TNF-α INHIBITOR TREATMENT AND THE RISK OF CARDIOVASCULAR EVENTS IN PATIENTS NEWLY DIAGNOSED WITH RHEUMATOID ARTHRITIS

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ABSTRACT

RISHI J DESAI: TNF-α inhibitor treatment and the risk of cardiovascular events in patients newly diagnosed with rheumatoid arthritis
(Under the direction of Dr. Joel Farley)

Rheumatoid arthritis (RA) is an autoimmune disease that is mainly treated with various non-biologic and biologic disease modifying anti-rheumatic drugs (DMARDs). RA patients experience cardiovascular diseases (CVD) at a higher rate compared to the general population. Biologic DMARDs that inhibit the effects of the pro-inflammatory cytokine, tumor necrosis factor (TNF)-α which is implicated in various atherosclerotic processes, may reduce the risk of CVD. Very little evidence exists evaluating the association between TNF-inhibitors (TNF-Is) and CVD in early RA patients.

Using data from Truven's MarketScan claims database for the period of 2007-2010, we first examined the factors influencing treatment with biologics in RA patients in a retrospective cohort study. We observed that treatment initiation with biologics in RA patients is associated with patient age, RA severity, RA type, pre-index non-biologic DMARD and steroid use, health insurance type, and drug benefit generosity. Neither the presence of cardiovascular risk factors, hypertension, hyperlipidemia or diabetes nor the history of CVD, including acute myocardial infarction, chronic heart failure, stroke or other CVD, were found to be associated with the initiation of biologic treatments.

We then evaluated the impact of treatment with TNF-Is on the risk of incident CVD events in patients newly diagnosed with RA using a nested case-control design with incidence density sampling. We observed that the risk of an incident CVD event was reduced by current treatment with TNF-Is and non-biologic DMARDs compared to no treatment with DMARDs. Further, we observed that this protective effect was found to be associated with the duration of TNF-I and non-biologic DMARD use in a linear manner. Finally, we examined the independent effects of infliximab, adalimumab and etanercept on the risk of CVD in the same cohort. We observed that treatment with adalimumab, but not with infliximab and etanercept, was found to be associated with a reduced risk of incident CVD events compared to no treatment with DMARDs.

In conclusion, we observed that early TNF-I or non-biologic DMARD treatment may play a vital role in reducing the increased CVD burden in RA patients, potentially by producing favorable changes in traditional cardiovascular risk factors and RA risk factors.

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LIST OF ABBREVIATIONS

AMI	Acute myocardial infarction
CAD	Coronary artery disease
CHF	Chronic heart failure
CVA	Cerebrovasculr accident
CVD	Cardiovascular disease
DMARD	Disease modifying anti-rheumatic agent
HR	Hazard ratio
IHD	Ischemic heart disease
IRR	Incidence rate ratio
MSA	Metropolitan statistical area
MTX	Methotrexte
OR	Odds ratio
RA	Rheumatoid arthritis
RR	Risk ratio
TNF-I	Tumor necrosis factor-α inhibitors

CHAPTER 1

INTRODUCTION

1.1 Overview:

Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammation of the synovium, a membrane that lines the joint capsule and produces lubricating fluid in the joint, leading to disability in most cases (1). Data from 2008 suggest that RA affects approximately 1.3 million adults in the United States (2). Disease onset generally occurs between ages 30 and 50 years, and the incidence is higher in women and older adults. During the past 20 years, pharmacotherapy of RA has evolved to include treatment with one or more disease modifying anti-rheumatic drugs (DMARD) with a goal of controlling inflammation and preventing joint damage (3). DMARDs are generally classified into non-biologic (traditional) and biologic agents. Non-biologic DMARDs include orally-administered medications such as methotrexate (MTX), sulfasalazine hydroxychloroquine, and leflunomide. These agents halt the progression of RA through reducing inflammation by suppressing systematic immune response; however their suppression of the immune system is non-selective. Biologics differ from non-biologic DMARDs because they target specific components of the immune system, specifically cytokines such as Tumor necrosis factor (TNF)-α and interleukins. Biologics are administered intravenously or subcutaneously.

Patients with RA experience cardiovascular diseases (CVD) at a higher rate compared to general population (4, 5). CVD is believed to contribute to as much as half of the deaths in RA patients (6). The increased rate of CVD in RA patients is driven by accelerated atherosclerosis that occurs as a result of increased inflammation (7). Structural damage to joints is known to occur aggressively within first few years of RA diagnosis (8, 9), so it is possible that acceleration of atherosclerosis may also be more aggressive during early stages of RA. Supporting this hypothesis, data from two small studies indicate that atherogenic lipid profile and subclinical atherosclerosis can be seen in RA patients at very early stages of the disease (10, 11). Therefore, it is important to evaluate the impact of various RA treatments on CVD events in early RA patients from a clinical standpoint.

The first step in evaluating outcomes of biologics treatment is to understand the factors that play a role in the treatment initiation in RA patients with biologics. The current literature lacks studies that specifically evaluate the factors influencing biologic treatment initiation. Identifying predictors of biologic treatment may in turn help to access and target the most important factors that facilitate treatment initiation. After understanding the patient characteristics that influence treatment initiation with biologics, the next logical step is to examine their association with CVD outcomes in RA patients. Among all of the currently-available treatments, TNF- α inhibitors (TNF-Is) are of special interest because of the involvement of TNF-α in the development and acceleration of atherosclerosis. Although, several observational studies have attempted to evaluate this association, most of these studies are conducted in patients with established RA and very limited information is available specific to early RA cases. The literature also lacks evidence for the independent effects of different individual TNF-I agents on CVD outcomes in RA patients. TNF-Is are a

heterogenous class of drugs and therefore it may not be appropriate to assume a class effect of TNF-Is in terms of their effects on reducing the risk of CVD.

Thus, the main goal of this dissertation is to understand the predictors of biologic treatment initiation in RA patients and to examine the effect of TNF-I treatment on the risk of CVD events in early RA patients.

