfragen und vorhandenen Epikrisen validiert. Die MedDRA-Kodierung der zerebrovaskulären Ereignisse diente der Einteilung in ischämische und hämorrhagische Ereignisse sowie in Subarachnoidalblutungen und TIAs. Ereignisse, bei denen keine Zuordnung möglich war, wurden als Schlaganfall unbekannter Ursache zusammengefasst. Für die Analyse wurden lediglich nicht-hämorrhagische Ereignisse betrachtet. In einer Subgruppe der bis Oktober 2011 gemeldeten Fälle wurde der Status durch Sichtung der Patientenakten beim behandelnden Rheumatologen durch die Autorin verifiziert (n=106).

Definition der Therapieexposition

Die DMARD-Therapie wurde in TNFi, andere Biologika und csDMARDs eingeteilt. Patienten galten bis drei Monate nach Absetzen des bDMARDs als exponiert (Rituximab: 9 Monate nach letzter Infusion). Der Einfluss von Glukokortikoiden und NSAR wurde als aktuelle und kumulative Therapie definiert (siehe auch 2.1).

Alle Patienten mit Hypertonie, KHK, Herzinsuffizienz oder Hyperlipoproteinämie zu Baseline, aber ohne Angabe zur ebenfalls erfragten medikamentösen Therapie dieser Komorbiditäten wurden als ‚nicht kardiovaskulär therapiert' definiert (siehe auch 2.2). Für die Komorbiditäten Osteoporose und Diabetes mellitus wurde analog verfahren.

Statistische Methoden

Die Berechnung der kumulativen Inzidenz (Fragestellung I) erfolgte in Anlehnung an so genannte Multi-state-Modelle: SUEs, die im Vorfeld des Schlaganfalls auftraten, wurden als Risikofaktor berücksichtigt; zusätzlich wurde der Zeitraum von SUE bis Schlaganfall

einbezogen (≤30 Tage vs. >30 Tage). Inzidenzraten wurden mit exakten Poisson-KI angegeben. Der Vergleich der mittleren Entzündungs- und Krankheitsaktivität (Fragestellung III) im ersten Beobachtungsjahr erfolgte zwischen Fällen, Kontrollen und der restlichen Kohorte; Werte im Sechs-Monats-Fenster vor dem Indexdatum wurden lediglich zwischen Fällen und Kontrollen untersucht. Risikofaktoren wurden durch Cox-Proportional-Hazard-Modelle in der Kohorte (Modell A) und im Fall-Kontroll-Design bestimmt (Modell B). Für letzteres wurde ein Shared-Frailty-Modell angewendet, um die gematchte Struktur zu berücksichtigen (29). Die Interpretation der Ergebnisse erfolgt analog zu Cox-Proportional-Hazard-Modellen. Um Risikofaktoren für Patienten ohne SUE zu ermitteln, wurden Cause-specific Hazards bestimmt. In diesem Modell werden Patienten am Ende der Beobachtungszeit (=Indexdatum) oder bei Auftreten eines SUEs zensiert, abhängig davon was zuerst erfolgt.

3. Ergebnisse

3.1 Risiko für Perforationen des unteren Darmtraktes

Patientencharakteristika zu Baseline

Zum Zeitpunkt der Rekrutierung waren die Patienten in den einzelnen Behandlungsgruppen 55-59 Jahre alt, der Frauenanteil lag bei 76-78%. Patienten, die mit einem bDMARD in RABBIT eingeschlossen wurden, waren im Durchschnitt 11-14 Jahre, Patienten der csDMARD-Gruppe 7 Jahre an RA erkrankt. Chronische GI Erkrankungen lagen bei 4% der csDMARD- und bei 5-6% der bDMARD-Patienten vor. Divertikulosen bzw. Divertikulitiden wurden von 0,2-0,5% der Patienten berichtet. Abatacept-Patienten hatten am häufigsten chronische GI Erkrankungen (7%) und Divertikulosen/ Divertikulitiden (1%).

Inzidenz von Perforationen des unteren Darmtraktes

Ausgehend von insgesamt 37 Perforationen des unteren Darmtraktes lagen die IRs pro 1.000 Patientenjahre (PJ) bei 0,6 [95% KI 0,3; 1,1] für csDMARDs, 0,5 [0,3; 0,9] für TNFi, 0,5 [0,01; 2,8] für Abatacept und 0,2 [0,01; 1,1] für Rituximab. Mit 2,7 [1,4; 4,8] war die IR für Tocilizumab signifikant höher.

Risikofaktoren für Perforationen des unteren Darmtraktes

In der univariaten Cox-Regression stellten sich zunehmendes Alter (pro 5 Jahre) sowie die Behandlung mit Tocilizumab, Glukokortikoiden (aktuell und kumulativ) und kumulativen NSAR als signifikante Risikofaktoren heraus. Unabhängig davon, ob die aktuelle (Modell A) oder kumulative (Modell B) Begleittherapie berücksichtigt wurde, waren zunehmendes Alter

(Modell A: HR 1,6 [95% KI 1,3, 1,8] / Modell B: 1,6 [1,3; 1,9]), Glukokortikoide (1,3 [1,2; 1,4] / 1,9 [1,5; 2,3]) und NSAR (2,2 [1,1; 4,3] / 3,0 [1,3; 6,8]) auch in der multivariaten Analyse mit einem höheren Perforationsrisiko assoziiert. Im Vergleich zur csDMARD-Behandlung war das Risiko für Perforationen unter Tocilizumab um das 5- (Modell A) bzw. 4,5-fache (Modell B) erhöht, wohingegen für TNFi, Abatacept und Rituximab kein Einfluss gezeigt werden konnte.

Klinische Symptome beim Auftreten der Perforation des unteren Darmtraktes

Von akuten Bauchschmerzen, einem häufigen Symptom bei Darmperforationen, berichteten 90% der Patienten unter csDMARD, 60% unter TNFi und 27% unter Tocilizumab. Bei sieben der elf Tocilizumab-Patienten wurden CRP-Werte zwischen 11-72 mg/l bestimmt, bei einem Patienten <1 mg/l, bei einem Patienten 228 mg/l und bei zwei Patienten waren keine Angaben verfügbar. Dagegen wurde bei den meisten der mit csDMARD und anderen Biologika behandelten Patienten von sehr hohen CRP-Werten (>100 mg/l) beim Auftreten der Perforation berichtet.

Einfluss von Divertikulitiden und Mortalität

Im Follow-up-Zeitraum wurden in RABBIT insgesamt 92 Divertikulitiden berichtet, (IR: 1,7 pro 1.000 PJ [95% KI 1,4; 2,1]). Davon traten 37 bei Patienten unter Tocilizumab auf (IR: 3,9 pro 1.000 PJ [2,2; 6,4]). Keine der berichteten Divertikulitiden perforierte im Beobachtungszeitraum. Unter der Annahme, dass alle Patienten mit einer Darmperforation eine zugrunde liegende Divertikulitis aufweisen, lag der Anteil perforierter Divertikulitiden unter einer Tocilizumab-Behandlung deutlich höher als unter anderen Therapien (68,7% [95% KI 41,3; 89,0] vs. 40,2% [30,1; 31,0]).

Insgesamt neun der 37 Patienten mit Perforation des unteren GI-Traktes verstarben innerhalb von 30 Tagen nach dem Ereignis, resultierend in einem Anteil von 24%. Mit 46% war der Anteil unter Tocilizumab signifikant höher als unter anderen Therapien.

3.2 Risiko für Myokardinfarkt

Patientencharakteristika zu Baseline

Fälle und Kontrollen stimmten gut in den Matching-Kriterien überein. Die gematchten Paare waren zu Studieneinschluss im Mittel 64 Jahre alt und damit acht Jahre älter als Patienten aus der (nicht gematchten) verbleibenden Kohorte. Der Frauenanteil lag bei 57% in den Fall-Kontroll-Paaren und bei 77% in der Kohorte. Außerdem wurden bei den Fall-Kontroll-Patienten wesentlich häufiger als in der Kohorte Hypertonie, KHK, Herzinsuffizienz und Hyperlipoproteinämie als Begleiterkrankungen angegeben. Im Vergleich zu den Kontrollen

wiesen Fälle signifikant höhere BSG- und CRP-Werte auf, hatten häufiger Adipositas und Diabetes mellitus und nahmen häufiger orale Glukokortikoide ein. Wesentliche Unterschiede zwischen Fällen und der restlichen Kohorte zeigten sich in den Entzündungsparametern, der Krankheitsaktivität und der Funktionskapazität, den Komorbiditäten sowie der Einnahme von Glukokortikoiden. Kardiovaskuläre Komorbiditäten wurden bei den Fallpatienten signifikant seltener therapiert (64%) als bei Kontrollen (83%) oder der restlichen Kohorte (79%).

Einfluss von Entzündung und Krankheitsaktivität

Fallpatienten zeigten signifikant höhere BSG- und CRP-Werte innerhalb der ersten sechs Monate nach Einschluss im Vergleich zu den gematchten Kontrollen und der restlichen Kohorte. In der Zeit vor dem Indexdatum unterschieden sich BSG und CRP signifikant zwischen Fällen und Kontrollen. Im DAS28 gab es dagegen keine Unterschiede.

Untersuchung der DMARD-Episoden

Fallpatienten wechselten im Beobachtungszeitraum häufiger die DMARD-Therapien als die entsprechenden Kontrollen: Nur eine DMARD-Episode wiesen 46% der Fälle im Vergleich zu 69% der Kontrollen auf, zwei Episoden dagegen 27% vs. 17% und drei oder mehr Episoden 28% vs. 14%. Von 50 Fall-Kontroll-Paaren, die mit einem bDMARD in RABBIT eingeschlossen wurden, waren nach zwölf Monaten noch 55% der Fälle und 77% der Kontrollen auf der Einschlusstherapie.

Bestimmung von Risikofaktoren

In der univariaten logistischen Regression zeigten sich folgende Parameter als statistisch signifikante Risikofaktoren für einen Myokardinfarkt: logarithmierte CRP-Werte pro 5 mg/l-Erhöhung sowohl im Sechs-Monats-Fenster vor dem Indexdatum als auch im gesamten Beobachtungszeitraum, fehlende Therapie von kardiovaskulären Begleiterkrankungen, orale Glukokortikoide in einer Dosierung von ≥10 mg/d sowie Rauchen. In beiden adjustierten multiplen Modellen (A: logCRP vor Myokardinfarkt / B: logCRP im gesamten Beobachtungszeitraum) stellten sich höhere Entzündungswerte definiert als CRP (Odds Ratio (OR) 1,6 [95% KI 1,1; 2,3] / 1,5 [1,0; 2,5]) und Rauchen (3,3 [1,5; 7,6] / 2,9 [1,3; 6,7]) als signifikante Risikofaktoren heraus. Eine Assoziation zwischen Myokardinfarkt und TNFi oder anderen Biologika konnte im Vergleich zu csDMARDs nicht gezeigt werden.

Subanalyse zur Bestimmung des Risikos inzidenter Myokardinfarkte

In einer Subanalyse wurden lediglich Patienten ohne Baseline-KHK betrachtet. Als einziger Risikofaktor zeigte sich die Entzündungsaktivität vor dem Myokardinfarkt (OR 1,6 [95% KI 1,0; 2,4]).

3.3 Risiko für zerebrovaskuläre Ereignisse

Insgesamt meldeten die Rheumatologen 199 zerebrovaskuläre Ereignisse, davon 50,8% ischämische und 11,1% hämorrhagische Schlaganfälle. TIAs wurden zu 22,6% und Subarachnoidalblutungen zu 5,5% berichtet; 10,1% der Ereignisse konnten nicht klassifiziert werden. Die Auswertungen in der Kohorte beziehen sich auf 166 Ereignisse (ischämische und unklassifizierte Schlaganfälle, TIAs), für die Fall-Kontroll-Studie konnten 163 Fälle gematcht werden.

Patientencharakteristika zu Baseline

Fall- und Kontrollpatienten waren mit 56 Jahren im Mittel sieben Jahre älter als Patienten aus der restlichen Kohorte, die Geschlechtsverteilung unterschied sich nicht in den Gruppen. Dagegen hatten Fälle wesentlich häufiger Begleiterkrankungen zum Zeitpunkt des Einschlusses. Fälle waren signifikant häufiger Rheumafaktor positiv, wiesen höhere Entzündungsparameter, eine höhere Krankheitsaktivität sowie stärkere Funktionseinschränkungen auf. Die Fall- und Kontrollgruppe stimmte sowohl in den Matching-Kriterien als auch in den meisten anderen Baseline-Kriterien überein. Auffällig war die medikamentöse Behandlung von Komorbiditäten: trotz vorliegender kardiovaskulärer Erkrankung erhielten 34% der Fälle keine adäquate Therapie, im Vergleich zu je 21% bei den Kontrollen und in der Kohorte. Diese Unterschiede wurden in der Behandlung von Osteoporose und Diabetes mellitus nicht festgestellt.

Kumulative Inzidenzen unter Berücksichtigung von SUEs

Nicht-hämorrhagische Schlaganfälle traten in der RABBIT-Kohorte mit einer IR [95% KI] pro 1.000 PJ von 3,2 [2,7; 3,7] auf. Während die IR von Schlaganfällen ohne weiteres vorheriges SUE bei 2,2 [1,8; 2,8] lag, erhöhten SUEs im Vorfeld des Schlaganfalls die IR auf 9,0 [7,3; 11,0]. Das höchste Risiko für einen Schlaganfall gab es in den ersten 30 Tagen nach dem Ereignis mit einer IR von 94,9 [72,6; 121,9].

Krankheitscharakteristika im zeitlichen Verlauf

Im ersten Beobachtungsjahr wiesen Patienten aus der Fallgruppe signifikant höhere Entzündungs- und Krankheitsaktivitätswerte als die restliche Kohorte auf. Die Werte in der

Kontrollgruppe hatten ein niedrigeres Niveau als in der Fallgruppe, allerdings ohne statistische Signifikanz. In den letzten sechs Monaten vor dem Indexdatum wurde der Unterschied in der Krankheitsaktivität signifikant. Es gab keine Unterschiede in der kumulativen Therapie mit Glukokortikoiden und NSAR zwischen Fällen und Kontrollen.

Bestimmung von Risikofaktoren

Das univariate Cox-Modell innerhalb der Kohorte (Modell A) resultierte in wesentlichen Unterschieden für zunehmendes Alter (pro fünf Jahre), Entzündung und Krankheitsaktivität, stärkere Funktionseinschränkungen (je 10 Prozentpunkte), diverse Komorbiditäten, und die aktuelle Therapie mit Glukokortikoiden pro 5mg/d Erhöhung. Im multivariaten Modell stellten sich Alter (HR 1,4 [95% KI 1,3; 1,5]), stärkere Funktionseinschränkungen (0,9 [0,8; 0,96]) und Rauchen (1,9 [1,3; 2,6]) als Risikofaktoren für Schlaganfall heraus. Die Therapie mit TNFi oder anderen Biologika hatte im Vergleich zu csDMARDs keinen Einfluss.

Der univariate Vergleich im Fall-Kontroll-Design (Modell B) zeigte signifikante Assoziationen von Schlaganfall mit Entzündung, Krankheitsaktivität, stärkerer Funktionseinschränkung, der Anzahl von bDMARD-Therapieversagen vor Einschluss, diversen Komorbiditäten, unbehandelten kardiovaskulären Begleiterkrankungen sowie SUEs, die innerhalb von sechs Monaten vor dem Schlaganfall aufgetreten sind. Das multivariate Modell bestätigte den Einfluss einer schlechteren Funktion (FFbH je 10 Prozentpunkte: HR 0,9 [95% KI 0,8; 0,9]), nicht-therapierter kardiovaskulärer Erkrankungen (3,3 [1,5; 7,2]), der Anzahl der Therapieversagen (1,3 [1,0; 1,8]) und von SUEs vor Schlaganfall. Der stärkste Effekt ging hierbei von im Vorfeld aufgetretenen schwerwiegenden Infektionen mit einer mehr als vierfachen Risikoerhöhung aus (4,4 [1,6; 12,5]), andere Ereignisse zeigten ein HR von 2,6 [1,4; 4,8]. Der Einfluss kardiovaskulärer SUEs erreichte keine statistische Signifikanz (2,9 [0,9; 8,7]), und operative Eingriffe beeinflussten das Schlaganfallrisiko nicht (0,9 [0,3; 2,3]).

Die Bestimmung von Cause-specific HR für Patienten ohne SUEs vor dem Schlaganfall zeigte einen signifikanten Einfluss einer schlechteren Funktionsfähigkeit (je 10 Prozentpunkte 0,9 [0,8; 0,97]) und kardiovaskulärer Komorbiditäten ohne Therapie (2,3 [1,2; 4,5]).

4. Diskussion

Mit der vorliegenden Arbeit konnten drei Aspekte der Langzeitsicherheit neuer Therapien zur Behandlung der RA dargestellt werden. Sie verdeutlicht den Stellenwert longitudinaler Beobachtungsstudien zur Bestimmung von Arzneimittelrisiken und zur Identifizierung von Risikofaktoren für das Auftreten unerwünschter Ereignisse. Die Untersuchung der Effekte von Medikamenten über einen langen Zeitraum unter Alltagsbedingungen ist unverzichtbar. Denn die für die Zulassung geforderten RCTs können keine Informationen über die Langzeitsicherheit solcher Arzneimittel liefern, die oftmals über Jahre oder – im Falle chronischer Erkrankungen – sogar lebenslang eingesetzt werden. Daher forderte die europäische Arzneimittelbehörde EMA bei der Markteinführung von Biologika zur RA-Therapie die Einhaltung von Risiko-Management-Plänen inklusive der Etablierung longitudinaler Kohorten.

In der ersten Arbeit wurden die Häufigkeit und das Risiko eines sehr seltenen Ereignisses untersucht. Perforationen des unteren GI-Traktes waren als Sicherheitssignal aus den RCTs zu Tocilizumab bekannt, zum Zeitpunkt der Veröffentlichung dieser Arbeit gab es allerdings keine vergleichenden Analysen von Daten aus der klinischen rheumatologischen Praxis. Die vorliegende Auswertung zeigte, dass Perforationen des unteren Darmtraktes signifikant häufiger unter der Behandlung mit Tocilizumab auftreten im Vergleich zu csDMARDs, TNFi, Abatacept oder Rituximab. Die IR betrug 2,7/1.000 PJ für Tocilizumab (vs. 0,2 - 0,6/1.000 PJ in allen anderen Therapiegruppen), 46% der Patienten verstarben innerhalb von 30 Tagen nach dem Ereignis (vs. 24% im Gesamtkollektiv).

Die IR unter Tocilizumab-Exposition ist vergleichbar mit IRs, die aus den entsprechenden Tocilizumab-RCTs, deren Langzeit-Verlängerungsstudien beziehungsweise von Spontan-meldungen bekannt sind, mit Darmperforationsraten pro 1.000 PJ von 2,8, 2,4 und 2-2,3 (10, 30, 31). Ob diese Raten in dem für diese Population erwarteten Rahmen liegen, konnte bislang nicht beurteilt werden, da sie in unterschiedlichsten methodischen Settings festgestellt worden waren. Eine nach Publikation unserer Analyse veröffentlichte Studie, basierend auf US-Versicherungsdaten, berichtet eine IR unter Tocilizumab von 1,3/1.000 PJ (32).

Als Risikofaktoren für untere Darmperforationen konnten zunehmendes Alter (pro 5 Jahre Erhöhung), sowie die Behandlung mit Tocilizumab, Glukokortikoiden (pro 5mg/d Erhöhung) und NSAR identifiziert werden, was sich mit Ergebnissen anderer Studien deckt (32).

Divertikulitiden sind als Risikofaktoren für Perforationen bekannt (33), jedoch konnte dies in der vorliegenden Auswertung nur bedingt abgebildet werden. Bei keinem der Patienten mit

Divertikulitis zu Baseline war im Beobachtungszeitraum eine Perforation aufgetreten. Aber auch aus dem Tocilizumab-Studienprogramm war berichtet worden, dass vorbestehende Divertikulitiden erst nach Auftreten der Perforation diagnostiziert wurden (34). Divertikulitiden werden in RABBIT womöglich nicht vollständig berichtet. Es ist aber davon auszugehen, dass der Divertikulitis-Anteil bei Tocilizumab-Patienten nicht höher ist als in anderen Gruppen, da in den Empfehlungen zur Tocilizumab-Therapie vorbestehende Divertikulitiden als Kontraindikation angegeben werden (https://dgrh.de/dam/jcr:4afdfeb8-f623-40fc-82c7-a528b16fe499/tocilizumab_korr_endf_feb_2010.pdf).

Epikrisen der Patienten mit Perforationen des unteren Darmtraktes ermöglichten eine umfassende Auswertung klinischer Informationen zum Ereignis, durch die wesentliche Unterschiede zwischen den einzelnen Therapiegruppen auffielen. Unter Tocilizumab gingen Darmperforationen oftmals mit untypisch milden Symptomen und niedrigen CRP-Werten einher. Diese Kombination kann die Diagnostik erschweren und verzögern. Patienten unter Tocilizumab sowie die behandelnden Rheumatologen sollten deshalb sorgfältig auf mögliche Symptome achten.

Die Arbeiten (2) und (3) befassten sich mit dem Risiko für und dem Einfluss von RA-Therapien auf kardio- und zerebrovaskuläre Ereignisse. Im Vergleich zur Allgemeinbevölkerung haben RA-Patienten nicht nur eine erhöhte Inzidenz kardiovaskulärer Ereignisse. Sie sind auch die Hauptmortalitätsursache. Die beiden Endpunkte Myokardinfarkt und nicht-hämorrhagischer Schlaganfall wurden getrennt voneinander betrachtet, um Gemeinsamkeiten beziehungsweise mögliche Unterschiede in den Outcomes zu erkennen. Basierend auf der grundlegenden Pathogenese liegt die Vermutung nahe, dass ähnliche Ursachen zum Auftreten des Ereignisses führen – Atherosklerose mit der Folge reduzierter Durchblutung von Blutgefäßen beziehungsweise von Gefäßverschlüssen. In Analysen wird daher häufig ein zusammengefasster kardio- und zerebrovaskulärer Endpunkt festgelegt, ohne zwischen den einzelnen Endpunkten zu unterscheiden (35, 36).

In den vorliegenden Arbeiten ist deutlich geworden, dass es zu Studieneinschluss Gemeinsamkeiten gibt zwischen Patienten, die im Laufe der Beobachtungszeit einen Myokardinfarkt oder einen Schlaganfall erleiden. Sie betreffen beispielsweise Alter, Erkrankungsdauer der RA, Nikotinstatus und einige Krankheitscharakteristika. Deutliche Unterschiede zeigten sich dagegen in der Geschlechterverteilung: während nur 57% der Myokardinfarkt-Patienten weiblich waren, lag der Anteil bei den Schlaganfall-Patienten bei 75%. Im Mittel traten Myokardinfarkte 31 Monate nach Studieneinschluss auf, bei

Schlaganfällen waren es 47 Monate. Zum Teil nur geringe Unterschiede gab es bei den Begleiterkrankungen, mit tendenziell höheren Anteilen in der Myokardinfarkt-Gruppe. Zudem waren Myokardinfarkt-Patienten häufiger adipös. Die Komedikation mit NSAR war vergleichbar, doch Myokardinfarkt-Patienten erhielten häufiger Glukokortikoide in Dosierungen ≥10 mg/d (31% vs. 20%). Ein vergleichbarer Anteil der Patienten mit zugrundeliegenden kardiovaskulären Therapien erhielt in beiden Arbeiten keine adäquate Behandlung (34% vs. 36%).

Da es auch Studien aus der Allgemeinbevölkerung zum Einfluss von Entzündung auf die Entstehung kardiovaskulärer Ereignisse gibt (14), wurde dies in beiden Arbeiten besonders berücksichtigt. Im Sechs-Monats-Zeitraum vor dem Ereignisdatum waren CRP und DAS28 bei beiden Outcomes vergleichbar, BSG-Werte zeigten bei den Myokardinfarkt-Patienten dagegen ein deutlich höheres Niveau.

Für beide Endpunkte wurde ein eingebettetes Fall-Kontroll-Design zur Bestimmung von Risikofaktoren gewählt. Die Rationale dafür war zum einen, dass sich die Fallpatienten in wesentlichen Punkten wie Alter und Komorbiditäten von der restlichen Kohorte stark unterschieden. Zudem sollten durch die Analyse nicht die bekannten traditionellen Risikofaktoren bestätigt, sondern mögliche RA-spezifische Faktoren erkannt werden. Fälle und Kontrollen wurden daher exakt zueinander gematcht - nach Alter, Geschlecht und ausgewählten Begleiterkrankungen. Das Risiko für einen Myokardinfarkt bzw. Schlaganfall war somit bei Fällen und Kontrollen zu Baseline vergleichbar. Die Risikofaktoren für die beiden Outcomes wurden mit unterschiedlichen statistischen Modellen analysiert. Für die Myokardinfarkt-Analyse wurde eine bedingte logistische Regression als Standardmethode für Fall-Kontroll-Studien angewendet. Risikofaktoren für einen Schlaganfall wurden durch Cox-Regression mit einem Shared-Frailty-Modell bestimmt. Die Ergebnisse der beiden Analysen, angegeben entweder als Odds oder als Hazard Ratio, sind zwar nicht direkt miteinander vergleichbar. In beiden Untersuchungen zeigte sich jedoch der Einfluss von Entzündung und nicht behandelten kardiovaskulären Komorbiditäten auf das Ereignis. Im Hinblick auf die Biologika-Therapie wurde bei beiden Endpunkten kein negativer Effekt gesehen. Der Einfluss von Glukokortikoiden stimmte mit existierender Literatur überein (37, 38): Die lineare Regression (Myokardinfarkt) zeigte eine rund zweifache, nicht signifikante Risikoerhöhung bei Dosierungen ≥10 mg/d. In der Cox-Regression (Schlaganfall) hatten die Steroide (pro 5mg/d) keinen erkennbaren Einfluss.

Ein wichtiger Aspekt der Analysen war die Betrachtung bereits vorliegender kardiovaskulärer Erkrankungen. Die Ergebnisse legen nahe, dass Patienten mit einem Myokardinfarkt oder Schlaganfall keine adäquate Therapie erhalten. Diese Ergebnisse bestätigen ein suboptimales

kardiovaskuläres Risikomanagement bei RA-Patienten (39, 40) trotz bestehender Empfehlungen (41, 42).

Die Gemeinsamkeit der drei vorliegenden Arbeiten liegt in der Auswertung von Sicherheitsaspekten einer Langzeitbeobachtungsstudie von Patienten mit RA. Die aufgetretenen Ereignisse wurden vor der Analyse sorgfältig validiert und der Einfluss von RA-Therapien durch angemessene Methoden bestimmt. Das prospektive Studiendesign des RABBIT-Registers mit dem Einschluss von Patienten zum Therapiewechsel und der einer in gleicher Intensität geführten adäquaten Kontrollgruppe unter csDMARD-Therapie ist an das Design von RCTs angelehnt.

Eine Limitation der vorliegenden Arbeiten ist ein mögliches Underreporting von (S)UEs durch den Rheumatologen. Beobachtungsstudien wie RABBIT sind darauf angewiesen, dass der berichtende Arzt über aufgetretene Ereignisse informiert wird, entweder durch einen Kollegen oder durch den Patienten selbst. Dieser Limitation wird durch ein umfassendes Monitoring der Patienten Rechnung getragen. Beim Fehlen von mehr als zwei aufeinanderfolgenden Messzeitpunkten erfolgt eine Drop-Out Recherche. Diese beinhaltet unter anderem die Abfrage des Vitalstatus des Patienten bei den entsprechenden Meldebehörden sowie, im Falle eines Todes, die Erfragung des Sterbedatums und der Todesursache bei den Gesundheitsbehörden.

In die Analysen wurde die Komedikation mit Glukokortikoiden und NSAR vor dem Hintergrund mit einbezogen, dass sie die untersuchten Endpunkte beeinflussen können. Insbesondere die Aussagekraft zur NSAR-Einnahme ist begrenzt, da diese Medikamente oftmals symptomatisch bei Bedarf und nicht täglich eingesetzt werden. Zudem liegen keine Informationen zur Anwendung nicht-verschreibungspflichtiger NSAR vor. Derartige methodische Limitationen sind bei der Durchführung multizentrischer Beobachtungsstudien kaum vermeidbar.

Die vorliegenden Ergebnisse zeigen die hohe Relevanz sorgfältig durchgeführter prospektiver Beobachtungsstudien für die Gewinnung von Evidenz zur Sicherheit neuer Medikamente unter Alltagsbedingungen. Sie ermöglichen es, Risiken der Therapie und Risiken der Krankheit selbst, die zum Beispiel durch schlecht kontrollierte Krankheitsaktivität entstehen, gegeneinander abzuwägen. Weitere Risikofaktoren sowie Begleiterkrankungen und deren Therapie können zudem berücksichtigt werden. Wie dies zu klinisch relevanten Ergebnissen führt, konnte in der vorliegenden Arbeit am Beispiel von Herzinfarkt und Schlaganfall gezeigt werden. Auch die Schärfung der Aufmerksamkeit für sehr seltene, aber gefährliche Risiken wie gastrointestinale Perforationen ist eine wichtige Funktion solcher Beobachtungsstudien. Die Daten werden in der klinischen Praxis erhoben, und die Ergebnisse gehen wieder in klinische Entscheidungen ein.

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Eidesstattliche Versicherung einschließlich Anteilserklärung

„Ich, Yvette Meißner, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Die Sicherheit der Therapie mit Biologika bei rheumatoider Arthritis“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -www.icmje.org) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.

Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Berlin, 10. Juli 2017 Unterschrift

Anteilserklärung an den erfolgten Publikationen

Yvette Meißner hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1:

Strangfeld A, Richter A, Siegmund B, Herzer P, Rockwitz K, Demary W, Aringer M, Meißner Y, Zink A, Listing J. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs.

Ann Rheum Dis. 2017 Mar;76(3):504-510.

Impact Factor: 12,811

Beitrag im Einzelnen:

Prüfung der Daten. Diagnosevalidierung sowie Validierung von Krankenhausberichten in Zusammenarbeit mit der Studienärztin Dr. Anja Strangfeld. Kritische Durchsicht des Manuskripts. Einreichung des Manuskripts.

Publikation 2:

Meissner Y, Zink A, Kekow J, Rockwitz K, Liebhaber A, Zinke S, Gerhold K, Richter A, Listing J, Strangfeld A. Impact of disease activity and treatment of comorbidities on the risk of myocardial infarction in rheumatoid arthritis.

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Datenerhebung in rheumatologischen Einrichtungen. Durchführung des Datenmanagements. Diagnosevalidierung in Zusammenarbeit mit der Studienärztin Dr. Kerstin Gerhold. Festlegung des Analyseplans*. Wahl und Anwendung der statistischen Methoden*. Durchführung der Datenanalyse*. Interpretation der Ergebnisse. Erstellung des Manuskripts. Erstellung von Abbildungen und Tabellen. Einreichung des Manuskripts. Beantwortung der Reviewer-Fragen.

Erstellung und Einreichung der Revisionen. *Diese Beiträge erfolgten zum Teil gemeinsam mit Joachim Listing.

Publikation 3:

Meissner Y, Richter A, Manger B, Tony HP, Wilden E, Listing J, Zink A, Strangfeld A. Serious adverse events and the risk for stroke in patients with rheumatoid arthritis. Results from the German RABBIT cohort.

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Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

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Unterschrift des Doktoranden/der Doktorandin

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Publikation 1: Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs.

Strangfeld A, Richter A, Siegmund B, Herzer P, Rockwitz K, Demary W, Aringer M, Meißner Y, Zink A, Listing J. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. Ann Rheum Dis. 2017 Mar;76(3):504-510.

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EXTENDED REPORT

Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs

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ABSTRACT

Objective To investigate the risk of developing lower intestinal perforations (LIPs) in patients with rheumatoid arthritis (RA) treated with tocilizumab (TCZ).

Methods In 13 310 patients with RA observed in the German biologics register *R*heumatoid *A*rthritis: *O*bservation of *Bi*ologic *T*herapy, 141 serious gastrointestinal events possibly associated with perforations were reported until 31 October 2015. All events were validated independently by two physicians, blinded for treatment exposure.

Results 37 LIPs (32 in the colon/sigma) were observed in 53 972 patient years (PYs). Only two patients had a history of diverticulitis (one in TCZ). Age, current/cumulative glucocorticoids and non-steroidal anti-inflammatory drugs were significantly associated with the risk of LIP. The crude incidence rate of LIP was significantly increased in TCZ (2.7/1000 PYs) as compared with all other treatments (0.2–0.6/1000 PYs). The adjusted HR (ref: conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs)) in TCZ was 4.48 (95% CI 2.0 to 10.0), in tumour necrosis factor-α inhibitor (TNFi) 1.04 (0.5 to 2.3) and in other biologic DMARDs 0.33 (0.1 to 1.4). 4/11 patients treated with TCZ presented without typical symptoms of LIP (acute abdomen, severe pain). Only one patient had highly elevated C reactive protein (CRP). One quarter of patients died within 30 days after LIP (9/37), 5/11 under TCZ, 2/13 under TNFi and 2/11 under csDMARD treatment.

Conclusions The incidence rates of LIP under TCZ found in this real world study are in line with those seen in randomised controlled trials of TCZ and higher than in all other DMARD treatments. To ensure safe use of TCZ in daily practice, physicians and patients should be aware that, under TCZ, LIP may occur with mild symptoms only and without CRP elevation.

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INTRODUCTION

Lower intestinal perforations (LIPs) are rare in the general population with an incidence rate of about 0.04/1000 persons/year in the European population.[1] The incidence of LIP increases with age and is higher in women than in men. In most cases, perforations appear as a result of infected or inflamed diverticular disease. Lethality is high, with rates of around 30%[2] and increases with age.[3]

In patients with rheumatoid arthritis (RA), perforations of the gastrointestinal (GI) tract have been a concern for quite a long time. In the prebiologic era, GI complications were among the most common causes of death in patients with RA.[4] At that time, concerns mainly referred to perforations of the upper GI tract, for which non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs) are the most important risk factors.[5] However, in addition to risks for the upper GI tract, for the lower GI tract a higher risk for diverticular complications was found on NSAIDs in several case-control studies with ORs ranging from 1.8 to 11.2.[6–8]

Similarly, GCs were found to be strongly associated with lower GI perforations[9–11] with HRs in patients with RA of 2.8 (95% CI 1.3 to 6.1) compared with non-users[9] or 4.7 (95% CI 1.9 to 12.0) when GCs and NSAIDs were used concomitantly.

Since the approval of the first biologics, the incidence of GI tract complications in RA was expected to decrease with the decreasing use of NSAIDs and high-dose GCs. However, this is only the case if concomitant GCs can be reduced by effective therapy. Curtis *et al* investigated the risk for GI tract complications on tumour necrosis factor-α inhibitors (TNFi) and found a higher incidence of hospitalised GI perforation with concomitant GCs (1.12 (95% CI 0.5 to 2.5)/1000 patient years (PYs)) than without (0.47 (95% CI 0.2 to 0.98)).[9] The British Biologics Register (BSRBR)[12] compared the risk of GI perforations in patients treated with TNFi and those on conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs) only. While there was no statistically important elevation of the risk associated with TNFi with an incidence rate of lower GI perforations of 0.39/1000 PYs, concomitant GCs were the most important risk factor, conveying a 2.9 (95% CI 1.5 to 5.3) times higher risk, confined to lower GI perforations with a HR of 8.0 (95% CI 2.6 to 24.1).

The clinical development programme of tocilizumab (TCZ) for the treatment of RA identified GI perforations as important risk. An integrated safety analysis of eight trials and long-term extension studies with TCZ reported that no GI perforation had occurred in the group treated with csDMARDs only, but 26 such cases were identified in patients of the group ever exposed to TCZ, resulting in an

incidence rate of 2.8/1000 PYs.[13] Eighteen of these perforations occurred in the colon. Due to the early escape design of the trials, only 825 PYs were available in the csDMARD group, limiting the significance of the finding.