1.2 Specific Aims:

This dissertation has the following Specific Aims.

Specific Aim 1: To identify factors influencing biologic treatment initiation in RA patients

We designed a retrospective cohort study to evaluate the influence of sets of various population characteristics on biologic treatment initiation using the Andersen's behavioral model (ABM) for health services use (11). ABM posits a process of health care use in which predisposing factors influence the ability (measured through enabling factors) of a person to obtain health care which, when adding the need for treatment, predicts the use of health care services. Predisposing factors included the variables that may influence the likelihood of need for health services. Patients' age, gender and geographic location were included in this set. Enabling factors included variables suggesting patients' ability to secure healthcare services. We included the following variables in this set: visit to a rheumatologist, health plan type, type of insurance and drug benefit generosity. Need factors included health conditions of patients that necessitate the utilization of health services. In this set, we included RA related factors such as RA type, RA severity, RA drug use in pre-index period, and other comorbid conditions. To understand the impact of various predictors on the initiation of a

biologic agent after controlling for other predictors in a multivariate manner, hierarchical logistic regression models were used in which the predictors were entered in 3 sets.

Specific Aim 2: To examine the effect of TNF-I treatment on incident CVD event in patients newly diagnosed with RA

In this specific Aim, we evaluated the association between TNF-I treatment and incident CVD events in patiently newly diagnosed with RA using several different definitions of treatment exposure to account for the timing and history of treatment with all the DMARDs. A nested case-control study was designed to evaluate this association. The outcome of interest was defined as a composite measure consisting of acute myocardial infarction, unstable angina, angina pectoris, chronic heart failure, other forms of chronic heart diseases, ischemic stroke; and transient ischemic stroke. Three unique exposure definition schemes were used. First classified TNF-I use as ever vs never use, second definition considered current use indicators for TNF-Is and other RA treatments, third definition considered current and past use indicators for TNF-I and other RA treatments. The estimates of the association between TNF-I use and CVD events were derived from conditional logistic regression models.

Specific Aim 3: To assess independent effects of individual TNF-Is (adalimumab, etanercept, infliximab) on the risk of incident CVD events in patients newly diagnosed with RA

In this specific Aim, we examined the association between the use of individual TNF-Is, infliximab, etanercept and adalimumab, and incident CVD events in patients newly diagnosed with RA. The outcome of interest was defined as a composite measure consisting

of acute myocardial infarction, unstable angina, angina pectoris, chronic heart failure, other forms of chronic heart diseases, ischemic stroke; and transient ischemic stroke. A nested case-control study design was used for this specific Aim.

We analyzed data from Truven's MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (COB) for the years 2007-2010 for this study. The Marketscan database contains claims submitted from health plans which have contracts with large private employers or public organizations in the United States (12). This longitudinal database covers all inpatient, outpatient, and prescription claims for individual patients as long as they remain enrolled in the health plan.

The results of of our Aim 1 can improve our understanding of the predictors of biologic treatment initiation in RA patients. This can help identify factors and target patient subgroups for biologic treatment initiation to maximize treatment benefit from these agents. Results from Aims 2 and 3 can add unique information to the literature by providing information on whether TNF-I therapy has an effect on improving CVD outcomes among newly diagnosed RA patients. These findings could guide therapeutic decision-making to improve the quality of care provided to patients with RA.

CHAPTER 2

BACKGROUND AND LITERATURE REVIEW

In section 2.1, we provide an overview of rheumatoid arthritis (RA) and current treatment options. Section 2.2 provides a review of the literature on the relationship between RA and cardiovascular diseases (CVD). In section 2.3, we present a review of the current evidence regarding TNF-α inhibitor (TNF-I) treatment and CVD events in RA patients. In section 2.4, we describe the limitations of previous studies and provide a rationale for the proposed study. Finally in section 2.5, we propose a theoretical framework for this study.

2.1 Rheumatoid arthritis overview:

RA is an autoimmune disease characterized by inflammation of the synovium, a membrane that lines the joint capsule and produces lubricating fluid in the joint. Uncontrolled synovial inflammation, or synovitis, leads to progressive erosion of bone and cartilage and, ultimately results in joint malalignment and secondary osteoarthritis (1). As the inflamed synovium destroys the joint, the surrounding muscles and tendons become weak, leading to disability in most cases. According to a 2008 estimate, RA affects approximately 1.3 million adults in the United States and is associated with substantial morbidity and mortality (2). Disease onset generally occurs between ages 30 and 50 years. and the incidence is higher in women and older adults.

Annually, approximately 9 million physician office visits and more than 250,000 hospitalizations occur as the result of arthritis and other rheumatic conditions (13, 14).The mean total annual direct cost to patients with RA is estimated to be $9,519 per person (15), and according to most studies, the indirect costs of RA are approximately twice the direct costs associated with this condition (16). The average number of days absent from work due to RA has been reported to be in the range of 2.7 to 30 days annually (17).

Patients with RA are typically treated with a combination of medications from one or more of the following therapeutic classes: 1) non-steroidal anti-inflammatory drugs (NSAIDs), 2) corticosteroids, and 3) disease modifying anti-rheumatic agents (DMARDs) (18). The overarching goal of pharmacological therapy in RA is to control inflammation and prevent joint damage. NSAIDs and corticosteroids provide symptomatic relief in RA patients while DMARDs halt the progression of the disease.

DMARDs are generally classified into non-biologic (traditional) and biologic treatments. Non-biologic DMARDs are orally-administered medications and include agents such as MTX, SSZ, HCQ, azathioprine, penicillamine and leflunomide. Non-biologic DMARDs halt the progression of the disease by suppressing inflammation, but they do not interfere with the functioning of specific components of the immune system. On the other hand, biologics are intravenously or subcutaneously administered and target specific components of the immune system, such as T cells, B cells, and cytokines, that play an important role in the pathogenesis of RA (19).