Since there is little information on the overall incidence of LIP in patients with RA exposed to specific treatments, no robust comparisons of the incidence rate of GI perforations could be made between TCZ-treated patients and those on other therapies. Several other factors, such as diverticular disease, high disease activity or long-standing high-dose GC or NSAID use, could also have accounted for the higher incidence in TCZ-treated patients. Further, the few studies existing in this field differ considerably in study design, case definition and population studied, the latter impacting on the background risk.

Prospective observational cohort studies, such as the German biologics register *R*heumatoid *A*rthritis O*b*servation of *Bi*ologic *T*herapy (RABBIT), have the advantage that all patients who start treatment with one of the approved biologic agents are eligible to be enrolled. In addition, a control group treated with csDMARDs only is observed under the same protocol. This design enables studying differences in incidence rates of adverse events occurring under different treatments. The aim of this study was to identify risk factors for LIP within the RABBIT register, taking concomitant (time varying) dosages of NSAIDs and GCs into account. We thereby aimed to examine the clinical signs and symptoms of LIP events to inform treating physicians how to advise their patients when starting a new treatment.

METHODS

Patients

We used data of the German biologics register RABBIT captured and validated until 31 October 2015.

RABBIT is an ongoing observational cohort study that started in May 2001. Since then, patients with RA are enrolled when starting a treatment with a biologic DMARD (bDMARD), or csDMARD after failure of at least one csDMARD. Once enrolled, patients are observed for at least 5 years regardless of treatment terminations and changes (with the option to extend observation for another 5 years, if the patient agrees).

The study protocol was approved in 2001 by the ethics committee of the Charité University School of Medicine, Berlin. Each patient participating in the study gave written informed consent before study entry.

Assessments and procedures

During follow-up, information from rheumatologists and patients is captured at regular intervals: at baseline, after 3 and 6 months, and thereafter every 6 months. Data collected include clinical status, disease activity (including disease activity score based on 28 joints (DAS28)), details on DMARD treatment (substance, dosage, application, start and stop dates, reasons for stopping) and concomitant treatments like NSAIDs (yes/no) and GCs (actual dose and mean dose since last questionnaire). At every time point of follow-up, all adverse events that occurred since last questionnaire are reported. At baseline and every 2 years, rheumatologists report comorbid conditions in predefined groups and in plain text. Patients report, among other items, physical function (using the Hannover Functional Status Questionnaire, FFbH).

Adherence to scheduled visits is monitored closely. Investigations of dropouts (defined as two missing follow-ups) are performed regularly. This includes inquiries to local administration offices regarding patient's vital status and, if the patient had died, obtaining the causes of death from the health authorities. Complete details have been published.[14]

Outcomes

Primary outcome

Incidence of LIPs in patients exposed to TCZ, csDMARDs, TNFi, abatacept or rituximab.

Secondary outcomes

Clinical signs and symptoms of LIPs in these patients.
Thirty-day mortality after LIPs.

Outcome validation

To capture all LIPs, we first identified all events that might be associated with GI perforations (including also haemorrhages and bleedings of the intestinal tract) via a predefined group of MedDRA terms. These included all events of the standard MedDRA query (SMQ) 'GI perforation' plus 51 additional MedDRA codes (see online supplementary table S1). Based on medical records and specific queries to the treating rheumatologists, all events were validated first by the leading physician of RABBIT (AS). An additional external validation was done by the Head of the Department for Gastroenterology of the Charité University Medicine (BS). At time of validation, both reviewers were blinded for the patient's treatment exposure. Only events with a definite, non-iatrogenic and non-traumatic LIP were selected for the analysis. We only counted perforations localised below the duodenojejunal junction (ligament of Treitz) as lower GI perforation. The topmost localised perforation included in the analysis was in the terminal ileum.

Definition of DMARD exposure

Treatment was assigned using a risk window for exposure to bDMARDs: a patient was considered exposed to a certain bDMARD at the time of the event if he/she had received at least one dose of the drug within 3 months (rituximab 9 months) prior to the event. Patients unexposed to bDMARDs in this risk window were assigned to the csDMARD group.

All substances targeting TNF (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) were subsumed under TNFi since we had not seen any differences in incidence rates.

Statistical analysis

Multiple Cox regression was applied to compare the risks of LIPs between the treatment groups. Adjustment was made for age, sex, treatment with GCs and NSAIDs. We distinguished current (Cox regression 1) and cumulative (Cox regression 2) treatment with NSAIDs and GCs. For each patient, the portion of visits with new or ongoing NSAIDs treatment was used as a proxy for NSAID use (range: 0 to 1). Regarding cumulative treatment with GCs, we proceeded in a similar way, but considered each month with a dose of >5–10 mg/day with a weight of 0.5 and each month with a dose of >10 mg/day with a weight of 1. Further covariables (body mass index (BMI), number of bDMARD failures, DAS28) were additionally investigated in univariate Cox regression. We applied two sensitivity analyses: (a) we restricted the cohort to a subgroup of patients recruited after 2009 and (b) we repeated Cox regression 1 and 2 but restricted the reference group to biologic naïve patients. Exact Poisson and Clopper-Pearson binomial CIs were calculated for incidence rates and proportions. The uncertainty of HRs is shown in 95% CIs.

RESULTS

Patients

Until 31 October 2015, 13 310 patients had been enrolled in the RABBIT register. Patients in the csDMARD-treated biologic naïve control group were older and had shorter disease duration at inclusion than TNFi-treated patients. Patients starting treatment with non-TNFi biologics had the longest disease duration and the highest number of prior treatment failures (table 1). Most of them (66.1%) had prior TNFi treatment.

The prevalence of chronic GI disease at baseline was lowest in the csDMARD-treated group and highest in patients starting treatment with abatacept. Chronic diverticulosis was reported in 33 patients. In two patients, a history of diverticulitis was known to the rheumatologist, one of these patients had a perforated diverticulum before inclusion in the register. None of the patients with chronic GI disease at baseline developed an intestinal perforation during follow-up.

Incidence of GI perforations

In 53 972 PYs of follow-up, 141 adverse events possibly describing GI perforations were reported. After internal and external medical review, 44 GI perforations were identified (figure 1). Seven were localised in the upper GI tract: three under TNFi resulting in an incidence rate of 0.12 (95% CI 0.02 to 0.35)/1000 PYs and four under csDMARD (0.22 (95% CI 0.06 to 0.57)/1000 PYs).

Thirty-seven GI perforations were localised in the lower GI tract: 32 in the colon/sigma, 4 in the appendix, and 1 in the terminal ileum. Similar incidence rates were observed for patients exposed to csDMARDs (0.6 (95% CI 0.3 to 1.1) /1000 PYs), TNFi (0.5 (95% CI 0.3 to 0.9)/1000 PYs), abatacept (0.5 (95% CI 0.01 to 2.8)/1000 PYs) and rituximab (0.2 (95% CI 0.01 to 1.1)/1000 PYs), whereas the incidence rate for patients exposed to TCZ was significantly higher (2.7 (95% CI 1.4 to 4.8)/1000 PYs) (figure 2). These crude incidence rates correspond to numbers needed to harm of 1647, 1911 and 371 in patients treated with csDMARDs, TNFi and TCZ, respectively. Sensitivity analysis (a) showed similar rates (see online supplementary figure S1).

Univariate and multivariate risk evaluation of LIP

Twenty-eight of the 37 patients who developed LIP had concomitant GCs, with a daily dose of ≥7.5 mg in 12 patients. Compared with those treated with TCZ, the average dose of GCs was higher in patients treated with TNFi and lower in csDMARD-treated patients (table 2). Further characteristics of patients who developed perforations did not differ significantly between the various treatment groups.

In the univariate analysis higher age, treatment with TCZ, current as well as cumulative GCs, and cumulative NSAIDs but none of the other risk factors (eg, sex, disease activity (DAS28), BMI and number of previous biologics) were significantly associated with LIP. In the multivariate analysis, higher age, current and cumulative use of GCs and NSAIDs were significantly associated with a higher risk of LIP, in addition to treatment with TCZ (table 3). Compared with csDMARDs, exposure to TCZ was associated with a 4.5 times higher risk for LIP (95% CI 2.01 to 9.99) (table 3, Cox regression 2), whereas no association was found for TNFi, abatacept or

Table 1 Patient characteristics at inclusion in the RABBIT register

Parameter	csDMARDs	TNFi	TCZ	ABA	RTX
N	4423	6711	877	371	928
Patient years, sum	18 113	24 851	4082	1976	4950
Age, years, mean (SD)	57.6 (12.3)	54.9 (12.6)	56.7 (12.8)	58.1 (12.9)	58.7 (12.1)
Female	3345 (75.6)	5113 (76.2)	685 (78.1)	282 (76.0)	719 (77.5)
Rheumatoid factor positive	2763 (62.6)	4983 (74.9)	608 (72.2)	267 (74.2)	764 (82.9)
No. of previous csDMARDs, mean (SD)	1.4 (0.9)	2.7 (1.4)	2.2 (1.1)	2.4 (1.3)	2.6 (1.2)
No. of previous bDMARDs, mean (SD)	0 (0.2)	0.2 (0.6)	1.0 (1.1)	1.4 (1.3)	1.4 (1.1)
NSAIDs	1497 (33.8)	2695 (40.2)	293 (33.4)	151 (40.7)	351 (37.8)
Glucocorticoids, not available	9 (0.2)	18 (0.3)	0	0	9 (1.0)
Glucocorticoids, <5 mg/day	1412 (31.9)	1682 (25.1)	240 (27.4)	80 (21.6)	215 (23.2)
Glucocorticoids, 5–10 mg/day	2057 (46.5)	3058 (45.6)	389 (44.4)	182 (49.1)	386 (41.6)
Glucocorticoids, ≥10 mg/day	945 (21.4)	1953 (29.1)	248 (28.3)	109 (29.4)	318 (34.3)
Disease duration, years, mean (SD)	7.2 (8.0)	10.7 (9.2)	10.6 (8.7)	12.0 (9.0)	13.8 (9.9)
DAS28, mean (SD)	4.7 (1.3)	5.4 (1.3)	5.2 (1.3)	5.4 (1.3)	5.3 (1.3)
CRP, mg/L, mean (SD)	14.1 (20.5)	21.2 (29.4)	18.0 (26.1)	19.6 (26.3)	18.3 (24.6)
FFbH, mean (SD)	69.4 (21.7)	61.4 (23.3)	62.6 (24.2)	58.6 (23.6)	55.9 (23.8)
BMI, mean (SD)	27.4 (5.3)	26.4 (5.3)	26.7 (5.4)	26.8 (5.8)	26.3 (5.1)
BMI ≥30 kg/m^2	1167 (26.4)	1412 (21.0)	218 (24.9)	81 (21.8)	181 (19.5)
Diabetes mellitus	436 (9.9)	668 (10.0)	102 (11.6)	46 (12.4)	111 (12.0)
Hyperlipoproteinemia	315 (7.1)	557 (8.3)	82 (9.4)	44 (11.9)	106 (11.4)
Diverticulosis/prior diverticulitis	12 (0.3)	11 (0.2)	3 (0.3)	4 (1.1)	5 (0.5)
Gastrointestinal diseases	159 (3.6)	339 (5.1)	43 (4.9)	26 (7.0)	59 (6.4)
Chronic renal disease	102 (2.3)	295 (4.4)	49 (5.6)	24 (6.5)	61 (6.6)

Values are numbers of patients (%) unless otherwise specified.
ABA, abatacept; bDMARDs, biologic disease-modifying anti-rheumatic drugs; BMI, body mass index; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, disease activity score based on 28 joints; FFbH, Funktionsfragebogen Hannover (physical function in %); NSAIDs, non-steroidal anti-inflammatory drugs; RABBIT, *R*heumatoid *A*rthritis *O*bservation of *Bi*ologic *T*herapy; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor-α inhibitor.

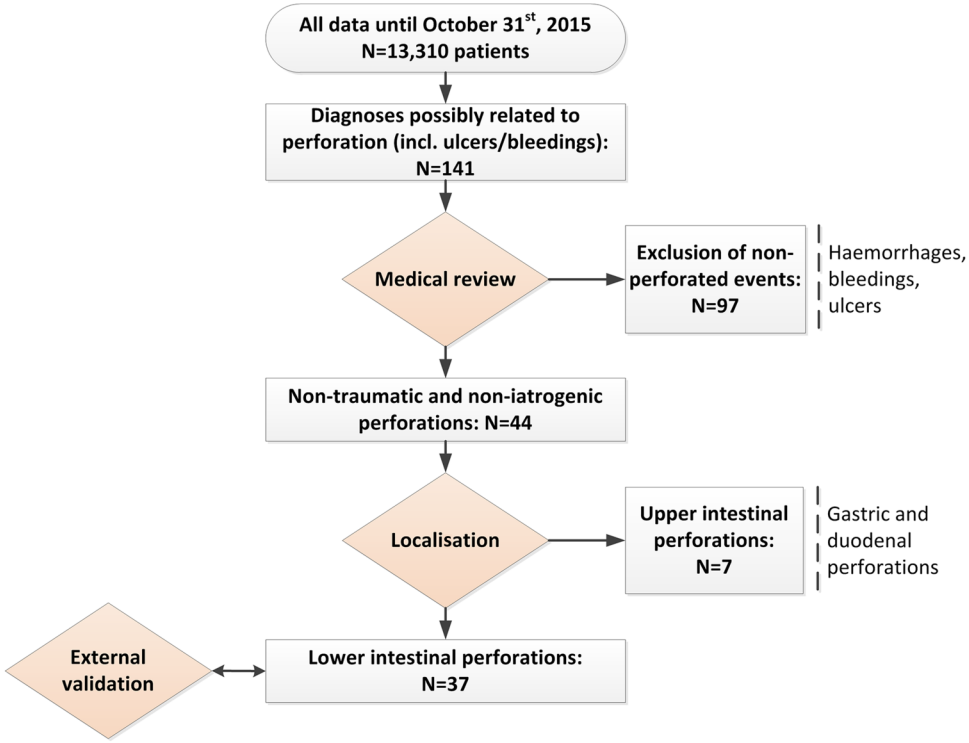

Figure 1 Flowchart of case selection and validation process.

rituximab. Sensitivity analyses (b) did not show different results (see online supplementary table S3).

Clinical signs and outcome of LIPs

While 90% of the patients with csDMARD and 60% of those on TNFi reported acute abdominal pain, this was only the case for 27% (three cases) on TCZ. The majority of patients treated with csDMARDs or other bDMARDs had very high C reactive protein (CRP) values (above 100 mg/L). In contrast, this was the case in only one patient treated with TCZ.

Online supplementary table S2 shows demographics, CRP values, features of clinical presentation and comedication with GC of each patient who developed LIP on TCZ.

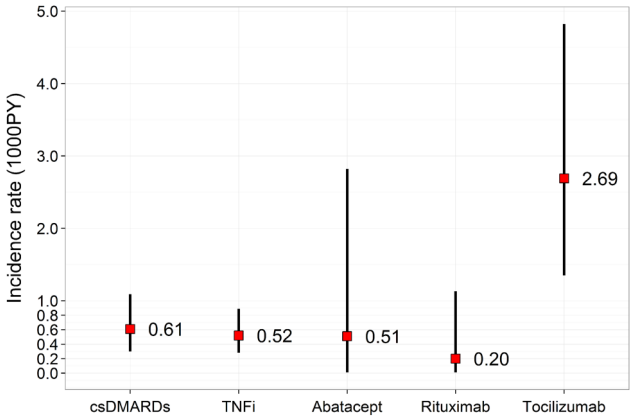

Figure 2 Incidence rates of lower intestinal perforation stratified by DMARDs. Events/patient years (PYs): csDMARDs=11/18 113; TNFi=13/24 851 (adalimumab=6, etanercept=6, infliximab=1); Abatacept=1/1976; Rituximab=1/4950; Tocilizumab=11/4082. csDMARD, conventional synthetic DMARD; TNFi, tumour necrosis factor-α.

According to classifications of colonic diseases, LIPs are considered as complicated diverticulitis (in contrast to diverticulitis without perforation). In total, 92 events of diverticulitis were reported during follow-up. The proportion of patients who developed a perforation was higher in patients treated with TCZ than in all other treatment groups (see table 4).

The 30-day mortality after perforation was 24% in all groups (9/37 patients). The mortality in patients on TCZ (46%) was considerably elevated, although not statistically significant (p=0.09, Fisher's exact test) (table 4).

DISCUSSION

Our objective was to evaluate the risk for LIP under various treatments by using the data of a large German RA cohort. We observed a significantly elevated risk for LIP in patients treated with TCZ compared with patients treated with csDMARD and also as compared with patients treated with TNFi or other biologics. LIPs are uncommon events that occurred in patients exposed to TCZ with an incidence of 2.7 per 1000 PYs only, but were associated with a 30-day mortality of 46%.

In patients treated with TCZ, symptomatic diverticulitis was more often associated with perforation than in other treatments. In these patients, the clinical presentation tended to be milder than in other patients. This might explain the finding from van Vollenhoven *et al*[15] that in the majority of patients in the TCZ clinical development programme who had a perforation, the diverticulitis was recognised only after the perforation had occurred.

The incidence rate of LIP in patients treated with TCZ in our cohort was comparable to that reported from randomised controlled trials with TCZ, postmarketing surveillance studies, spontaneous reports or US-based healthcare data in which per 1000 PYs 2.8, 2.4 and 2–2.3 LIPs, respectively, were observed.[13 16 17] Observational cohort studies reported lower incidence rates in patients with RA not treated with TCZ: in the

Table 2 Clinical characteristics during follow-up of patients who developed LIP

Parameter	csDMARDs	TNFi	TCZ	ABA	RTX
N	11	13	11	1	1
Age at LIP, years, mean (SD)	66.8 (4.8)	67.3 (8.3)	69.2 (7.6)	[73]	[61]
Female	7 (63.6)	7 (53.8)	9 (81.8)	[1 (100)]	[1 (100)]
Rheumatoid factor positive	11 (100)	12 (92.3)	6 (54.5)	[1 (100)]	[1 (100)]
No. of previous bDMARDs, mean (SD)	0.7 (1.3)	1.8 (0.8)	3.3 (1.6)	[4]	[4]
Cumulative NSAID treatment*, mean (SD)	0.4 (0.4)	0.4 (0.3)	0.3 (0.4)	[1]	[0.5]
Disease duration at LIP, years, mean (SD)	13.2 (9.1)	13.0 (7.5)	15.7 (8.4)	[13]	[12]
DAS28 prior to LIP					
≤6 months, mean (SD)	3.8 (0.7)	4.0 (1.7)	3.5 (2.1)	[5.0]	[5.4]
≤12 months, mean (SD)	3.8 (0.7)	4.0 (1.6)	3.7 (2.0)	[5.0]	[5.5]
CRP (mg/L) prior to LIP					
≤6 months, mean (SD)	8.1 (7.9)	25.8 (33.4)	11.5 (17.6)	[0.7]	[3.8]
≤12 months, mean (SD)	10.6 (8.5)	28.3 (33.0)	16.0 (21.5)	[0.7]	[4.2]
ESR (mm/hour) prior to LIP					
≤6 months, mean (SD)	19.4 (11.6)	36.0 (27.6)	14.8 (15.8)	[12.0]	[12.0]
≤12 months, mean (SD)	18.8 (11.3)	36.0 (27.1)	16.3 (13.9)	[12.0]	[13.7]
Glucocorticoids prior to LIP					
Average over 6 months, mean (SD)	5.6 (3.8)	9.7 (9.3)	7.5 (7.5)	[5.0]	[10.0]
Average over 12 months, mean (SD)	5.6 (3.4)	9.6 (9.0)	8.1 (7.3)	[5.0]	[10.0]

*Cumulative treatment with NSAID (range: 0 to 1) was calculated for each patient as: no. of follow-ups with concomitant NSAID use divided by the total no. of follow-ups.
ABA, abatacept; bDMARDs, biologic disease-modifying anti-rheumatic drugs; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, disease activity score based on 28 joints; ESR, erythrocyte sedimentation rate; LIP, lower intestinal perforation; NSAID, non-steroidal anti-inflammatory drug; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor-α inhibitor.

Table 3 Univariate HRs and results of multiple Cox regression

	Univariate		Multiple Cox regression 1		Multiple Cox regression 2	
	HR	95% CI	HR	95% CI	HR	95% CI
Age at event (by 5 years)	1.48	(1.25 to 1.75)	1.55	(1.30 to 1.84)	1.57	(1.32 to 1.87)
Male	1.68	(0.84 to 3.34)	1.58	(0.79 to 3.20)	1.45	(0.72 to 2.90)
BMI	1.00	(0.94 to 1.06)				
bDMARD failures (reference: 0)						
1 bDMARD	1.54	(0.67 to 3.52)				
≥2 bDMARDs	0.71	(0.17 to 3.00)				
DAS28 (current)	1.14	(0.92 to 1.42)				
DAS28 (average last 12 months)	1.16	(0.91 to 1.48)				
DMARD (reference: csDMARDs)						
TNFi	0.84	(0.39 to 1.80)	1.00	(0.46 to 2.20)	1.04	(0.48 to 2.26)
Other bDMARDs	0.40	(0.09 to 1.78)	0.41	(0.09 to 1.84)	0.33	(0.08 to 1.44)
Tocilizumab	4.17	(1.87 to 9.27)	5.11	(2.31 to 11.3)	4.48	(2.01 to 9.99)
GCs						
Current GC (by 5 mg)	1.22	(1.13 to 1.31)	1.28	(1.18 to 1.38)		
Cumulative GCs*	1.81	(1.47 to 2.22)			1.87	(1.50 to 2.33)
NSAIDs						
Current NSAID	1.80	(0.92 to 3.53)	2.18	(1.11 to 4.31)		
Cumulative NSAIDs†	2.71	(1.20 to 6.12)			3.00	(1.33 to 6.82)

In Cox regression 1, we adjusted for current doses of GCs and NSAIDs, whereas in Cox regression 2 for cumulative doses.
*Concomitant GC use (range: 0 to 1) was calculated for each patient as the area under curve of follow-up month with medium doses (>5 to 10 mg/day, weight of 0.5) plus follow-up month with high doses (>10 mg/day, weight of 1) and then divided by total no. of follow-up months.
†Cumulative treatment with NSAIDs (range: 0 to 1) was calculated for each patient as: no. of follow-ups with concomitant NSAIDs use divided by the total no. of follow-ups.
bDMARD, biologic disease-modifying anti-rheumatic drug; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, disease activity score based on 28 joints; GC, glucocorticoid; NSAIDs, non-steroidal anti-inflammatory drugs; other bDMARDs, abatacept and rituximab; TNFi, tumour necrosis factor-α inhibitor.

Rochester cohort, a rate of 1.3/1000 PYs[18] in 813 patients diagnosed with RA between 1980 to 2008 (and followed until 2009) was observed. Only 17% of the patients had ever been exposed to bDMARDs and 77% had concomitant GCs. From US claims data,[19] a rate of 0.87/1000 PYs in patients with RA was reported. In the British Biologics Register, an incidence of LIP of 0.39/1000 PYs in patients on TNFi treatment and of 0.15/1000 PYs in biologic naïve csDMARD-treated patients was

Table 4 Incident diverticulitis, perforations and lethal perforations

	PYs	Total no. of diverticulitis (Incidence rate/1000 PYs (95% CI))	Thereof: no. of LIP (proportion, (95% CI*))	No. of patients died within 30 days after LIP (proportion, (95% CI*))
csDMARDs	18 113	34 (1.9 (1.3 to 2.6))	11 (32.4 (17.4 to 50.5))	1 (9.1 (0.0 to 41.3))
TNFi	24 851	37 (1.5 (1.1 to 2.1))	13 (35.1 (20.2 to 52.5))	3 (23.1 (5.0 to 53.8))
Tocilizumab	4082	16 (3.9 (2.2 to 6.4))	11 (68.7 (41.3 to 89.0))	5 (45.5 (16.8 to 76.6))
Abatacept	1976	1 (0.5 (0.0 to 2.8))	1 (100 (2.5 to 100))	0 (0 (0 to 97.5))
Rituximab	4950	4 (0.8 (0.2 to 2.1))	1 (25.0 (0 to 80.6))	0 (0 (0 to 97.5))
Total	53 972	92 (1.7 (1.4 to 2.1))	37 (40.2 (30.1 to 31.0))	9 (24.3 (11.8 to 41.2))

*Exact Clopper-Pearson 95% CI for the proportion.
csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; IR, incidence rate per 1000 PYs; LIP, lower intestinal perforations; PYs, patient years; TNFi, tumour necrosis factor-α inhibitor.

found.[12] GCs were the most important risk factor for LIP in this study.

Comparable to other studies, we also observed a higher risk for patients who were older, male or treated with GCs in higher dosages or NSAIDs in higher frequency. Minor differences in the distribution of these risk factors between the treatment groups did, however, not explain the higher incidence of LIPs in TCZ-treated patients. Adjustment for these factors did not decrease the HR for developing a LIP under TCZ.

Biological mechanisms may also support the increased risk of LIP in patients treated with TCZ: the interleukin 6 (IL-6) receptor targeted by TCZ seems to have an important function of the intestinal barrier. It is hypothesised that locally accumulated fat tissue may cover inflamed diverticula, similar to creeping fat in Crohn's disease which covers inflamed intestinal segments and where IL-6 is predominantly found.[20 21] Creeping fat may limit the transmural intestinal inflammation to the intestine.[22 23]

Our study has strengths and limitations. An important risk factor of LIP is previous diverticulitis that was likely underreported at enrolment into RABBIT. Adjustment for this risk factor was not possible since none of the patients with a history of diverticulitis, diverticulosis or another chronic GI disease developed a LIP. However, patients with prior diverticulitis are unlikely to be overrepresented in patients treated with TCZ since first clinical trials of TCZ reported a higher risk of LIP and the German Society for Rheumatology recommended not using TCZ in patients with a history of diverticulitis (http://dgrh.de/rheumatocilizumab.html). This may have caused a lower reporting threshold for LIP under TCZ treatment. Nevertheless, we do not assume different reporting behaviour for LIPs due to the severity of the events requiring hospitalisation and possibly leading to severe sequelae. An underreporting of LIPs is therefore not likely under any treatment. The rather constant reporting rates over time support this assumption. In addition, all LIPs were diagnosed by treating gastroenterologists or surgeons of general hospitals and not the rheumatologists participating in RABBIT.

The low numbers of LIPs observed in the register were another limitation which restricted the number of covariables in the Cox regression to adjust for confounding by indication. In addition, the risk conveyed by cumulative NSAID use could only be considered by a proxy since exact doses and start/stop dates of NSAIDs as well as the exposure prior to enrolment in RABBIT are not comprised in our data. The effect of long-term NSAID use in high doses might therefore be inadequately estimated.

The strengths of our study are the prospective design, the comprehensive case validation with independent external validation, the availability of clinical information on the course and outcome of LIP and the long-term follow-up of patients exposed to different treatments including treatment switches which allows comparative analyses.

CONCLUSION

This is the first comparative analysis of real-life data on the risk of LIP, covering all DMARDs available in Germany for the treatment of RA. In agreement with the results from the TCZ clinical development programme which qualified LIP as important identified risk, we found a rate of 2.7/1000 PYs in patients treated with TCZ. This rate was significantly higher than in other biologic agents or csDMARDs. It is of clinical importance that the majority of patients who experienced a LIP on TCZ did not have a history of diverticulitis. Further, some patients with LIP presented with relatively mild symptoms. In combination with the suppressed values of CRP under TCZ treatment, this may lead to a delayed diagnosis by non-specialised physicians not familiar with TCZ. Rheumatologists should be aware that IL-6 inhibition can be associated with an increased risk of LIP in patients with prior diverticulitis. Patients should be advised to observe signs and symptoms of LIP carefully and to inform non-specialised doctors that CRP, in their case, cannot be interpreted as a marker of diverticular inflammation. This could contribute to reduce a rare but serious risk in daily care.

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Impact of disease activity and treatment of comorbidities on the risk of myocardial infarction in rheumatoid arthritis

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Abstract

Background: The aim was to estimate the impact of individual risk factors and treatment with various disease-modifying antirheumatic drugs (DMARDs) on the incidence of myocardial infarction (MI) in patients with rheumatoid arthritis (RA).

Methods: We analysed data from 11,285 patients with RA, enrolled in the prospective cohort study RABBIT, at the start of biologic (b) or conventional synthetic (cs) DMARDs. A nested case–control study was conducted, defining patients with MI during follow-up as cases. Cases were matched 1:1 to control patients based on age, sex, year of enrolment and five cardiovascular (CV) comorbidities. Generalized linear models were applied (Poisson regression with a random component, conditional logistic regression).

Results: In total, 112 patients developed an MI during follow-up. At baseline, during the first 6 months of follow-up and prior to the MI, inflammation markers (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) but not 28-joint-count disease activity score (DAS28) were significantly higher in MI cases compared to matched controls and the remaining cohort. Baseline treatment with DMARDs was similar across all groups. During follow-up bDMARD treatment was significantly more often discontinued or switched in MI cases. CV comorbidities were significantly less often treated in MI cases vs. matched controls (36 % vs. 17 %, $p < 0.01$). In the adjusted regression model, we found a strong association between higher CRP and MI (OR for log-transformed CRP at follow-up: 1.47, 95 % CI 1.00; 2.16). Furthermore, treatment with prednisone ≥10 mg/day (OR 1.93, 95 % CI 0.57; 5.85), TNF inhibitors (OR 0.91, 95 % CI 0.40; 2.10) or other bDMARDs (OR 0.85, 95 % CI 0.27; 2.72) was not associated with higher MI risk.

Conclusions: CRP was associated with risk of MI. Our results underline the importance of tight disease control taking not only global disease activity, but also CRP as an individual marker into account. It seems irrelevant with which class of (biologic or conventional) DMARD effective control of disease activity is achieved. However, in some patients the available treatment options were insufficient or insufficiently used - regarding DMARDs to treat RA as well as regarding the treatment of CV comorbidities.

Keywords: Myocardial infarction, Cardiovascular disease, Inflammation, Disease activity, Tumour necrosis factor inhibitors, Biologicals

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Background

In rheumatoid arthritis (RA), increased morbidity and mortality due to myocardial infarctions (MI) cannot entirely explained by traditional cardiovascular (CV) risk factors [1–3]. There is evidence that the rheumatic disease itself contributes to the risk of CV events [1, 4–6], with inflammation as the link between RA and CV disease (CVD). Some of the pivotal pro-inflammatory mediators, including the cytokines tumour necrosis factor (TNF), interleukin 1 (IL-1) and interleukin 6 (IL-6) [7, 8], as well as the acute-phase reactant C-reactive protein (CRP), are involved in atherogenesis and eventually in the development of coronary artery diseases like MI [9].

A recent meta-analysis of studies investigating single nucleotide polymorphisms (SNPs) hypothesized a causal role of the IL6R-gene signalling via the inflammatory markers CRP and fibrinogen in the development of coronary heart disease (CHD) [10]. The awareness of even relatively low levels of CRP as a risk factor for MI has increased in the rheumatologic community. A few studies of MI in RA examined prospectively collected CRP [11–15]. Nevertheless, other studies have identified erythrocyte sedimentation rate (ESR) as a relevant inflammation marker in CVD [16–19]. Similarly, high disease activity measured by the composite score based on 28 joints (DAS28) is discussed to have an important influence on the risk of MI [17, 19]. The European League Against Rheumatism (EULAR) recommendations for CV risk management require "adequate control of disease activity" [20]. However, global disease activity might not be sensitive enough in patients at increased risk of MI. Therefore, the question remains whether CRP and/or ESR should be taken into account as additional targets in a treat-to-target approach. Randomised clinical trials are unable to answer this question due to the long latency to the outcome of MI, the restricted follow-up time and the exclusion of patients with major CVD. Observational studies, on the other hand, should be suitable to investigate risk factors for MI. However, comparisons between patients with RA who develop MI and the rest of the cohort are difficult to interpret in observational studies, due to significant differences in age, sex and CV comorbidities [12, 19].

To control for these confounding factors, a few studies applied a matched case-control design [21, 22], but the results are conflicting. Radovits et al. could neither confirm CRP nor DAS28 as risk factors for MI [22], whereas Mantel et al. observed significantly elevated ESR, CRP and DAS28 in cases compared to controls [21]. These contradictory results may be caused by sparse matching procedures: matching for disease duration only [22] and matching for sex, year of RA diagnosis and rheumatologic unit [21].

We pursued two aims with this study: First, to show the influence of risk factors, especially the effect of inflammation, on the incidence of MI in patients with RA. Second, we were interested in the impact of treatment: (1) the treatment of RA with disease-modifying antirheumatic drugs (DMARDs) and concomitant glucocorticoids and (2) the treatment of CV comorbidities. To preclude distorting effects we applied a case–control study with an extended matching algorithm comprising traditional CV risk factors such as age, sex and CV comorbidities.

Methods

Data source

Data from the German biologics register Rheumatoid Arthritis: Observation of Biologic Therapy (RABBIT) were used. RABBIT is an ongoing observational cohort study in which patients are included at the start of treatment with a biologic (b)DMARD or a conventional synthetic (cs)DMARD after failure of at least one prior csDMARD [23, 24]. In brief, once enrolled, patients stay in the cohort for at least the next 5 (if possible, 10) years. At regular predefined times (0, 3 and 6 months, and then every 6 months) rheumatologists complete assessment forms at clinical routine visits capturing current clinical status, treatment and all adverse events that have occurred since the last follow-up. Additionally, weight, height as well as existing comorbidities and their treatment are assessed at baseline. At all follow-up visits patients report their global health status using numerical rating scales and their disability by the Hannover Functional Status Questionnaire (FFbH), in which 100 % indicates full functional capacity [25]. Smoking habits are stated at baseline. The study protocol of RABBIT was approved by the ethics committee of the Charité University Medicine Berlin.

Study design and matching algorithm

We performed a nested case–control analysis based on exact matching where each case was randomly matched to one control patient from the same original cohort. Matching criteria were sex, age at baseline (±3 years) and CV comorbidity at baseline (hypertension, CHD, heart failure, prior cerebrovascular event and hyperlipoproteinaemia). To ensure similar availability of treatment options for each case–control pair, the year of inclusion into RABBIT (±2 years) was also added as matching criteria. Eligible controls had to to be still under observation and without a CV event at follow-up prior to the index date of the corresponding case (calendar date of the MI).

Case definition

Cases were defined as patients observed in RABBIT with an MI as the first CV event after enrolment up to

October 2013. The case definition included the following reported diagnoses: MI (acute, silent or not otherwise specified), ST segment elevation MI, non ST segment elevation MI and anterior or posterior wall infarction. For all reported MIs supplemental information on clinical symptoms, cardiac biomarkers, electrocardiographic changes and imaging results were requested on standardized forms from the rheumatologist. If available, hospital discharge letters and death certificates were reviewed. Individual patients were eligible as a case if their first ever MI had occurred prior to enrolment in RABBIT. These events are possibly subsumed in the comorbidity defined as CHD.

Validation of cases and controls

In a subgroup of patients (MIs reported to RABBIT until October 2011 and their matching controls, $n_{pairs} = 75$), on-site visits were performed to revalidate CV events and to verify the control status of the corresponding controls. During these on-site visits, the entire patient records or electronic patient files were reviewed. This comprised inpatient and outpatient records, laboratory results and hospital discharge letters. A CV event listed in the patient record during follow-up, which had not been previously reported to RABBIT, was considered as an event for the analysis. If this event was an MI and had occurred in a control patient, this patient was recategorized as a case patient and a new control patient was matched for that case. After data collection in the rheumatologic units, the diagnoses of all reviewed patients were validated in a blinded process by a physician (KG) to verify the case and control status. Only confirmed events were included.