The US Food and Drug Administration (FDA) approved the first biologic (infliximab) for treatment of RA in 1998. Since that time, nine more agents have been approved: etanercept (1998), anakinra (2001), adalimumab (2002), abatacept (2005), rituximab (2006),

certolizumab pegol (2008), golimumab (2009), tocilizumab (2010), and tofacitininb (2012). Infliximab, adalimumab, golimumab, etanercept and certolizumab produce their primary effect by blocking TNF-α from interacting with cell surface TNF receptors, thereby blocking the inflammatory effects of TNF- α (20); these medications are classified as TNF-Is. Other biologic agents act on different components of the immune system. Anakinra and Tocilizumab block interleukins (IL), abatacept inhibits T-cell activation by binding to CD80 and CD86 surface antigens, tofacitinib,is a janus kinase inhibitor. and rituximab causes depletion of B-cells by blocking CD 20 surface antigen (21).

Since the 1990s, treatment of RA has evolved from a traditional pyramid approach in which treatment with DMARDs was reserved for patients with refractory disease to an "inverted pyramid" approach in which patients with early RA symptoms are treated with a combination of DMARDs in an attempt to control inflammation and prevent joint damage (3). Non-biologic DMARDs are recommended for all the RA patients while the use of TNF-Is is recommended in RA patients with moderate to high disease activity with features of poor prognosis (22). If the patients do not respond to TNF-Is, then they may be moved to other biologic agents. For RA patients with low disease activity, TNF-Is are reserved for patients who fail to respond to non-biologic DMARDs.

2.2 Rheumatoid arthritis and cardiovascular diseases:

The association between RA and CVD has been the focus of recent attention, primarily because of the increasing recognition of the major role that inflammation plays in the development of atherosclerosis in the general population (7, 23, 24).

2.2.1 The role of inflammation and the development of cardiovascular disease

The pathway leading to CVD-related events begins with the development of atherosclerosis (25). RA is hypothesized to be associated with early initiation of atherosclerosis through endothelial cell dysfunction (26). TNF-α, a pro-inflammatory cytokine involved in the pathogenesis of RA, may mediate endothelial cell dysfunction by inducing expression of leukocyte adhesion molecules that facilitates the penetration of monocytes into the vessel wall (27). After entry, the monocytes differentiate into macrophages that ingest lipoproteins to form "Foam cells" and fatty streak (25). Foam cells express pro-inflammatory cytokines, including TNF-α that promotes proliferation of smooth muscle cell into the intima of blood vessels and formation of a fibrofatty plaque (28). TNF-α is also synthesized in the plaque (29) and is thought to increase collagen breakdown and facilitate plaque rupture (25). Nearly three-quarters of all acute MIs are believed to be caused by plaque rupture (25). Several reports suggest that endothelial functioning may improve with TNF-I treatment (30-34).

TNF-α also has an effect on traditional CVD risk factors such as insulin resistance and dyslipidemia (35). TNF-α is considered to be an important mediator of insulin resistance because it decreases tyrosine kinase activity of insulin receptors and impedes insulin-mediated uptake of glucose in skeletal muscle (36). TNF-α also directly interferes with the metabolic pathways of triglycerides and cholesterol (35)resulting a higher level of low-density lipoprotein (25). Numerous studies have shown a positive impact of TNF-I treatment on these traditional CVD risk factors in RA patients (37-40).

Thus, TNF-α may play an important role in the development and acceleration of atherosclerosis in RA patients. Therefore, it is plausible to hypothesize that treatment with

TNF-Is in RA patients may be able to halt the progression of atherosclerosis, ultimately leading to reduction in risk of CVD events.

2.2.2 Data on the relationship between rheumatoid arthritis and cardiovascular disease

Several epidemiological studies indicate that RA patients have an increased risk of CVD-related morbidity and mortality compared to the general population (4, 5, 41). A case-control study of data from the UK General Practice Research Database showed that RA patients had a 47% higher odds of developing a first episode of acute myocardial infarction (AMI) compared to non-RA patients (41). Maradit-Kremers et al.(4) also reported that patients with RA have a significantly higher risk of chronic heart diseases (CHD) and are more likely to suffer an unrecognized myocardial infarction (MI) compared to patients without RA. Data from the Nurses Health Study showed that women with RA had a two-fold increase in the risk of AMI compared to women without RA (5). A meta-analysis reported that CVD-related mortality is approximately 50% higher in RA patients compared to the general population(6).

Studies indicate that the increased risk of CVD-related morbidity and mortality in RA patients cannot be satisfactorily explained by traditional risk factors such as hypertension, dyslipidemia, smoking and diabetes mellitus. Gonzalez et al.(42) reported that traditional risk factors imparted significantly less risk for the development of CVD in RA patients compared to patients without RA. This finding suggests that extraneous RA-related risk factors may also play a role in the development of CVD. Solomon et al. (43) observed an improvement in the prediction of CVD events in RA patients when RA-related risk factors such as disease duration > 5 years, the presence of radiographic joint erosions, the presence of subcutaneous nodules, a prior total joint replacement, modified health assessment questionnaire (HAQ)

score ≥ 2, a Clinical Disease Activity Index score > 22, and seropositivity were added to traditional CVD risk factors.

Thus, the increased CVD risk in RA patients is well demonstrated in the literature. This increased risk is believed to be driven by sustained inflammatory activity in these patients.

2.3 Current evidence for the impact of anti-rheumatic agents on cardiovascular events in rheumatoid arthritis patients:

Because of the increased burden of CVD in RA patients, investigators have focused on examining the effect of various RA drug treatments on reducing CVD events. In general, randomized controlled trials (RCTs) lack sufficient power to study rare CV outcomes. Thus, most of the evidence for the effect of different RA treatment options on the risk of CVD events is based on observational data. In the following sections, we review the previous observational studies that evaluated the effect of traditional DMARDs (Section 2.3.1) and biologic DMARDs (Section 2.3.2) on the risk of CVD events in RA patients.