DMARD exposure and concomitant treatment

Data on DMARD treatment are captured in RABBIT at every follow-up time point, and include agent, dose, frequency of administration and start/stop-dates. Concomitant treatment with oral glucocorticoids including dosage in prednisone-equivalents, nonsteroidal anti-inflammatory drugs (NSAIDs) and inhibitors of cyclooxygenase-2 (COX-2) are prospectively collected. In addition, rheumatologists report comorbidities and their medical treatment at baseline. Patients with hypertension, CHD, heart failure or hyperlipoproteinaemia, but without respective treatment, were labelled as having no CV treatment.

For the analysis, bDMARDs were categorized into (1) TNF inhibitor (TNFi) (adalimumab, certolizumab, etanercept, golimumab and infliximab), (2) other bDMARDs (abatacept, anakinra, rituximab and tocilizumab) and (3) csDMARDs. In groups (1) and (2) combination with csDMARD treatment was possible; group (3) was exclusively treated with one or more csDMARDs. We applied two different definitions of bDMARD exposure: to examine treatment changes in the use of bDMARDs and to determine length and frequency of bDMARD episodes we considered the first missed dose or the switch between bDMARDs as discontinuation. In contrast, in the multivariable analysis of the influence of RA treatments on the risk of MI we considered patients as being exposed to a certain DMARD class or glucocorticoid if at least one dose of the drug was prescribed within the last 6 months prior to the MI/index date.

Statistical analysis

For baseline comparison of MI cases and the remainder of the RABBIT cohort we used the *t* test and Chi-squared test. Comparisons in the matched case–control design were drawn using the paired *t* test or McNemar's test. CRP, ESR and DAS28 were analysed at different times: at baseline, within the first 6 months after enrolment and up to 18 months before the MI/index date. Persistence with enrolment therapy was investigated using Kaplan-Meier estimates. In addition, we were interested in the cumulative number of treatment changes (sequence of DMARD episodes). The switch from a csDMARD to a bDMARD or the reverse and any switch between bDMARDs were counted as treatment changes and were used to calculate treatment episodes. We assumed that the number of switches follow a Poisson distribution and applied a generalized linear mixed model with a random component for the matched case–control design.

Multiple conditional logistic regression analysis was applied to investigate the impact of risk factors on the likelihood of developing an MI (cases vs. controls). The regression model was additionally adjusted for non-matching criteria: CRP, smoking, diabetes and insufficient treatment of underlying CVD. CRP was included as reported values within 6 months prior to the MI/index date (analysis I) and as the average of all reported values from baseline until the MI/index (analysis II). Due to the skewed distribution of CRP values, log-transformed CRP values (logCRP) were calculated. A sub-analysis was applied, excluding patients with a reported CHD at baseline (N_{pairs} for the analysis = 77).

The most frequently missing data among case–control pairs were on patient-reported smoking status (25/224, 11.2 %) at baseline. In subsequent analyses these patients were considered in a separate category (unknown smoking status) and not excluded. Missing data on ESR (CRP) were less frequent: 1.4 % (0 %) at baseline and during follow-up 9.5 % (8.1 %) at most in case–control pairs. In the 6 months prior to MI, values of CRP were not available for seven pairs (six (5.4 %) cases and one (0.9 %) control). For the analysis of the course of disease activity we applied multiple imputations ($n_{Imputation} = 5$) of missing values. In conditional logistic regression we considered only pairs with observed values of ESR (CRP).

P values <0.05 were regarded as statistically significant without adjustment for multiple testing in univariate comparisons. The matching was applied using the R-package Optmatch of the freely available software R [26]. All other analyses were applied using the Statistical Analysis System (SAS) version 9.4.

Results

Between 1 May 2001 and 31 October 2013, a total of 11,285 patients were enrolled into the RABBIT register (Fig. 1). Within that period of time, rheumatologists reported 115 MIs as a first CV event. Due to the exact matching algorithm matching controls were not found for four male cases (aged 62, 64, 68 and 76 years) with heart failure as a comorbidity. They were matched to controls with heart failure but were allowed to differ from their corresponding case in no more than two comorbidities (differences in hypertension in one pair, in CHD in two pairs, in previous cerebrovascular events in two pairs and in hyperlipoproteinaemia in one pair). For two further male MI cases no appropriate controls were found, due to their comorbidity status. These two patients were excluded. Similarly, patients with non-confirmed MI (n = 3) were excluded. During on-site visits, patients with non-reported MI (n = 2) were identified and included with a matching control. In total 112 eligible case–control pairs remained for the analyses (Fig. 1).

Characteristics of matched pairs and the remainder of the cohort at baseline

Case–control pairs differed significantly from other patients in the RABBIT cohort in all matching parameters except for previous cerebrovascular events. In addition, cases differed from the cohort in most of the non-matching criteria (Table 1). Cases had significantly higher CRP, ESR and DAS28, and more impaired physical function (FFbH) and comorbidities (diabetes and chronic lung or renal disease). Compared to the cohort, MI cases were more often treated with oral glucocorticoids (93.6 % vs. 79.6 %, $p < 0.01$).

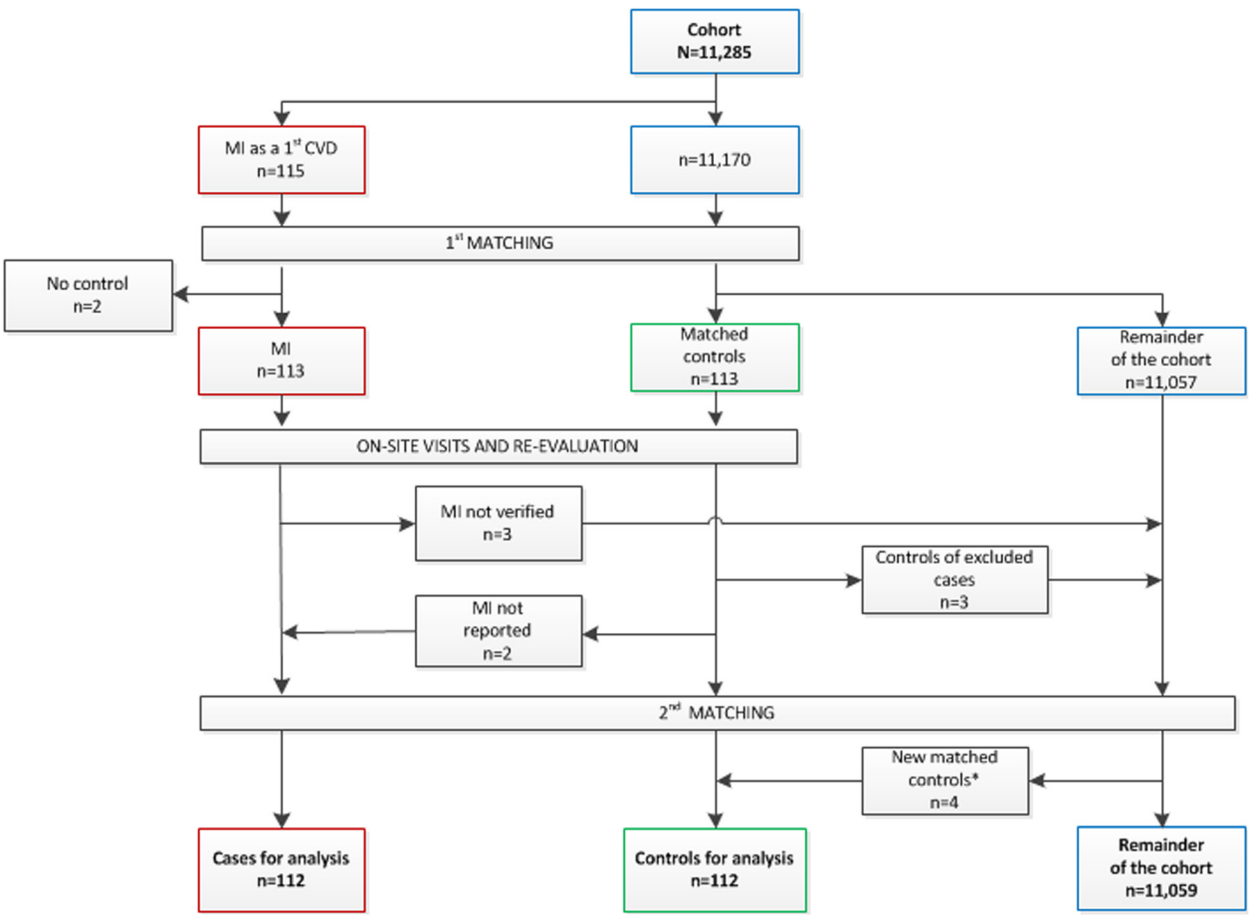

Fig. 1 Flow chart for patient selection. *Because two controls turned out to be cases, four new controls had to be found in the second matching. *MI* myocardial infarction, *CVD* cardiovascular disease

Table 1 Baseline characteristics of cases, controls and the remainder of the RABBIT cohort

	Cases n = 112	Controls n = 112	Remainder of the cohort[a] n = 11,059
Matching criteria			
Sex, male	48 (42.9)	48 (42.9)	2536 (22.9)‡
Age, years, mean (SD)	63.7 (9.1)	63.7 (9.1)	55.9 (12.5)‡
Hypertension	67 (60.4)	68 (60.7)	4102 (37.1)‡
Coronary heart disease	28 (25.2)	26 (23.2)	622 (5.6)‡
Heart failure	7 (6.3)	7 (6.3)	242 (2.2)‡
Previous cerebrovascular event	0 (0)	2 (1.8)	146 (1.3)
Hyperlipoproteinemia	19 (17.1)	18 (16.1)	869 (7.9)‡
Time to MI/index date, month, mean (SD)	31.0 (24.9)	29.5 (23.9)	NA
Unmatched criteria			
Observation time, months, mean (SD)	52.6 (28.6)	60.2 (28.0)†	44.4 (32.7)‡
Disease duration, years, mean (SD)	11.4 (10.6)	11.4 (9.4)	10.0 (9.1)
Rheumatoid factor positive	83 (74.1)	85 (75.9)	7942 (72.1)
CRP, mg/L, mean (SD)	23.5 (27.0)	16.5 (22.1)†	18.4 (26.6)‡
ESR, mm/h, mean (SD)	39.2 (28.9)	30.7 (20.6)†	31.3 (23.0)‡
DAS28, mean (SD)	5.6 (1.3)	5.5 (1.3)	5.2 (1.3)‡
FFbH, mean (SD)	53.1 (24.8)	58.4 (23.3)	63.0 (23.3)‡
Smoking, current	25 (22.3)	19 (17.0)	2355 (21.3)
Smoking, former	35 (31.3)	24 (21.4)	2589 (23.4)
Smoking, never	35 (31.3)	61 (54.5)	4698 (42.5)
Smoking, unknown	17 (15.2)	8 (7.1)	1417 (12.8)
BMI, mean (SD)	28.1 (5.6)	26.7 (4.0)†	26.6 (5.3)‡
BMI ≥30 kg/m^2	34 (30.4)	19 (17.0)†	2514 (22.7)
Diabetes mellitus	26 (23.4)	14 (12.5)†	1075 (9.7)‡
Chronic renal disease	11 (9.9)	8 (7.1)	397 (3.6)‡
COPD	12 (10.8)	13 (11.6)	495 (4.5)‡
No. of previous csDMARDs, mean (SD)	2.6 (1.4)	2.8 (1.5)	2.4 (1.3)
No. of previous bDMARDs, mean (SD)	0.5 (1.0)	0.4 (0.9)	0.3 (0.7)
Oral glucocorticoids	103 (93.6)	87 (77.7)†	8788 (79.6)‡
Glucocorticoids, <5 mg/day	12 (10.9)	29 (25.9)	2981 (27.0)
Glucocorticoids, 5–10 mg/day	64 (58.2)	46 (41.1)	4997 (45.3)‡
Glucocorticoids, ≥10 mg/day	34 (30.9)	37 (33.0)	3048 (27.6)‡
Non-selective NSAIDs	47 (42.0)	39 (34.8)	4260 (38.5)
COX-2 inhibitors	17 (15.2)	23 (20.5)	1699 (15.4)
Any NSAIDs	62 (55.4)	62 (55.4)	5895 (53.3)
No CV treatment[b]	27/75 (36.0)	13/75 (17.3)†	967/4584 (21.1)‡

Values are numbers of patients (%) unless otherwise specified. [a]Patients without myocardial infarction (*MI*) at follow-up and patients who were not matched controls. [b]No cardiovascular (*CV*) treatment: one or more of the reported cardiovascular disease (*CVD*) at baseline (hypertension, coronary heart disease, heart failure or hyperlipoproteinaemia) is not reported as being treated

BMI body mass index, *SD* standard deviation, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28* disease activity score based on 28 joints, *FFbH* Hannover Functional Status Questionnaire, *COPD* chronic obstructive pulmonary disease, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *bDMARD* biologic DMARD, *NSAID* nonsteroidal anti-inflammatory drug, *COX-2* cyclooxygenase-2, *NA* not applicable. †$P < 0.05$ for comparison with cases (paired *t* test or Mc Nemar´s test). ‡$P < 0.05$ for comparison with cases (unpaired *t* test or chi-squared test)

The enrolment therapies (TNFi, other bDMARDs or csDMARDs) were similarly distributed between cases, controls and the cohort, with 45.5 % of cases on TNFi, 21.4 % on other bDMARDs and 33.1 % on csDMARDs; the corresponding figures among controls were 42.9 %, 21.4 % and 35.7 %, and among the cohort, 50.8 %, 16.2 % and 33.0 %, respectively.

Despite good agreement in the matching criteria, there were significant differences between cases and controls in CRP and ESR, obesity (body mass index (BMI) ≥30 kg/m^2), diabetes and use of glucocorticoids. Importantly, among 75 case–control pairs with at least one baseline CV comorbidity, those patients who developed an MI during follow-up (cases) were significantly less likely to receive medical treatment for their CV comorbidity than their corresponding controls (36 % vs. 17 %, $p < 0.01$, Table 1).

Treatment with DMARDs during follow-up

The number of different DMARD episodes was significantly higher in patients with MI than in matched controls, with one episode in 51 cases (45.5 %), two episodes in 30 cases (26.8 %) and ≥3 episodes in 31 cases (27.7 %); in controls the corresponding figures were 77 (68.8 %), 19 (16.9 %) and 16 (14.3 %), respectively ($p < 0.01$, paired t test).

Persistence with bDMARD enrolment therapy was significantly lower in cases compared to controls ($p < 0.01$, log rank test). In 50 pairs who started simultaneously with a bDMARD, 54.9 % (95 % CI 38.5; 68.5) of the cases compared to 76.5 % (95 % CI 60.4; 86.7) of the controls were still on the enrolment therapy at month 12. In addition, prior to the MI/index date the number of treatment switches (between different DMARDs) was about 53 % higher in cases (Poisson regression 1.53, 95 % CI 1.04; 2.27) than in respective controls. The median duration of a DMARD episode was 7 months in cases (IQR 4–17) and 13 months in controls (IQR 6–23).

Disease activity and inflammation during follow-up

During the first 6 months from baseline, the inflammation markers CRP and ESR were significantly elevated in MI cases (Fig. 2, left; Table 2). In contrast, matched controls achieved similar improvements to the rest of the cohort (Table 2).

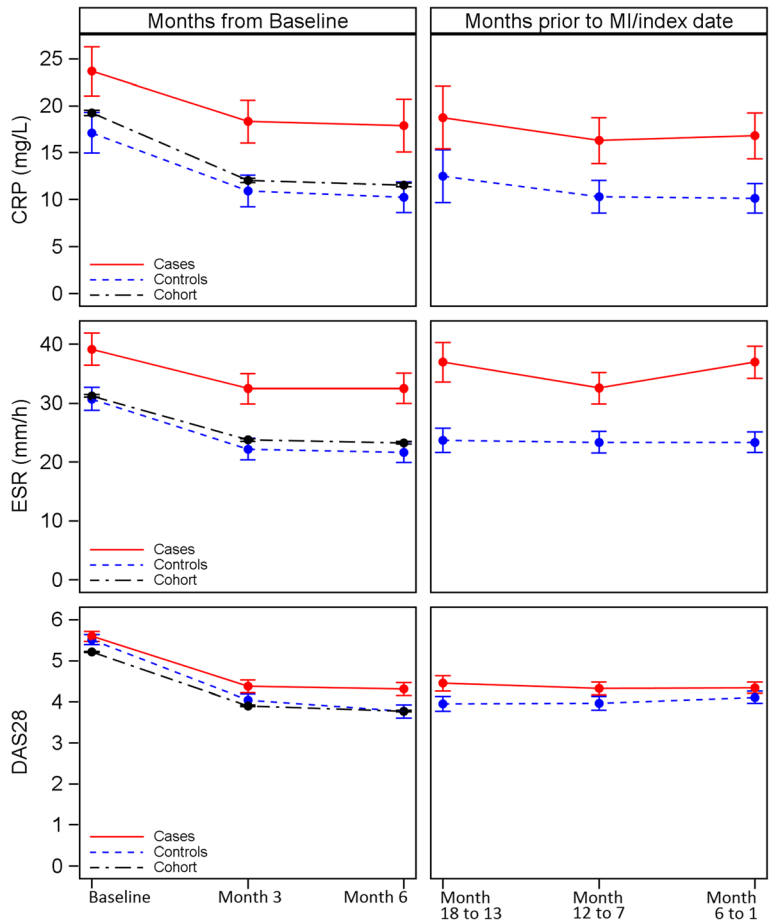

Fig. 2 Development of mean C-reactive protein (*CRP*, mg/L), mean erythrocyte sedimentation rate (*ESR*, mm/h) and mean disease activity score based on 28 joints (*DAS28*) (all presented with *error bars*) at baseline, month 3 and month 6 in cases, matched controls and the remainder of the RABBIT cohort (*left*) and 18 months prior to the myocardial infarction (*MI*)/index date in cases and matched controls (*right*)

Table 2 Development of inflammation and disease activity in cases, controls and the remainder of the RABBIT cohort stratified by enrolment therapy