2.3.1 Non-biologic DMARDs and cardiovascular events in rheumatoid arthritis patients:

Non-biologic DMARDs are believed to exert a cardio-protective effect by its ability to control inflammation in RA. In addition some more specific mechanisms for specific agents are also suggested. For instance, it is reported that through adenosine A2A receptor activation, methotrexate (MTX) promotes reverse cholesterol transport and limits foam cell formation in THP-1 macrophages and thus hinders the process of atherosclerosis (44). By contrast, some authors have argued that MTX can in fact promote atherosclerosis by increasing circulating levels of homocysteine (45). Nine studies have examined the

association between non-biologic DMARDs and CVD events in RA patients (46-54) . Table 2.1 summarizes these studies.

These studies varied considerably with respect to the study populations and outcomes evaluated. Three studies used data from nationwide registries (46, 52, 54), 2 studies used data from RA patients registered at a single outpatient RA clinic (47, 50), 2 studies used administrative claims data (49, 51), 1 study used electronic medical records from department of Veterans Affairs (VA) integrated service network (48) and 1 study used data from an international collaboration project that recruited patients in 15 different countries (53). Eight of these 9 studies evaluated were conducted in cohorts of established RA patients, and the duration of RA varied from 6-15 years in these studies. Only one study (51) was conducted in a cohort of new RA patients. Two studies used mortality due to CVD as the primary outcome (46, 47), 5 studies used a composite CVD outcome (48, 50, 51, 53, 54), 1 study used stroke (52) and 1 study used AMI (49) as the outcome of interest.

All the 9 studies evaluated the association between MTX treatment and CVD outcomes. Five of these nine studies found significant reduction in the risk of CVD outcomes with MTX treatment (Range: 15% to 89% reduction) (47, 48, 50, 51, 53). Three studies reported no significant association between MTX treatment and CVD outcomes (49, 52, 54). One study reported a significant increase in the risk of CVD mortality with MTX treatment (46). Association between non-MTX DMARDs and CVD events were reported less frequently in these studies. However, two studies documented statistically significant reduction in the risk of CV endpoints with SSZ treatment compared to no treatment with SSZ (50, 53). Two studies reported significant reduction in risk of CV outcomes with leflunomide treatment (49, 53).

Table 2.1: Summary of studies evaluating impact of traditional DMARD therapy on cardiovascular outcomes in RA patients

Study	Population	RA duration	Exposure	Comparison	Outcomes	Effect size
Landewe et al., 2000 (46)	623 RA patients from 11 rheumatology outpatient clinics in hospitals that are geographically distrib-uted throughout The Netherlands	NR but prevalent cases not excluded	MTX treatment in patients with CVD history	Other DMARD treatment in patients without CVD history	CVD mortality	RR 3.40 (p=0.0054)
Choi et al., 2002 (47)	1,240 RA patients at a single arthritis outpatient clinic in Wichita, KS	9 years	MTX use	MTX use never (May use other DMARDs)	CV mortality	*HR 0.3 (0.2-0.7)*
Prodanowich et al., 2005 (48)	6,707 RA patients at the Veterans Integrated Service Network 8 (Florida and Puerto rico)	NR but prevalent cases not excluded	MTX use	No use of MTX	Composite endpoint (CVD, CVA and atherosclerosis)	*OR 0.73 (0.55-0.98)*
Suissa et al., 2006 (49)	107,908 RA patients identified between 1999 and 2003 from a US administrative claims data source	NR but prevalent cases not excluded	MTX LEF Other DMARDs*	No current DMARD use	First AMI	RR 0.81 (0.60-1.08) *RR 0.28 (0.12-0.65)* *RR 0.67 (0.46-0.97)*
Van Halm et al., 2006 (50)	613 RA patients randomly sampled from a larger RA population registered in the Jan van Breemen Institute, a large rheumatology outpatient clinic in Amsterdam, the Netherlands	7-10 years	MTX only SSZ only HCQ only MTX & SSZ MTX & HCQ SSZ & HCQ MTX, HCQ & SSZ	Never use of MTX, SSZ or HCQ	Composite endpoint (MI, CVA, TIA, PAD)	*OR 0.11 (0.02-0.56)* *OR 0.37 (0.14-0.99)* OR 0.47 (0.15, 1.46) *OR 0.16 (0.06-0.42)* OR 0.19 (0.04-1.02) OR 0.37 (0.11-1.24) *OR 0.16 (0.06-0.43)*
Hochberg et al., 2008 (51)	16,752 incident RA patients identified	0 years	MTX Other DMARDs**	No use of DMARDs	Composite endpoint (AMI, CHF, CVA,	*HR 0.74 (0.69-0.80)* HR 0.99 (0.93-1.05)

	between 1999 and 2006 from a US administrative claims data source				angina, IHD)	
Nadareishvili et al., 2008 (52)	5,765 RA patients registered in the National Data Bank (NDB) for Rheumatic Diseases within the USA	15 years	MTX	No use of MTX	Stroke	OR 0.77 (0.39-1.54)
Naranjo et al., 2008 (53)	4,383 RA patients from 48 sites in 15 countries	11 years	MTX GC Antimalarials (HCQ, CQ) SSZ Gold LEF	No use of that particular DMARD (May use other drugs other DMARD)	Composite endpoint (AMI/Stroke/ angina/ CAD)	*HR 0.85 (0.81-0.89)* *HR 0.95 (0.92-0.98)* HR 0.98 (0.94-1.02) *HR 0.92 (0.88-0.97)* HR 0.96 (0.92-1.00) *HR 0.55 (0.41-0.75)*
Greenberg et al., 2010 (54)	10,156 RA patients registered in the CORRONA registry†	6 years	MTX	Non-biologic DMARDs** other than MTX	CVD composite endpoint (AMI, stroke, TIA)	HR 0.94 (0.49-1.80)

*Other DMARDs in this study included HCQ, CQ, SSZ, gold, azathioprine, minocycline, penicillamine, chlorambucil, cyclophosphamide, cyclosporine
List of abbreviations used:
** The list of individual agents is not reported in the study
†CORRONA (Consortium of Rheumatology Researchers of North America) registry includes a network of 268 participating academic and community rheumatologists at 103 sites and 35 states within the USA

AMI Acute myocardial infarction
CAD Coronary artery disease
CHF Chronic heart failure
CQ Chloroquine
CVA Cerebrovasculr accident
CVD Cardiovascular disease
DMARD Disease modifying anti-rheumatic agent
GC Glucocorticoid
HCQ Hydroxychorloquine
HR Hazard ratio
IHD Ischemic heart disease
LEF Leflunomide
MTX Methotrexte
OR Odds ratio
PAD Peripheral arterial disease
RA Rheumatoid arthritis
RR Risk ratio
SSZ Sulphasalazine
TIA Transient ischemic attack

2.3.2 TNF-α inhibitors and cardiovascular events in rheumatoid arthritis patients:

Given the role that TNF-α plays in facilitating the development and acceleration of atherosclerosis in RA patients, it is plausible that TNF-I treatment may halt the progression of atherosclerosis and ultimately lead to a reduction in the risk of CVD events. Several observational studies have been conducted to test this hypothesis. In this section, we briefly summarize the studies testing this hypothesis available in the literature.

Table 2.2 summarizes the 12 studies that evaluated the impact of use of TNF-Is on CVD events (49, 51-61). These studies differ significantly in terms of the data sources, population included, exposure definitions, and outcomes evaluated. Six of these studies used data from nationwide registries (52, 54, 55, 57, 59, 61), 1 study used data from an international collaboration project that recruited patients in 15 different countries (53), 1 study used data from a statewide registry (58), 1 study used a cohort of Medicare enrollees from Pennsylvania (56),1 study used electronic medical records from department of VA (60), and 2 study used administrative claims data (49, 51). Five studies evaluated composite CVD outcomes,(51, 54-56, 61), 4 studies evaluated AMI (49, 57-59) while 1 study evaluated stroke (52) and 2 studies evaluated cerebrovascular accident (CVA) and AMI individually in addition to a composite CVD outcome as the outcomes of interest (53, 60). Seven studies used non-exposure to TNF-Is as the comparison group (49, 51-53, 55, 59, 61) , while 5 studies used active comparators (54, 56-58, 60). Two studies compared TNF-I therapy with MTX monotherapy (56, 58), one study used non-biologic DMARDs other than MTX as the comparison (54), one study used only non-biologic DMARDs as comparison (57) and one study compared use of TNF-I with use of any other DMARD, pooling traditional and

biologic drug users in a single group (60). Only 2 studies evaluated the impact of TNF-I treatment on the risk of CVD events in early RA patients (51, 61).

Two studies comparing TNF-I use vs no use in established RA patients reported significant reduction in the risk of composite CVD outcome with TNF-I treatment (54-58% reduction) (53, 55). Two other studies using same definition and population did not find a significant associations between TNF-I treatment and evaluated outcomes (52, 59). One study reported increasing trend of AMI with biologic treatment including TNF-Is compared to no DMARD use in established RA cases, but the estimate was not statistically significant (OR: 1.30, 95% CI: 0.92-1.82) (49). Three studies reported that treatment with TNF-I was significantly better in improving CVD outcomes (17-80% reduction) against a variety of active comparators (54, 58, 60) in established RA patients. Two studies found no difference in the risk of CVD outcomes between TNF-I treatment and comparator groups (56, 57) in similar population. One analysis reported an increase in trend of CVA with TNF-Is, but the results were not statically significant (HR: 1.07, 95% CI: 0.997-1.155) (60). The two studies that only included early RA cases reported a statistically non-significant reduction in the risk of CVD events after TNF-I treatment compared to no use of these agents (51, 61).

Table 2.2: Summary of studies comparing the impact of TNF-I therapy with no use of TNF-I therapy on cardiovascular outcomes in RA patients

Study	Poulation	RA duration	Exposure	Comparison	Outcomes	Results
Jacobsson et al., 2005 (55)	983 RA patients from rheumatology outpatient clinics in South Sweden. Uses historical comparison cohort of 543 patients from 1997 (pre-tnf period) as comparison group	11 years	TNF-Is (Etanercept and Infliximab)	Never treated with TNF-Is	Composite CVD event (ICD 401-448)	RR 0.46 (0.25-0.85)
Solomon et al., 2006 (56)	3,501 RA patients from Medicare enrollees who were also beneficiaries in the PACE program in Pennsylvania	NR but prevalent cases not excluded	Current use of Biologics (Etanercept, Adalimumab, Infliximab, Anakinra) defined as a filled prescription 90 days prior to the event 1. Monotherpay 2. Biologic+MTX 3. Biologic+other DMARDs	MTX monotherapy	Composite endpoint (AMI and stroke)	OR 1.00 (0.5-1.9): biologics monotherapy vs MTX monotherapy OR 0.8 (0.3-2): Biologics+ MTX vs MTX monotherapy OR 1.2 (0.7, 2.2): Biologics+ other DMARDs* vs MTX monotherapy
Suissa et al., 2006 (49)	107,908 RA patients identified between 1999 and 2003 from a USA administrative claims data source	NR but prevalent cases not excluded	Current use of Biologics (Defined as a filled prescription of Etanercept, infliximab, anakinra in 30 days prior to event)	No current use of any DMARD	First AMI	RR 1.30 (0.92-1.83)