	Treatment at baseline	Number	Mean at baseline (95 % CI)	Mean at month 3 (95 % CI)	Mean at month 6 (95 % CI)
CRP (mg/L)					
Cases	csDMARD	37	21.6 (12.4; 30.8)	16.3 (9.0; 23.6)	14.3 (7.3; 21.2)
	bDMARD	75	24.4 (18.2; 30.6)	19.5 (14.5; 24.5)	19.4 (13.5; 25.4)
Controls	csDMARD	40	10.2 (6.1; 14.3)	9.8 (5.1; 14.5)	8.0 (4.7; 11.3)
	bDMARD	72	20.0 (14.1; 25.9)	11.4 (7.4; 15.4)	11.0 (6.9; 15.0)
Cohort remainder	csDMARD	3656	14.1 (13.5; 14.8)	11.4 (10.8; 11.9)	11.0 (10.4; 11.5)
	bDMARD	7403	20.75 (20.1; 21.4)	12.9 (12.4; 13.3)	12.7 (12.2; 13.1)
ESR (mm/h)					
Cases	csDMARD	37	30.4 (23.9; 36.9)	27.7 (20.9; 34.5)	31.4 (23.8; 39.0)
	bDMARD	75	43.2 (35.9; 50.4)	36.8 (30.5; 43.2)	34.7 (28.7; 40.7)
Controls	csDMARD	40	26.8 (20.2; 33.4)	22.4 (16.5; 28.2)	19.4 (13.1; 25.7)
	bDMARD	72	32.8 (28.1; 37.5)	22.7 (18.4; 27.1)	22.6 (18.8; 26.4)
Cohort remainder	csDMARD	3656	27.4 (26.7; 28.0)	23.9 (23.3; 24.5)	23.5 (22.8; 24.2)
	bDMARD	7403	33.3 (32.7; 33.8)	24.4 (24.0; 24.9)	24.4 (24.0; 25.0)
DAS28					
Cases	csDMARD	37	5.2 (4.8; 5.5)	4.0 (3.5; 4.4)	3.9 (3.4; 4.3)
	bDMARD	75	5.8 (5.5; 6.1)	4.6 (4.2; 5.0)	4.6 (4.2; 5.0)
Controls	csDMARD	40	4.8 (4.4; 5.3)	4.0 (3.6; 4.5)	3.5 (3.0; 4.0)
	bDMARD	72	5.9 (5.6; 6.1)	4.1 (3.7; 4.4)	3.9 (3.6; 4.3)
Cohort remainder	csDMARD	3656	4.8 (4.7; 4.8)	3.8 (3.7; 3.8)	3.7 (3.6; 3.7)
	bDMARD	7403	5.4 (5.4; 5.5)	4.0 (3.9; 4.0)	3.9 (3.8; 3.9)

Mean values are averaged over five imputations and CI were corrected for the imputation variance
CI confidence interval, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28* disease activity score based on 28 joints, *bDMARD* biologic disease-modifying antirheumatic drug, *csDMARD* conventional synthetic DMARD

The distinct differences between cases and controls were still observed during the last 6 months (Table 3) and the last 18 months prior to the MI/index date (Fig. 2, right). Notably, no differences were found in DAS28.

The exclusion of patients with underlying CHD at baseline did not alter the course of inflammation and disease activity (Additional file 1).

Evaluation of risk factors for MI

In the univariate logistic comparison of cases and controls there was an increased risk of MI with an increase of CRP per 5 mg/L (OR 1.13 (95 % CI 1.02; 1.22) based on values obtained within 6 months prior to the MI/index date). The association with risk of MI was stronger with log-transformed CRP (1.75 (1.24; 2.46)). Similarly, averaged and log-transformed CRP over the total observation time was significantly associated with risk of MI (1.75 (1.26; 2.43)). Other significant predictors were absence of baseline CV treatment (3.60 (1.28; 12.40)) and glucocorticoids at a dosage of 5–10 mg/day (1.97 (0.98; 4.11) and ≥10 mg/day (3.02 (1.11; 8.25) vs. glucocorticoids <5 mg/day). Previous or current smoking (3.15 (1.47; 7.34)) and unknown smoking status (2.68 (1.06; 7.30)) were significant risk factors compared to not smoking. There was no significant association between increased risk of MI and TNFi or other bDMARD treatment (reference csDMARDs). The adjusted multiple conditional logistic regression revealed no association between risk of MI and treatment with TNFi or other bDMARDs, and no significantly higher risk with glucocorticoid treatment of 5–10 mg/day or ≥10 mg/day (Table 4). There was a strong association between log CRP and MI, but not between raw CRP values and MI, confirming the expected non-linear association. Smoking was confirmed as another significant risk factor.

The risk imposed by elevated CRP remained in a subanalysis of patients without CHD at baseline, although this was no longer statistically significant for values averaged over the complete observation period (until the MI/index date).

Discussion

We investigated the risk of MI in a large observational cohort study of 11,285 patients with established RA. An in-depth comparison of patients who developed MI with the remaining cohort revealed wide-ranging differences in patient characteristics and exemplified the need for an

Table 3 Characteristics of cases and matched controls within six months before the MI/index date

	Cases n = 105	Controls n = 105	*P* value
CRP, mg/L, mean (SD)	17.6 (25.0)	10.4 (14.6)	0.011
ESR, mm/h, mean (SD)	36.1 (26.5)	22.6 (16.2)	<0.001
DAS28, mean (SD)	4.3 (1.4)	4.0 (1.5)	0.22
Tender joint count, mean (SD)	4.2 (5.0)	4.4 (5.6)	0.71
Swollen joint count, mean (SD)	3.8 (5.0)	4.6 (5.4)	0.17
NRS patient global health 0–10, mean (SD)	5.1 (2.2)	4.9 (2.0)	0.41
FFbH, mean (SD)	58.7 (27.1)	61.0 (24.2)	0.32
TNFi	50 (47.6 %)	55 (52.4 %)	0.41
Other bDMARDs	21 (20.0 %)	23 (21.9 %)	0.66
csDMARDs only	33 (31.4 %)	23 (21.9 %)	0.11
Glucocorticoids, <5 mg/day	44 (41.9 %)	62 (59.6 %)	
Glucocorticoids, 5–10 mg/day	45 (42.9 %)	34 (32.7 %)	0.008
Glucocorticoids, ≥10 mg/day	16 (15.2 %)	8 (7.7 %)	
Non-selective NSAIDs	60 (57.1 %)	62 (59.0 %)	0.77
COX-2 inhibitors	28 (26.7 %)	36 (34.3 %)	0.19
Any NSAID	72 (68.6 %)	78 (74.3 %)	0.33

Case–control pairs with missing C-reactive protein (*CRP*) values were not included in this analysis. Data represent averages of all reported values within 6 months before the myocardial infarction (*MI*)/index date. All values are numbers of patients (%) unless otherwise specified. Tumour necrosis factor inhibitors (*TNFi*), other biologic disease-modifying antirheumatic drugs (*bDMARDs*) and conventional synthetic DMARDS (*csDMARDs*) were counted if the patient received at least one dose of the drug within 6 months before the MI/index date. For nonsteroidal anti-inflammatory drugs (*NSAIDs*) and cyclooxygenase-2 (*COX-2*) inhibitors, data represent use in the 24 months before the MI/index date

SD standard deviation, *ESR* erythrocyte sedimentation rate, *DAS28* disease activity score based on 28 joints, *NRS* numeric rating scale, *FFbH* Hannover Functional Status Questionnaire

Table 4 Multivariate odds ratios for the risk of MI in the nested case–control analysis

	All matched case–control pairs				Subset of cases and controls without CHD			
	I		II		I		II	
	OR	(95 % CI)	OR	(95 % CI)	OR	(95 % CI)	OR	(95 % CI)
Log CRP, prior MI[a]	1.58	(1.07; 2.33)			1.60	(1.04; 2.46)		
Log CRP, total observation[a]			1.47	(1.00; 2.16)			1.44	(0.94; 2.19)
csDMARDs only	Ref.		Ref.		Ref.		Ref.	
TNFi	0.96	(0.41; 2.22)	0.91	(0.40; 2.10)	1.24	(0.49; 3.16)	1.22	(0.49; 3.05)
Other bDMARDs	1.13	(0.34; 3.71)	0.85	(0.27; 2.72)	0.86	(0.19; 3.84)	0.53	(0.13; 2.18)
Glucocorticoids <5 mg/day	Ref.		Ref.		Ref.		Ref.	
5–10 mg/day	1.33	(0.61; 2.89)	1.22	(0.56; 2.68)	1.42	(0.59; 3.43)	1.32	(0.55; 3.17)
≥10 mg/day	2.17	(0.69; 6.81)	1.83	(0.57; 5.85)	2.48	(0.72; 8.59)	2.18	(0.61; 7.79)
No CV treatment[b]	2.76	(0.91; 8.32)	2.66	(0.88; 8.00)	2.42	(0.55; 10.77)	2.66	(0.60; 11.72)
Smoking never	Ref.		Ref.		Ref.		Ref.	
Smoking ever	3.33	(1.45; 7.63)	2.93	(1.29; 6.66)	2.13	(0.85; 5.32)	2.03	(0.69; 5.93)
Smoking status unknown	2.15	(0.82; 5.66)	2.12	(0.80; 5.65)	1.74	(0.62; 4.88)	1.84	(0.65; 5.21)
Diabetes	2.08	(0.84; 5.18)	2.32	(0.94; 5.71)	1.95	(0.68; 5.63)	1.92	(0.67; 5.51)

Case–control pairs with missing C-reactive protein (*CRP*) values were not considered in this analysis. [a]All CRP values were log-transformed. Analysis I: CRP values of the last 6 months prior to the myocardial infarction (*MI*)/index date, Analysis II: averaged CRP values from baseline until the MI/index date. [b]No CV treatment: one or more of the types of reported cardiovascular disease (CVD) at baseline (hypertension, coronary heart disease, heart failure and hyperlipoproteinaemia) is not reported as being treated. Baseline information was used for no CV treatment, smoking and diabetes. All other treatments are values within 6 months before the MI/index date

OR odds ratio, *CI* confidence interval, *CHD* coronary heart disease, *bDMARD* biologic disease-modifying anti-rheumatic drug, *csDMARD* conventional synthetic DMARD, *TNFi* tumour necrosis factor inhibitor

appropriate study design beyond covariate adjustment. To account for these differences we applied a nested case–control design using an extensive matching algorithm that enabled us to link homogeneous case–control pairs.

In a setting that controlled for traditional risk factors, we found that inflammation and smoking were significantly associated with the risk of MI in patients with RA. At baseline, during the first 6 months of follow-up and, more importantly, prior to the MI/index date (Fig. 2), there was a distinct difference in CRP and ESR levels between cases and controls. The significant differences in CRP values remained throughout the period of observation. This result confirms recent findings of others who report that the risk of MI is highest for patients with RA who have high CRP [15]. Similar to the results of the Emerging Risk Factors Collaboration [27], our data suggest a nonlinear increase in risk of MI with rising CRP. Compared with the significantly increased risk of MI with high sensitivity CRP values above 1 mg/L among the general population [28], our data suggest that the complete suppression of systemic inflammation in RA may reduce the risk of MI.

Others have reported lower risk of MI in TNFi responders vs. TNFi non-responders [29, 30]. However, based on the DAS28, patients can respond even when CRP remains high [31], which is in line with our data. Patients with MI presented with similar values of the DAS28 prior to the MI/index date compared to control patients, but with significantly elevated CRP and ESR. We conclude that the evaluation of RA disease activity solely based on the DAS28 may not be sufficient to predict risk of MI. The assessment should also comprise the inflammatory marker CRP, particularly in patients with present CVD or at increased risk of CVD.

We identified comparable treatment with DMARDs in patients who developed MI and in the matched controls at baseline only. During follow-up there were significant differences: rheumatologists switched the bDMARD treatment in cases significantly more often than in respective controls, which indicates continuous attempts to adapt the DMARD treatment. Nevertheless, switches remained ineffective in reducing CRP (Fig. 2). This result suggests that the available RA treatment options for these patients were insufficient. New biologic drugs with alternative targets have been available since 2007. A recent meta-analysis discussed IL-6 inhibition as a possible treatment target to prevent CVD [10]. This may be appropriate for patients not responding to other bDMARDs and with high average CRP. Due to the small number of tocilizumab episodes (13 of 242 cases (5.4 %) and 9 of 184 controls (4.9 %)), we could not study the impact of this treatment separately.

There are conflicting results from previous studies regarding the influence of glucocorticoid treatment on the risk of CVD. Some studies report a risk associated with higher doses of glucocorticoids [32–36]. As expected, in the univariate analysis we observed stronger association between prednisone dose and MI risk than in the multivariate analyses after adjustment for average CRP. These results suggest that the harmful effects of glucocorticoids reported by others are likely partly a result of patient channelling: patients who did not respond to the primary treatment with bDMARDs were consequently treated with glucocorticoids in higher doses. In this matter, concomitant glucocorticoids were used by rheumatologists as a kind of rescue therapy. We observed that the risk remained with glucocorticoid use ≥10 mg/day, but this was not statistically significant and needs to be investigated further in studies with sample sizes larger than ours.

An obvious but rather unexpected risk factor was detected in our data: in patients with a future MI, preexisting CV comorbidities were less frequently treated than in the corresponding control patients. This suggests that insufficient consideration of CV risk in patients with known CV comorbidities is a further risk factor for MI. There seems to be a gap between the knowledge about CV risk in RA, respective recommendations [20, 37] and the daily management of patients. Our findings confirm suboptimal risk management of CVD [38, 39]. One of the weaknesses of this study is the uncertainty about the first-ever MI. In some of the patients the information about the first MI was subsumed in the comorbidity of CHD at baseline. Therefore, we performed a sub-analysis in patients without reported CHD at baseline. We calculated consistent estimates. A strength of this study is the comprehensive on-site validation process, which revealed low numbers of underreported MI in patients with elevated risk of a CV event. However, on-site validation was stopped after reviewing 75 case–control pairs, as very little additional information was obtained on laboratory parameters or CV treatment. The size of the nested case–control study was too small to estimate the separate effects of abatacept, rituximab and tocilizumab [40, 41], or those of methotrexate, leflunomide or other csDMARDs. The total amount of missing data during follow-up was low (<10 %). Nevertheless, we applied multiple imputations but the impact on estimates was statistically and clinically insignificant when compared to an analysis of pairs with observed data only.

Conclusion

In conclusion, our results underline the importance of a treat-to-target approach, which has to take the global disease activity and CRP into account. As inflammation is the link to CVD, we consider CRP the most reliable marker to assess the risk of MI. For many patients it

seems less important by which DMARD treatment (TNFi, other bDMARD or csDMARD) the treatment target is reached. In some patients however, the available treatment options were insufficient or insufficiently used. This adds to the evidence indicating the necessity of tight disease control and adequate treatment of comorbidities.

Additional file

Additional file 1: Figure S1. Course of RA disease represented by CRP, ESR and DAS28, and restricted to patients without coronary heart disease at baseline. (DOCX 128 kb)

Abbreviations

bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; CVD, cardiovascular disease; DAS28, disease activity score based on 28 joints; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; FFbH, Hannover Functional Status Questionnaire; IL, interleukin; IQR, interquartile range; logCRP, log-transformed C-reactive protein; MI, myocardial infarction; NRS, numeric rating scale; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; RABBIT, Rheumatoid Arthritis Observation of Biologic Therapy; SD, standard deviation; SNP, single nucleotide polymorphism; TNF, tumour necrosis factor

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Authors' contributions

YM, AZ, KG, AR, JL and AS had full access to all data in this study and take responsibility for data integrity and accuracy of the analysis. Study concept and design: AZ, JL and AS. Acquisition of the data: YM, JK, KR, AL and SZ. Analysis and interpretation of the data: YM, AZ, AR, JL and AS. Drafting the manuscript: YM. Critical revision of the manuscript for important intellectual content: YM, AZ, JK, KR, AL, SZ, KG, AR, JL and AS. Obtaining funding: AZ, JL and AS. Study supervision: AZ, JL, AS and JK. All authors read and approved the manuscript.

Competing interests

Yvette Meissner: no competing interest. Angela Zink: grants and personal fees from AbbVie, BMS, MSD, Pfizer, Roche and UCB outside the submitted work. Jörn Kekow: no competing interest. Karin Rockwitz: personal fees from Roche, AbbVie, UCB, BMS and Celgen outside the submitted work. Anke Liebhaber: no competing interest. Silke Zinke: no competing interest. Kerstin Gerhold: personal fees from BMS outside the submitted work. Adrian Richter: no competing interest. Joachim Listing: personal fees from Sandoz and Pfizer outside the submitted work. Anja Strangfeld: Personal fees from BMS, MSD, Pfizer, Roche and Sanofi-Aventis outside the submitted work.

Ethical approval and consent to participate

The study protocol of RABBIT was approved by the ethics committee of the Charité University Medicine Berlin. Prior to enrolment, all patients have to give their written informed consent.

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EXTENDED REPORT

Serious adverse events and the risk of stroke in patients with rheumatoid arthritis: results from the German RABBIT cohort

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ABSTRACT

Objective In the general population, the incidence of stroke is increased following other serious events and hospitalisation. We investigated the impact of serious adverse events on the risk of stroke in patients with rheumatoid arthritis (RA), taking risk factors and treatment into account.

Methods Using data of the German biologics register RABBIT (Rheumatoid Arthritis: Observation of Biologic Therapy) with 12354 patients with RA, incidence rates (IRs) and risk factors for stroke were investigated using multi-state and Cox proportional hazard models. In addition, in a nested case–control study, all patients with stroke were matched 1:2 to patients with identical baseline risk profile and analysed using a shared frailty model.

Results During follow-up, 166 strokes were reported. The overall IR was 3.2/1000 patient-years (PY) (95% CI 2.7 to 3.7). It was higher after a serious adverse event (IR: 9.0 (7.3 to 11.0)), particularly within 30 days after the event (IR: 94.9 (72.6 to 121.9)). The adjusted Cox model showed increased risks of age per 5 years (HR: 1.4 (1.3 to 1.5)), hyperlipoproteinaemia (HR: 1.6 (1.0 to 2.5)) and smoking (HR: 1.9 (1.3 to 2.6)). The risk decreased with better physical function (HR: 0.9 (0.8 to 0.96)). In the case–control study, 163 patients were matched to 326 controls. Major risk factors for stroke were untreated cardiovascular disease (HR: 3.3 (1.5 to 7.2)) and serious infections (HR:4.4 (1.6 to 12.5)) or other serious adverse events (HR: 2.6 (1.4 to 4.8)).