Dixon et al., 2007 (57)	10,755 RA patients registered in the BSRBR*	7-12 years	TNF-Is (Etanercept, Adalimumab, Infliximab)	Non-biologic DMARDs (list of agents not reported)	First AMI	IRR 1.44 (0.56-3.67)
Singh G et al., 2007 (58)	19,223 RA patients from a registry of medical assistance patients in California (MediCal database)	NR but prevalent cases not excluded	TNF-Is +MTX	MTX monotherapy	First AMI	RR 0.20 (0.05-0.88)
Hochberg et al., 2008 (51)	16,752 incident RA patients identified between 1999 and 2006 from a US administrative claims data source	0 years	Biologics use (defined as a filled prescription of etanercept, adalimumab, infliximab or anakinara in the pre-index period	No use of biologics	Composite endpoint (AMI, CHF, CVA, angina, IHD)	HR 0.99 (0.83-1.18)
Nadareishvili et al., 2008 (52)	5,765 RA patients registered in the National Data Bank (NDB) for Rheumatic Diseases within the USA	15 years	TNF-Is (Etanercept, Adalimumab, Infliximab) 1. In the 6 months pre-index period 2. In the baseline period	Not treated with TNF-Is in the respective time periods	Stroke	OR for TNF-I use in 6 months pre-index Vs no use in that period: 0.8 (0.34-1.82) OR for TNF-I use at baseline Vs no use in that period: 0.37 (0.18-1.66)
Naranjo et al., 2008 (53)	4,383 RA patients from 48 sites in 15 countries	9 years	TNF-Is exposure time (in years)	Not treated with TNF-Is (exposure time to tnf=0)	Composite AMI Stroke	HR 0.64 (0.49-0.83) HR 0.42 (0.21-0.81) HR 0.64 (0.39-1.05)

Wolfe and Michaud, 2008 (59)	17,738 RA patients registered in the National Data Bank (NDB) for Rheumatic Diseases within the USA	NR but prevalent cases not excluded	TNF-Is (Etanercept, Adalimumab, Infliximab) 1. Ever use & 2. Current use (6 months prior to event)	Not treated with TNF-Is in the respective time period	First AMI	OR: 1.1 (0.8-1.6): Ever use vs Never use OR: 1.3 (0.9-1.6): Current use vs no current use
Greenberg et al., 2010 (54)	10,156 RA patients registered in the CORRONA registry**	8 years	TNF-Is 1. New+prevalent use 2. Only new use	Non-biologic DMARDs† other than MTX	CV composite endpoint (AMI, stroke, TIA)	HR 0.39 (0.19-0.82) for new and prevalent use of TNF-I vs non-biologic DMARDs HR 0.45 (0.13-1.56) for only new users ot TNF-I vs non-biologic DMARD use
Al-aly et al., 2011 (60)	20,811 RA patients from Veterans Administration EMR (USA)	NR but prevalent cases not excluded	TNF-Is (Etanercept, Adalimumab, Infliximab)	Other DMARDs (HCQ, Gold, Penicillamine, SSZ, MTX, LEF, Azathioprine, Cyclophosphamide, Cyclosporine, Anakinara)	Composite CVA CHF PAD CAD	HR 0.96 (0.89-1.04) HR 0.83 (0.74-0.89) HR 1.05 (0.91-1.22) HR 0.85 (0.69-1.05) HR 1.07 (0.99-1.15)
Ljung et al., 2012 (61)	6,496 patients with early RA in the Swedish Rheumatology Register	< 1 year	Exposure to TNF-Is (First time use)	Never exposed to TNF-Is	Composite endpoint (ACS events)	HR 0.80 (0.52–1.24)

* Other DMARDs in this study included HCQ, CQ, SSZ, gold, azathioprine, minocycline, penicillamine, chlorambucil, cyclophosphamide, cyclosporine
List of abbreviations used:
*CORRONA (Consortium of Rheumatology Researchers of North America) registry includes a network of 268 participating academic and community rheumatologists at 103 sites and 35 states within the USA
† List of individual agents not reported

AMI Acute myocardial infarction
BSRBR British Society for Rheumatology Biologics Register
CAD Coronary artery disease
CHF Chronic heart failure
CQ Chloroquine
CVA Cerebrovasculr accident
CVD Cardiovascular disease
DMARD Disease modifying anti-rheumatic agent
GC Glucocorticoid
HCQ Hydroxychorloquine
HR Hazard ratio
IHD Ischemic heart disease
LEF Leflunomide
MTX Methotrexte
OR Odds ratio
PAD Peripheral arterial disease
RA Rheumatoid arthritis
RR Risk ratio
SSZ Sulphasalazine
TIA Transient ischemic attack

Thus, very limited information exists in the literature for the association of TNF-I treatment with incident CVD events in patients with early RA. It is known that structural damage to joints occur aggressively within first few years of RA diagnosis (8, 9), so it is possible that acceleration of atherosclerosis may also be more aggressive during early stages of RA. A couple of small studies have indicated that atherogenic lipid profile and subclinical atherosclerosis are features of early RA (10, 11). The epidemiological evidence of the effect of TNF-Is on early RA CVD events is limited to only two studies limited to modest sample sizes (61) and mixed treatment exposure with TNF-Is and other biologics, which could bias results (51).

2.4 Significance of this research:

The first step in evaluating outcomes of biologics treatment is to understand the factors that play a role in the treatment initiation of RA patients with biologics. The current literature lacks studies that specifically evaluate the factors influencing biologic treatment initiation. Only 2 studies have looked at this issue and both have important limitations. The study by Bonafede et al. (62) used insurance claims data to study the predictors of DMARD treatment initiation in patients with newly diagnosed RA. This study provides limited information regarding biologics specifically since the factors were not differentially evaluated for non-biologic and biologic DMARDs. It is well-understood that these two subgroups of DMARDs differ drastically in their mechanism of actions, effectiveness and cost of treatment. So to study those as a single group may not give us estimates that are relevant to biologic agents. DeWitt et al. (63) studied specific predictors of biologic initiation in 1,545 RA patients in an observational database using patient self-reported data. However, this study suffers from limitation of very small sample size and lack of generalizability, given its inclusion of only 7

centers for patient recruitment in the entire nation. They also did not consider patient enabling factors such as drug benefit coverage and insurance type, which are important from a policy perspective to understand biologic treatment initiation. Moreover, they used data up to 2006, at which point there were only 5 biologics compared to 10 which are available currently. Therefore, our study addressed limitations by addressing the important phenomenon of biologic treatment initiation in RA patients with the help of a theoretical framework using recent data from a large insurance claims database in Aim1.