Conclusions Incident adverse events, in particular serious infections, and insufficient treatment of cardiovascular diseases are independent drivers of the risk of stroke. Physicians should be aware that patients who experience a serious event are at increased risk of subsequent stroke.

INTRODUCTION

Cerebrovascular diseases are a major health concern worldwide representing the second most common cause of death and the most frequent reason for disability.[1] Two main types are distinguished—ischaemic and haemorrhagic strokes—depending on their aetiology. In the general population, risk factors for stroke are divided into *non-modifiable* such as age, gender, family predisposition or genotype and *modifiable* such as management of underlying comorbidities (eg, hypertension) or lifestyle (eg, smoking).[2 3] Recently, elevated levels of the cytokines tumour necrosis factor (TNF)-alpha and interleukin 6, as well as of high-sensitivity C reactive protein (CRP) were discussed additionally as ischaemic stroke promoters.[3]

Compared with the general population, the risk of stroke is higher in patients with rheumatoid arthritis (RA). A recently published meta-analysis states significantly higher risks for ischaemic (OR: 1.64) and haemorrhagic (OR: 1.68) strokes in patients with RA.[4] Nonetheless, investigations of risk factors for stroke in RA are scarce. In a matched case–control study, ischaemic stroke was predicted by RA severity and prevalent comorbidities.[5] Other authors identified elevated erythrocyte sedimentation rate (ESR)[6 7] and CRP values[7] as risk factors for ischaemic stroke.

Novel approaches in the general population have taken precedent adverse events (AEs) into account and showed significant associations of incident stroke with infections,[8 9] hospitalisation[10] and cancer.[11] The authors hypothesised pathogenic mechanisms of serious infections, dehydration during hospitalisation and pathophysiological complications of cancer as triggering events for stroke.

These findings suggest that prior AEs should also be considered in RA as possible triggers for stroke in addition to known risk factors. Calabrese *et al*[12] found a time-dependent risk for stroke after herpes zoster, being highest within the first 90 days after diagnosis. So far, it is unclear whether similar mechanisms or pathways also apply to other AEs in patients with RA.

The aim of our study was to investigate risk factors for non-haemorrhagic stroke in patients with RA using data of a large observational cohort study. We were interested in the impact of RA-specific disease characteristics such as inflammation, treatment with conventional synthetic (cs) or biological (b) disease-modifying antirheumatic drugs (DMARDs) and the role of other AEs regarding the risk to develop stroke. To address confounding by different risk profiles in patients with and without stroke, we performed a nested case–control study which allowed controlling for known risk factors.

PATIENTS AND METHODS

Data source and assessments

Data of the German biologics register RABBIT (Rheumatoid Arthritis: Observation of Biologic Therapy), a prospective cohort study, were used. Patients with RA are enrolled when starting treatment with a bDMARD or csDMARD after at least

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one csDMARD failure. Clinical-derived and patient-derived data are reported at predefined time points of follow-up (baseline, at 3 and 6 months, thereafter every 6 months). Regularly collected data comprise disease activity measures, treatment details (eg, start/stop dates of DMARDs and dosages of glucocorticoids) and AEs. Rheumatologists are requested to give additional information about serious AEs (SAEs) and to provide hospital discharge letters.

Comorbidities and whether they were medically treated were reported by the rheumatologists at baseline. Among others, patients specified their physical function (Hannover Functional Status Questionnaire (FFbH)[13]) and their global health. Further details of RABBIT were reported elsewhere.[14–16] The study protocol of RABBIT was approved by the ethics committee of the Charité University Medicine Berlin. Patients have to give their written informed consent prior to enrolment.

Outcome definition

All incident cerebrovascular events reported until 31 October 2015 were reviewed by the study physician of RABBIT (AS). Events were categorised as ischaemic, haemorrhagic and unclassified strokes as well as transient ischaemic attacks (TIAs) and subarachnoid haemorrhages. Only the first event of a non-haemorrhagic stroke (ischaemic or unclassified strokes or TIAs) in a patient was considered in this analysis.

In addition, all reported AEs apart from stroke classified as being serious according to the International Council for Harmonisation (ICH) definition[17] with event dates either reported by rheumatologists or from hospital discharge letters were investigated. We categorised the SAEs into: infections, cardiovascular (CV) events but not stroke, surgeries and all remaining SAEs.

Study design: cohort study and nested case–control study

Risk factors for stroke were first analysed with data from the entire cohort. Second, we performed a nested case–control study. Patients who developed a stroke were selected as cases. We applied an extensive matching algorithm with a 1:2 ratio (one case: two controls; they form one cluster). Exact agreement of cases and their controls was required regarding gender, hypertension, coronary heart disease, heart failure, diabetes,

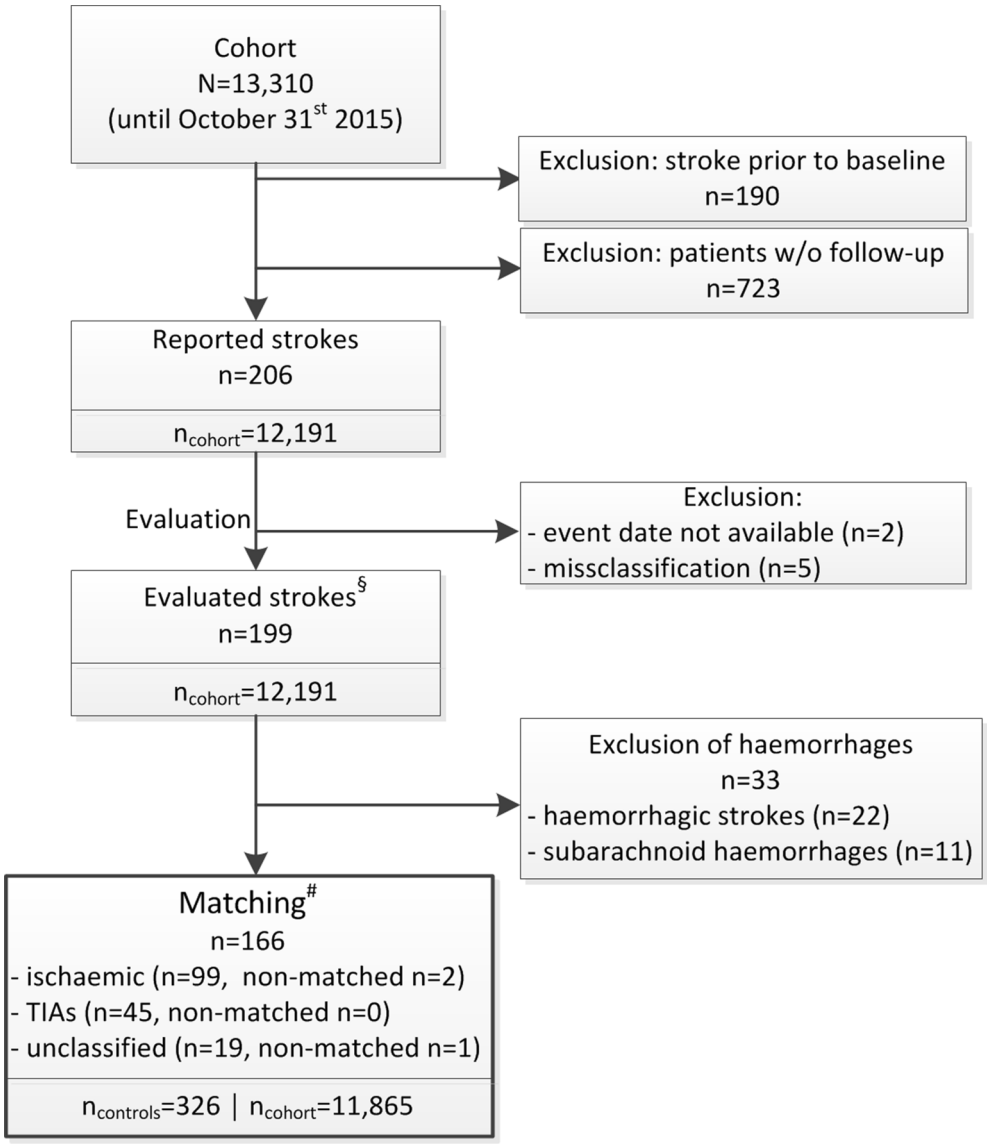

Figure 1 Flow chart for patient selection and matching. §Diagnoses of evaluated events are listed in the online Supplementary table 1. #Cases were matched to potential controls in a 1:2 manner using the following criteria: gender, age at baseline (±5 years), enrolment episode (2001–2006 and 2007–2015), four baseline comorbidities (hypertension, coronary heart disease, heart failure and diabetes) and smoking habits (never and ever/unknown). Patients with no possible matching are listed in the online Supplementary table 2. TIA, transient ischaemic attack; w/o, without.

smoking habits (never vs ever/unknown) and enrolment episode (2001–2006 and 2007–2015). Age had to be similar in cases and controls (±5 years). Eligible controls had to be under observation at the date of stroke of the matching case (index date).

Definition of treatment exposure

Treatment with DMARDs was categorised into (1) TNF-inhibitors (TNFi) (adalimumab, certolizumab, etanercept, golimumab and infliximab), (2) other bDMARDs (abatacept, anakinra, rituximab and tocilizumab) and (3) csDMARDs. In (1) and (2), a combination with csDMARDs was possible; group (3) was exclusively treated with one or more csDMARD(s). Patients were considered to be exposed to a certain bDMARD up to 3 months after treatment discontinuation (rituximab: 9 months after last infusion).

Current and cumulative treatment was investigated for the use of non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids. The cumulative treatment with NSAIDs was calculated for each patient as the portion of observation time exposed to NSAIDs (range: 0–1). Similarly, cumulative treatment with glucocorticoids was calculated, but additionally weighted for different doses: each month with a dose of >5–10 mg/day was considered with a weight of 0.5 and each month with a dose of >10 mg/day with a weight of 1. The total sum over all weights was divided by the number of follow-up months (range: 0–1).

Patients with hypertension, coronary heart disease, heart failure or hyperlipoproteinaemia but without drug treatment

Table 1 Baseline characteristics of the RABBIT cohort, cases (patients who developed stroke during follow-up) and their matched controls

	Remainder of the cohort, n=11 865	Controls, n=326	Cases, n=163
Matching criteria			
Gender, female	9071 (76.5)	244 (74.8)	122 (74.8)
Age (years), mean (SD)	55.8 (12.5)*	62.6 (10.2)	63.4 (10.7)
Hypertension	4354 (36.7)*	184 (56.4)	92 (56.4)
Coronary heart disease	672 (5.7)	30 (9.2)	15 (9.2)
Heart failure	262 (2.2)	6 (1.8)	3 (1.8)
Diabetes mellitus	1157 (9.8)*	54 (16.6)	27 (16.6)
Smoking, never	5153 (43.4)	132 (40.5)	66 (40.5)
Smoking, ever and unknown	6712 (56.6)	194 (59.5)	97 (59.5)
Enrolment period (prior 2007)	4773 (40.2)*	174 (53.4)	87 (53.4)
Unmatched criteria			
Time to event/index date (months), mean (SD)	.	46.6 (31.9)	46.6 (32.0)
Observation time (months), mean (SD)	48.9 (33.0) *	73.7 (32.8)	68.3 (32.3)
Disease duration (years), mean (SD)	9.7 (9.0)	11.3 (9.7)	10.9 (9.2)
Rheumatoid factor positive	8379 (71.2)*	250 (77.2)	128 (79.0)
CRP (mg/L), mean (SD)	18.4 (26.0)*	21.4 (39.6)	24.2 (31.3)
ESR (mm/hour), mean (SD)	30.7 (22.7)*	33.2 (23.3)	35.6 (25.6)
DAS28, mean (SD)	5.1 (1.3)*	5.4 (1.4)	5.4 (1.3)
% of full physical function, mean (SD)	64.0 (23.1)*	60.3 (22.8)	54.0 (23.8)
NRS patient global health 0–10, mean (SD)	6.0 (2.1)*	6.1 (2.1)	6.5 (2.2)
BMI ≥30 kg/m^2	2818 (23.8)	76 (23.3)	41 (25.2)
Hyperlipoproteinaemia	921 (7.8)*	39 (12)	27 (16.6)
Chronic renal disease	437 (3.7)*	24 (7.4)	12 (7.4)
Osteoporosis	2089 (17.6)*	77 (23.6)	49 (30.1)
≥2 comorbidities	4634 (39.1)*	181 (55.5)†	102 (62.6)
No CV treatment	1038/4849 (21.4)*	41/195 (21.0)†	35/104 (33.7)
No diabetes treatment	226/1157 (19.5)	16/54 (29.6)	4/27 (14.8)
No osteoporosis treatment	325/2089 (15.6)	13/77 (16.9)	6/49 (12.2)
No of previous csDMARDs, mean (SD)	2.2 (1.4)	2.6 (1.4)	2.6 (1.5)
No of previous bDMARDs, mean (SD)	0.3 (0.7)	0.3 (0.6)	0.4 (0.9)
Enrolment therapy: csDMARD	3874 (32.9)	110 (34.2)	47 (29.6)
Enrolment therapy: TNFi	6009 (51.0)	157 (48.8)	81 (50.9)
Enrolment therapy: other bDMARD	1907 (16.2)	55 (17.1)	31 (19.5)
Glucocorticoids, <5 mg/day	4748 (40.0)	136 (41.7)	49 (30.1)
Glucocorticoids, 5–10 mg/day	4718 (39.8)	133 (40.8)	82 (50.3)
Glucocorticoids, ≥10 mg/day	2351 (19.8)	54 (16.6)	32 (19.6)
Any NSAID	6150 (51.8)	189 (58)	89 (54.6)

Values are numbers of patients (%) unless otherwise specified.
*p<0.05 in unpaired tests versus cases (t-test or χ^2 test).
†p<0.05 in paired tests versus cases (linear mixed effects model with a random component, differences in comorbidity treatment were analysed with χ^2 test).
bDMARD, biological disease-modifying anti-rheumatic drug; BMI, body mass index; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; DAS28, disease activity based on 28 joint count; ESR, erythrocyte sedimentation rate; NRS, numeric rating scale; NSAID, non-steroidal antirheumatic drug; TNFi, inhibitors of tumour necrosis factor alpha.

Table 2 Disease characteristics in the cohort and in the nested case–control study in different time periods

	Cohort study	Nested case–control study	
	Remainder of the cohort	Controls	Cases
Disease activity and inflammation			
Averages during the first year of follow-up after enrolment			
DAS28 (95% CI)	**4.25 (4.23 to 4.27)**	4.37 (4.24 to 4.51)	4.62 (4.45 to 4.80)
CRP (mg/L) (95% CI)	**13.42 (13.10 to 13.73)**	14.27 (12.23 to 16.31)	18.50 (14.32 to 22.68)
ESR (mm/hour) (95% CI)	**25.69 (25.36 to 26.02)**	27.03 (24.94 to 29.12)	30.79 (27.61 to 33.96)
Values within a 6 months risk window before the event/index date			
DAS28 (95% CI)		**3.50 (3.31 to 3.69)**	4.06 (3.79 to 4.34)
CRP (mg/L) (95% CI)		8.02 (6.12 to 9.93)	16.19 (8.12 to 24.26)
ESR (mm/hour) (95% CI)		21.45 (18.93 to 23.97)	27.98 (23.68 to 32.29)
Treatment			
Time from baseline until event/index date			
Cumulative doses of GC			
Exposure to 0–5 mg/day		77.7% (74.2 to 81.3)	73.0% (68.2 to 77.7)
Exposure to ≥10 mg/day		4.1% (2.5 to 5.8)	5.2% (2.8 to 7.5)
Cumulative use of Cox-2-Inh.		0.12% (0.09 to 0.15)	0.15% (0.11 to 0.19)

Bold indicates significant values compared to case patients.
Cox-2-Inh., inhibitors of cyclooxygenase-2; CRP, C-reactive protein; DAS28, disease activity based on 28 joint count; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; NSAIDs, non-steroidal anti-inflammatory drugs.

for this condition(s) were labelled as having 'no CV treatment'. Patients with diabetes or osteoporosis and no treatment were marked accordingly.

Statistical analysis

For baseline comparisons in the cohort study, t-test and χ^2 test were applied. In the matched case–control study, univariate linear mixed effects models with a random component for each cluster were used to test for differences between cases and controls.

Risk factors for stroke were investigated using two different approaches: In approach 1, we applied univariate and multiple Cox proportional hazard (PH) models in (1) the whole cohort and (2) the nested case–control study. In the case–control study, we considered the matching structure by the application of a shared frailty Cox regression model,[18] which can be interpreted like Cox-PH models (for further explanations see online Supplementary text).

In approach 2, we adapted the idea of *multi-state models*[19 20] (online Supplementary figure 1). In brief, we were interested in the cumulative incidence of stroke in patients who (1) did not develop or (2) developed an SAE other than cerebrovascular prior to stroke. Exact Poisson confidence intervals were calculated for incidence rates (IRs). Furthermore, we estimated cause-specific hazards to investigate risk factors for stroke in patients without prior SAEs. In this model, patients were censored at the end of the observation (index date) or when other SAEs occurred, whatever came first.

Due to the skewed distribution of CRP values, we used a log-transformation (logCRP) in all models.

Missing data at baseline most frequently concerned smoking status (10.2%), CRP (6.5%), disease activity based on 28 joint count (DAS28) (4.6%) and ESR (3.6%). To analyse the course of disease activity and inflammation, we applied five multiple imputations of missing values. Missing smoking status was coded as a separate category (smoking unknown).

Estimates are shown with 95% CI. Matching was applied using the R-package Optmatch.[21] Data were analysed using SAS V.9.4 software.