After understanding the patient characteristics that influence treatment initiation with biologics, the next logical step is to examine their association with CVD outcomes in these patients. Among all of the currently-available treatments, TNF-Is are of special interest because of the involvement of TNF-α in the development and acceleration of atherosclerosis. Although, several observational studies (discussed in section 2.3) have attempted to evaluate this association, limited information is available specific to early RA cases. The first of these two studies that evaluated the association in new RA patients had a small sample size (198 acute coronary syndrome cases only) and hence may be underpowered to detect treatment effect (61). The second study did not differentially define exposure to TNF-Is form other biologics (51). Since these agents differ vastly in their mechanism of actions, we believe that categorizing them into a single group may produce biased estimates. Therefore, in Aim 2 of our study we evaluated the association between TNF-I treatment and CVD events in early RA cases to contribute new knowledge to the literature for this specific population. We have tried to overcome these limitations by ensuring sufficient sample size and detailed exposure classification.

Additionally, precise exposure definition is extremely important in evaluating any exposure-outcome association. It is especially important for RA since the use of treatments in these patients is complex and patients are known to stop and switch DMARDs frequently. No study to our knowledge has systematically tried to evaluate the impact of exposure definition on the association of RA treatment and CVD events. Therefore, in our Aim 2 we take up that challenge to provide some justification to the contrasting estimates of the RA treatment-CVD outcome association available in the literature. In this study we use 3 different exposure definitions that are summarized below and compare the resulting estimates.

The first approach that is used in a couple of studies (51, 55) is to define the use of TNF-Is or biologic DMARDs as ever-treated vs never-treated, meaning once a patient begins therapy with TNF-Is he or she is considered to be treated for the entire follow-up period. This over-simplified definition of exposure into a binary variable leads to non-differential misclassification of exposure by ignoring the recency of exposure as well as the frequency of exposure. For example, in this scheme, a patient who uses the treatment only for 1 day would be considered no different than a patient who uses the treatment for 1 year and pharmacologically this makes little sense because these patients are likely to have different treatment effects. Although, some authors argue that such non-differential misclassification of the exposure would produce a bias towards the null and hence provide a conservative estimate of the treatment-outcome association (47), there is also evidence in the literature that this may not be true under all circumstances (64). Therefore, it is complicated to predict the direction of the bias produced by such misclassification. The best way to address this issue is to avoid the misclassification by using finer exposure definitions.

Another approach used by several studies (49, 54, 56) is to classify the use of TNF-Is as 'current use' vs 'no current use' based on a prescription filled within a certain time period prior to the event. This approach addresses some of the misclassification by considering the recency of the exposure, which may be closely associated with the outcome. However, this definition still ignores the treatment history of the patients. In other words, if a patient has used the treatment in the past before discontinuing it and the reason for discontinuation is associated with the outcome, we are likely to miss out on this important finding because these patients would not be classified as drug users in this exposure scheme. Therefore, it is also important to consider treatment history while defining exposure.

Because of the reasons discussed above, for this research we also added the determinants of past DMARDs use, along with current use while defining exposure. This approach has been advocated previously as the most effective in reducing the non-differential exposure misclassification (65). This definition however, does not take into account the cumulative exposure to the treatment and therefore to quantify the impact of duration of drug use, we defined the duration of TNF-Is as cumulative days of use in to derive estimates of the association between TNF-I duration and CVD events.

The literature also lacks evidence for the independent effects of different individual TNF-I agents on CVD outcomes in RA patients. TNF-Is are a heterogenous class of drugs. These agents include a chimeric [IgG.sub.1] monoclonal antibody (infliximab); monoclonal antibodies with fully human amino acid sequences produced by phage display (adalimumab) or from mice transgenic for the human immunoglobulin locus (golimumab); an engineered p75 TNFRII dimer with a fully human amino acid sequence linked to the Fc portion of

human [IgG.sub.1] (etanercept); and a pegylated Fab' fragment that lacks an Fc portion (certolizumab) (20).

Certolizumab and golimumab have been on the market for approximately two years and there are limited pharmacological and epidemiological data for these agents. Therefore, we limit our discussion to differences among etanercept, infliximab and adalimumab. These agents possess unique pharmacokinetic and pharmacodynamic properties (66). The p75 TNFRII dimer, Etanercept, has been shown to bind with lymphotoxin B and does not induce neutralizing antibodies, unlike the monoclonal antibodies, adalimumab and infliximab. Infliximab has been reported to form more stable complexes with soluble TNF compared to etanercept (67). These three agents have not been compared head-to-head in RCTs for their efficacy in RA. However, recent evidence from a mixed treatment comparison using data from RCTs reported that the odds of achieving ACR50 response (American College of Rheumatology response criteria for 50% improvement in joint function), were higher with etanercept compared to infliximab and adalimumab both (etanercept vs infliximab OR: 4.17, 95% CrI 2.00-11.17, etanercept vs adalimumab OR: 3.50, 95% CrI 1.37-7.63) (68).

They also differ with respect to their effectiveness in treating other rheumatologic diseases. Unlike adalimumab and infliximab, etanercept lacks efficacy in treating granulomatous diseases, such as Crohn's disease, Wegener's granulomatosis and sarcoidosis (69, 70). These agents are also reported to have differences in their safety profiles. Infliximab, but not etanercept, is found to be associated with an increased risk of granulomatous infections such as mycobacterium tuberculosis and histoplamosis (71). Evidence from mixed treatment comparisons using withdrawals due to adverse events reported in RCTs as an outcome suggest that etanercept has more favorable tolerability

profile compared to infliximab and adalimumab (etanercept versus infliximab OR:0.30, 95% CrI 0.16-0.62, etanercept versus adalimumab OR: 0.50, 95% CrI 0.25-0.91) (72).