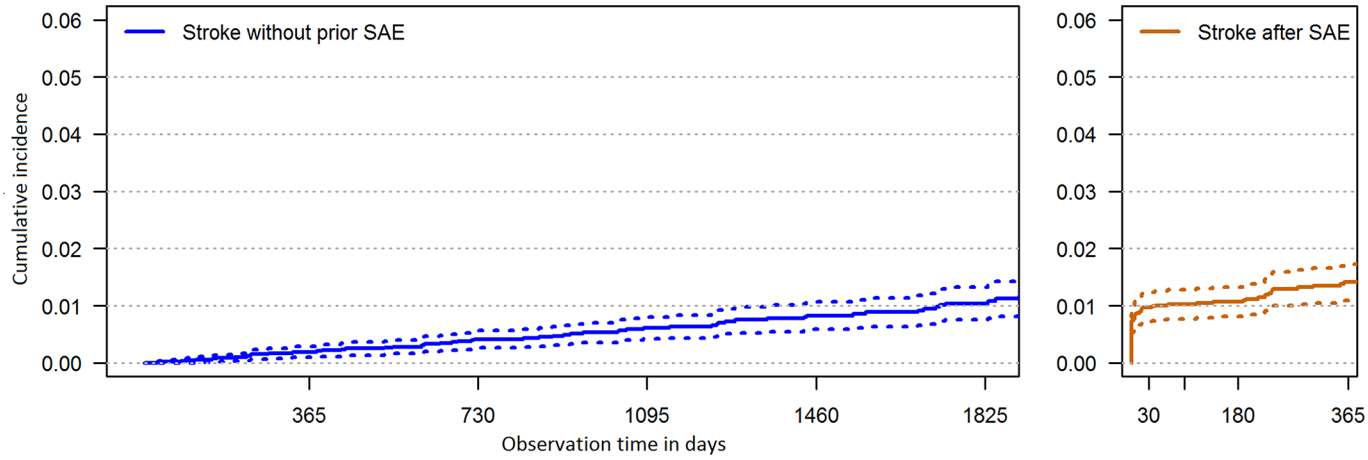

Figure 2 Probability of stroke in patients with and without prior SAE.
(Left) The probability of stroke after enrolment in patients without any serious adverse event (SAE) prior to stroke; time in days from baseline. (Right) The probability of stroke after SAE; time in days after SAE.

RESULTS

Until 31 October 2015, 206 incident cerebrovascular events were reported (figure 1). We excluded two patients without an available event date and five patients with a misclassification of the reported event. Of 199 events, the majority were ischaemic strokes (n=101, 50.8%), followed by TIAs (n=45, 22.6%), haemorrhagic (n=22, 11.1%) and unclassified strokes (n=20, 10.1%) as well as subarachnoid haemorrhages (n=11, 5.5%). Corresponding baseline characteristics are presented in the online Supplementary table 3. Of the 166 events considered in this analysis (ischaemic strokes, unclassified strokes and TIAs), 163 could be matched to controls (n=326). For one female and two male cases, matching was not possible (online Supplementary table 2).

Patient characteristics at baseline

Case and control patients were 7 years older than the average cohort patient and differed significantly in comorbid hypertension, diabetes, enrolment period and disease activity at baseline (table 1).

A significant difference between cases and controls was found regarding the treatment of comorbidities. Of 104 case patients with at least one baseline CV comorbidity, 35 (34%) did not receive CV drug treatment, compared with 21% in controls and in the remaining cohort. Thereof, major gaps were seen regarding hyperlipoproteinaemia (no drug treatment in 78% of cases, 44% of controls and 47% in the cohort) and coronary heart disease (no drug treatment in 40% of cases, 30% of controls and 19% in the cohort). These significant differences in the management

Table 3 Investigation of risk factors for stroke

	Cohort study		Nested case–control study	
	Univariate analysis	Adjusted Cox-PH model	Univariate analysis	Adjusted shared frailty model
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age per 5 years*	1.42 (1.32 to 1.54)	1.37 (1.25 to 1.50)		
Gender, male*	1.19 (0.84 to 1.70)	1.03 (0.70 to 1.52)		
logCRP	1.30 (1.12 to 1.52)	1.16 (0.99 to 1.35)	1.41 (1.17 to 1.70)	1.17 (0.98 to 1.40)
ESR	1.07 (1.04 to 1.11)		1.06 (1.02 to 1.09)	
DAS28	1.28 (1.15 to 1.42)		1.33 (1.17 to 1.51)	
% of full physical function per 10 points	0.83 (0.78 to 0.88)	0.90 (0.84 to 0.96)	0.92 (0.86 to 0.98)	0.85 (0.78 to 0.93)
Hypertension*	2.47 (1.81 to 3.37)	1.33 (0.95 to 1.86)		
Coronary heart disease*	1.91 (1.12 to 3.25)			
Heart failure*	1.12 (0.36 to 3.52)			
Hyperlipoproteinaemia	2.57 (1.70 to 3.89)	1.60 (1.04 to 2.45)	1.60 (1.05 to 2.44)	
Diabetes mellitus*	2.13 (1.41 to 3.21)	1.26 (0.82 to 1.94)		
Chronic renal disease	2.91 (1.61 to 5.25)	1.28 (0.69 to 2.36)	1.92 (1.06 to 3.49)	
Osteoporosis	1.84 (1.32 to 2.57)	1.09 (0.77 to 1.56)	1.47 (1.05 to 2.06)	
≥2 comorbidities	2.89 (2.10 to 3.97)		1.99 (1.44 to 2.76)	
No CV disease (Reference)				
CV disease with therapy	2.41 (1.70 to 3.42)		1.51 (0.98 to 2.32)	1.81 (0.85 to 3.82)
CV disease and no therapy	4.31 (2.83 to 6.54)		3.11 (1.89 to 5.10)	3.31 (1.52 to 7.19)
csDMARD (Reference)				
TNFi	0.82 (0.60 to 1.12)	0.85 (0.60 to 1.20)	1.23 (0.87 to 1.73)	0.82 (0.52 to 1.28)
Other bDMARDs	0.89 (0.60 to 1.31)	0.89 (0.58 to 1.37)	0.83 (0.55 to 1.27)	0.64 (0.37 to 1.13)
No of previous bDMARDs	1.16 (0.96 to 1.39)		1.26 (1.05 to 1.51)	1.34 (1.00 to 1.79)
No of previous csDMARDs	1.00 (0.89 to 1.12)		0.88 (0.79 to 0.98)	
Glucocorticoids, current by 5 mg/day	1.11 (1.00 to 1.24)		1.25 (0.99 to 1.58)	0.90 (0.71 to 1.14)
Glucocorticoids, weighted†	1.72 (0.85 to 3.44)	1.17 (0.56 to 2.45)	0.80 (0.22 to 3.00)	
Non-selective NSAIDs, weighted†	1.04 ([0.74 to 1.47)		1.19 (0.85 to 1.68)	
Cox-2 inhibitors, weighted†	1.34 (0.85 to 2.13)	1.30 (0.82 to 2.06)	1.22 (0.77 to 1.93)	
Smoking, never* (Reference)				
Smoking, ever	1.37 (0.99 to 1.89)	1.87 (1.33 to 2.64)		
Smoking, unknown	1.14 (0.60 to 2.17)	1.19 (0.63 to 2.28)		
SAEs, 6 months prior stroke				
Overall			3.31 (2.18 to 5.02)	
Serious infections			4.23 (2.03 to 8.81)	4.39 (1.55 to 12.46)
CV events (other than stroke)			3.02 (1.38 to 6.65)	2.87 (0.94 to 8.74)
Surgeries			1.00 (0.49 to 2.04)	0.87 (0.33 to 2.27)
All other SAEs			3.36 (2.10 to 5.37)	2.61 (1.42 to 4.81)

Baseline information was used for age, all comorbidities, CV treatment and smoking.
*Matching criteria were not considered in the model of the case–control study.
†The weighted approach is explained in the methods section.
bDMARD, biological disease-modifying antirheumatic drug; COX-2 inhibitors, inhibitors of cyclooxygenase-2 ; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; DAS28, disease activity based on 28 joint count; ESR, erythrocyte sedimentation rate; NSAID, non-steroidal antirheumatic drug; SAE, serious adverse event; TNFi, inhibitors of tumour necrosis factor alpha.

of comorbid conditions were not found for diabetes and osteoporosis.

Cumulative incidence of stroke and influences of SAEs in the cohort

The overall rate of incident non-haemorrhagic strokes (n=166) in the RABBIT cohort was 3.2/1000 patient-years (PY) (95% CI 2.7 to 3.7) (online Supplementary figure 2). The IR in patients with no prior SAE was 2.2/1000 PY (95% CI 1.8 to 2.8] and with prior SAE 9.0/1000 PY (95% CI 7.3 to 11.0).

We found a linear increase in the cumulative incidence of stroke in patients who did not experience any SAE prior to stroke (figure 2, left). In contrast, there was an excess risk within the first 30 days after SAEs (figure 2, right). In this interval, the IR was 94.9/1000 PY (95% CI 72.6 to 121.9), dropping significantly to 3.4 (95% CI 2.4 to 4.8) in the period thereafter. Of all reported SAEs, 87.0% led to hospitalisation.

Disease characteristics and treatment of cases, controls and the remaining cohort during follow-up

Patients with stroke presented with significantly higher DAS28 and inflammation markers during the first year of follow-up compared with the remaining cohort in unadjusted analyses. In the nested case–control study, values were insignificantly higher in cases than in controls (table 2). Within 6 months before the event/index date, the mean DAS28 was significantly higher in cases compared with controls.

No differences were observed in the cumulative doses of glucocorticoids, or the use of non-selective NSAIDs and Cox-2 inhibitors.

Risk factors for stroke

In the cohort study, univariate analysis showed a significantly lower risk for stroke in patients with better physical function (FFbH) (table 3). Older age, high values of CRP, ESR and the DAS28 were significantly associated with a higher risk for stroke. Comorbidities such as hypertension, hyperlipoproteinaemia, diabetes, osteoporosis and particularly chronic renal disease were associated with a higher risk for stroke. Except for the current treatment with glucocorticoids, none of the treatments with csDMARDs or bDMARDs, non-selective NSAIDs or Cox-2 inhibitors were associated with the risk for stroke. The highest risk for stroke was found in patients with untreated CV diseases (HR 4.3 (95% CI 2.8 to 6.5)). In the adjusted cohort analysis, only the impact of higher age, physical function and hyperlipoproteinaemia were affirmed. Smoking (ever vs never) was additionally identified as risk factor.

In the nested case–control study, univariate analysis showed likewise that high levels of CRP, ESR and DAS28 as well as a poor physical function were significantly associated with a higher risk for stroke (table 3). Significant but smaller effects were found for the comorbidities hyperlipoproteinaemia, chronic renal disease and osteoporosis. Untreated CV comorbidities and the development of SAEs ≤6 months prior to stroke had the strongest association with the risk for stroke. This effect was confirmed in the adjusted shared frailty model with a HR of 3.3 (95% CI 1.5 to 7.2) for untreated CV disease. Regarding SAEs, we found the largest impact for prior serious infections with an HR of 4.4 (1.6 to 12.5). Further significant influences were found for physical function and the number of bDMARD treatments before entering RABBIT. In contrast, current treatment with TNFi, other bDMARDs and glucocorticoids had no association.

To investigate the impact of risk factors in patients without a prior SAE, a cause-specific hazard model was applied (approach 2, table 4). In this model, the associations between physical function as well as untreated CV comorbidities and stroke remained significant. However, the effect size of untreated CV diseases was attenuated to an HR of 2.3 (1.2 to 4.5). The influence of the number of bDMARD treatments before cohort entry was no longer significant.

Table 4 Cause-specific hazard ratios of stroke in patients without prior SAE

Nested case–control study	
	HR (95% CI)
logCRP	1.14 (0.90 to 1.45)
% of full physical function, per 10 points	0.88 (0.79 to 0.97)
No CV disease (Reference)	
CV disease with therapy	1.13 (0.65 to 1.98)
CV disease and no therapy	2.27 (1.15 to 4.49)
csDMARD (Reference)	
TNFi	0.73 (0.43 to 1.24)
Other bDMARDs	0.65 (0.30 to 1.41)
No of previous bDMARDs	1.18 (0.86 to 1.62)
Glucocorticoids, current by 5 mg/day	0.74 (0.52 to 1.04)
Non-selective NSAIDs	1.34 (0.78 to 2.32)
Cox-2 inhibitors	1.38 (0.70 to 2.71)

Patients are censored at the end of the observation (index date) or at the occurrence of other SAEs, whatever comes first.
bDMARD, biological disease-modifying anti-rheumatic drug; COX-2 inhibitors, inhibitors of cyclooxygenase-2.; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; NSAID, non-steroidal antirheumatic drug; SAE, serious adverse events; TNFi, inhibitors of tumour necrosis factor alpha.

DISCUSSION

We examined the incidence and risk for stroke in a large cohort of patients with RA. The known risk factors age and smoking as well as hyperlipoproteinaemia and a poor physical function were associated with an increased risk. The IR for stroke was highest in patients who experienced another SAE within 30 days prior to stroke. In a nested case–control study with patients at comparable risk for stroke, the absence of CV treatment despite CV comorbidity was associated with a high risk for incident stroke. The highest impact was found for prior serious adverse events, particularly serious infections.

Our results support findings in the general population[8 9] and in patients with autoimmune diseases,[12] which suggest that stroke may be triggered by other adverse events. Compared with the overall IR of 3.1 strokes per 1000 PY, we observed a high IR of 8.7/1000 PY for patients with a previous adverse event other than cerebrovascular. The association was clearly time-dependent being highest within 30 days (IR: 93.3/1000 PY) after the serious event and dropping thereafter to 3.2. This is in line with results from Smeeth *et al* who reported an IR ratio (IRR) of 3.2 (95% CI 2.8 to 3.6) during the first 3 days after respiratory tract infections, gradually decreasing in the following weeks.[22] Others observed more strokes within 6 days after hospital admission.[10] In patients with autoimmune diseases, the risk was highest within 90 days after herpes zoster with an IRR of 1.4 (95% CI 1.1 to 1.7).[12]

Reasons for the contribution of SAEs to the occurrence of stroke may be diverse. Patients may rest in bed during their illness, with consequences of dehydration and hypercoagulability that can promote embolic events. Previous studies characterised

patients with in-hospital onset ischaemic strokes, indicating, among others, fever, high blood pressure, dehydration,[10] female gender and atrial fibrillation as risk factors.[23]

Our data revealed a more than fourfold risk for stroke after serious infections, followed by other SAEs. For CV events, the estimator did not reach statistical significance. Interestingly, surgeries had no effect on the occurrence of stroke (adjusted HR 0.9 (95% CI 0.3 to 2.3)).

Insufficient treatment of CV diseases[24 25] and inadequate risk management in RA[26 27] were debated widely in recent years. We found that patients who experienced a stroke had been treated less often for their underlying CV diseases compared with control patients or the remaining cohort. This finding is in line with our study on myocardial infarction.[28] To preclude a general underreporting of treatment for comorbidity in patients with stroke, we examined the reporting of other comorbidities. Osteoporosis and diabetes were more stringently managed in patients with a future stroke, indicating that awareness for comorbidities differs. However, the guidelines consider the rheumatologist responsible for risk management of CV diseases in RA, in collaboration with cardiologists and other disciplines.[29]

The treatment with bDMARDs did not influence the occurrence of strokes which is consistent with previous findings.[5 30–33] Regarding the effect of glucocorticoids we did not find an association with stroke in the adjusted model and in the nested case–control study. This is in line with previous studies that did not find a negative effect of glucocorticoids on the risk for stroke.[5 34 35]

Inflammation is discussed as a risk factor for stroke in the general population and in patients with RA,[3 6 7] and even considered in the current guidelines for primary stroke prevention of the American Heart Association.[36] The association between markers of inflammation and disease activity with the incidence of stroke persisted in our study only in unadjusted analyses. This is in contrast to findings for myocardial infarction.[28] However, it implies the possibility of an SAE-driven elevation of inflammation markers. In the cause-specific model, which estimates the risk for stroke without the influence of SAEs, the estimator of logCRP was non-significant (HR 1.1 (95% CI 0.9 to 1.5)) not supporting the idea of CRP as a risk factor for stroke.

Our study has several strengths and limitations. The large RABBIT cohort with well-monitored follow-up data[16] enabled us to analyse patients with similar baseline risk for incident stroke, using a nested case–control design. Stroke is a slowly evolving event,[37] and controls were required to have a minimum observation time corresponding to their matching case. Requesting the same observation time as matching criteria is a limitation of the study design too, which may imply a selection bias of patients with better controlled disease and less frequent SAEs. This peculiarity may bias the cumulative incidence of strokes after the development of SAEs. Therefore, we omitted this criterion in a sensitivity analysis which confirmed the findings of the main analysis (data not shown). A remaining limitation of shared frailty models rests with the lack of diagnostic tools for evaluation of model assumptions beyond the distribution of random effects.

CONCLUSION

Aside from traditional risk factors, we found that insufficient CV treatment and the occurrence of other SAEs increased the risk for stroke in patients with RA. These findings, on the one hand, underline the need for rigorous management of CV diseases, on the other hand support results found in the general population which suggest expanding the traditional risk model for stroke by incident other adverse events. This could help to identify patients and clinical situations at increased risk for stroke.

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Contributors YM, AR, JL, AZ and AS: had full access to all data of this study and take responsibility for data integrity and accuracy of the analysis. YM, AR, JL, AZ and AS: study concept and design. BM, HPT and EW: acquisition of the data. YM, AR, and AS: analysis and interpretation of the data. YM: drafting the manuscript. YM, AR, BM, HPT, EW, JL, AZ and AS: critical revision of the manuscript for important intellectual content. AZ and AS: obtaining funding. All authors read and approved the manuscript.

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Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Komplette Publikationsliste

Meissner Y, Richter A, Manger B, Tony HP, Wilden E, Listing J, Zink A, Strangfeld A. *Serious adverse events and the risk for stroke in patients with rheumatoid arthritis. Results from the German RABBIT cohort.* Ann Rheum Dis. 2017 Sep.;76(9):1583-1590.

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