No study has provided estimates for the independent effects of these individual TNF-I agents for their effects on the risk of CVD events in RA patients. Because these agents differ with respect to their pharmacological properties, effectiveness profiles in various rheumatologic diseases and tolerability, we believe that it is not appropriate to assume a class effect in terms of these agents' effect on the risk of CVD events in RA patients. Therefore, in Aim 3 of the proposed study, we added novel information to the literature by providing estimates for the independent effects of these 3 TNF-Is on the risk of CVD events.

This dissertation used the data from administrative claims submitted from health plans which have contracts with large private employers or with public organizations in the United States for the years between 2007 and 2010. The use of this recent data from 'real-world' strengthened the external validity of the study by inclusion of patients with multiple comorbid conditions in the study cohort, which can not be achieved with RCTs. In addition, RCTs examining the efficacy of TNF-Is in RA patients are usually under-powered for studying CV outcomes. The accelerated onset of atherosclerosis in RA patients often leads to events such as AMI and stroke that can be detected in observational studies using administrative data. This provided us with a valuable opportunity to evaluate the effect of TNF-I treatment on the risk of CVD events in RA patients using secondary databases that document the use of medications and clinical events.

Results from our Specific Aim 1 may be useful in accessing and targeting the most important factors that facilitate treatment initiation. Results from Specific Aims 2 and 3 may

help in guiding therapeutic decision-making to improve the quality of care provided to patients with RA.

2.5 Theoretical model:

A conceptual model forms the basis for the consideration of appropriate variables in any research study. For our Specific Aim 1, we used a conceptual framework based on Andersen's Emerging Behavioral Model of Health Services Use (73). This model posits that the *use of healthcare services and subsequent health outcomes* are influenced by a set of population characteristics. More specifically, these characteristics are divided in to three groups,

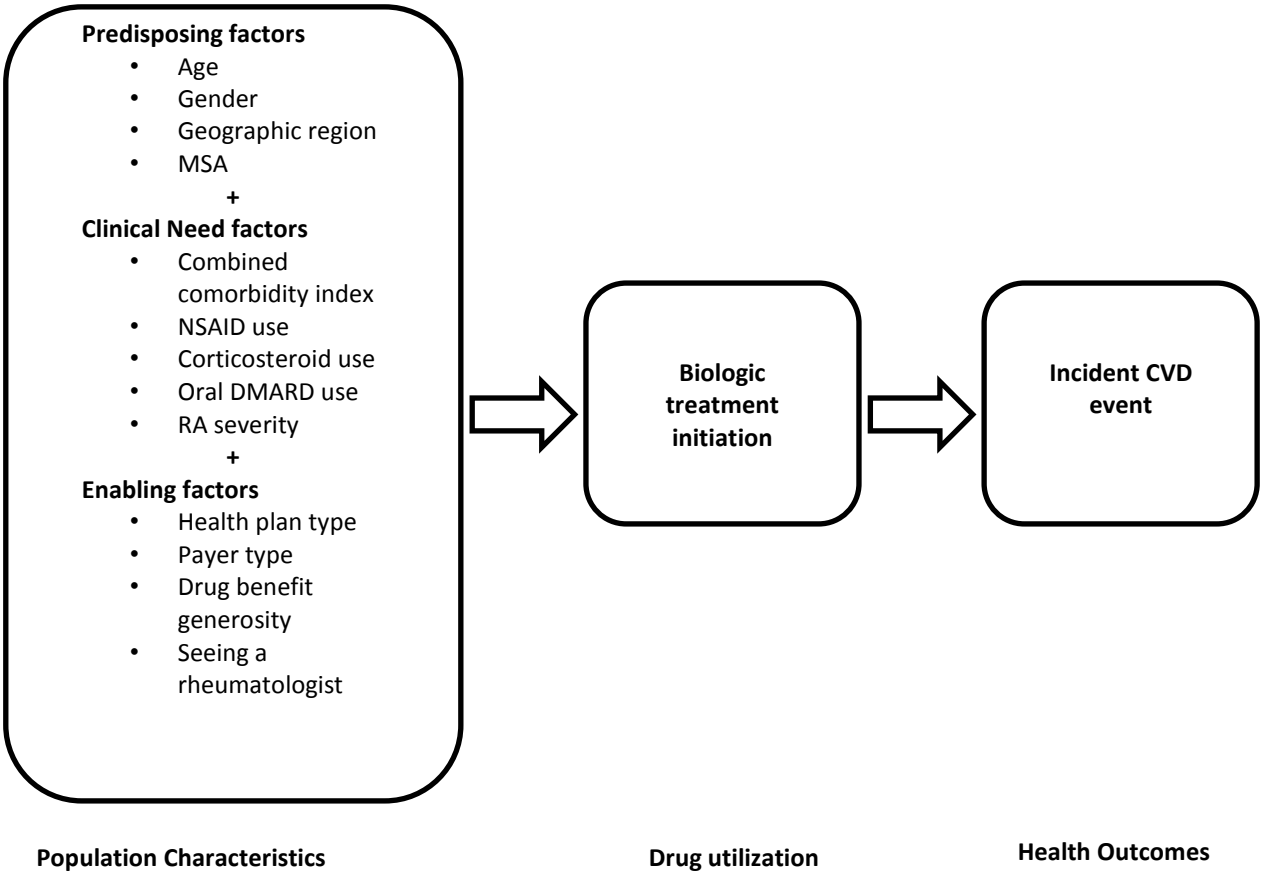
1) Predisposing factors: include patient characteristics that predisposes them to the utilization of health services (eg, age, sex, geographical factors)

2) Need factors: include health conditions of patients that necessitates the utilization of health services (eg, comorbid conditons, severity of illness, use of other medications) &

3) Enabling factors: include variables depicting patients' ability to secure the healthcare services (eg, health insurance, drug coverage).

The Andersen behavior model has been used to study utilization of healthcare services and subsequent outcomes in numerous studies in the literature (74-76). Based on these principles, we adapted this model to fit our research needs. Figure 2.1 shows the Andersen model with variables of interest for our analysis.

Figure 2.1: Andersen's Emerging Behavioral Model of Health Services Use (Adapted)



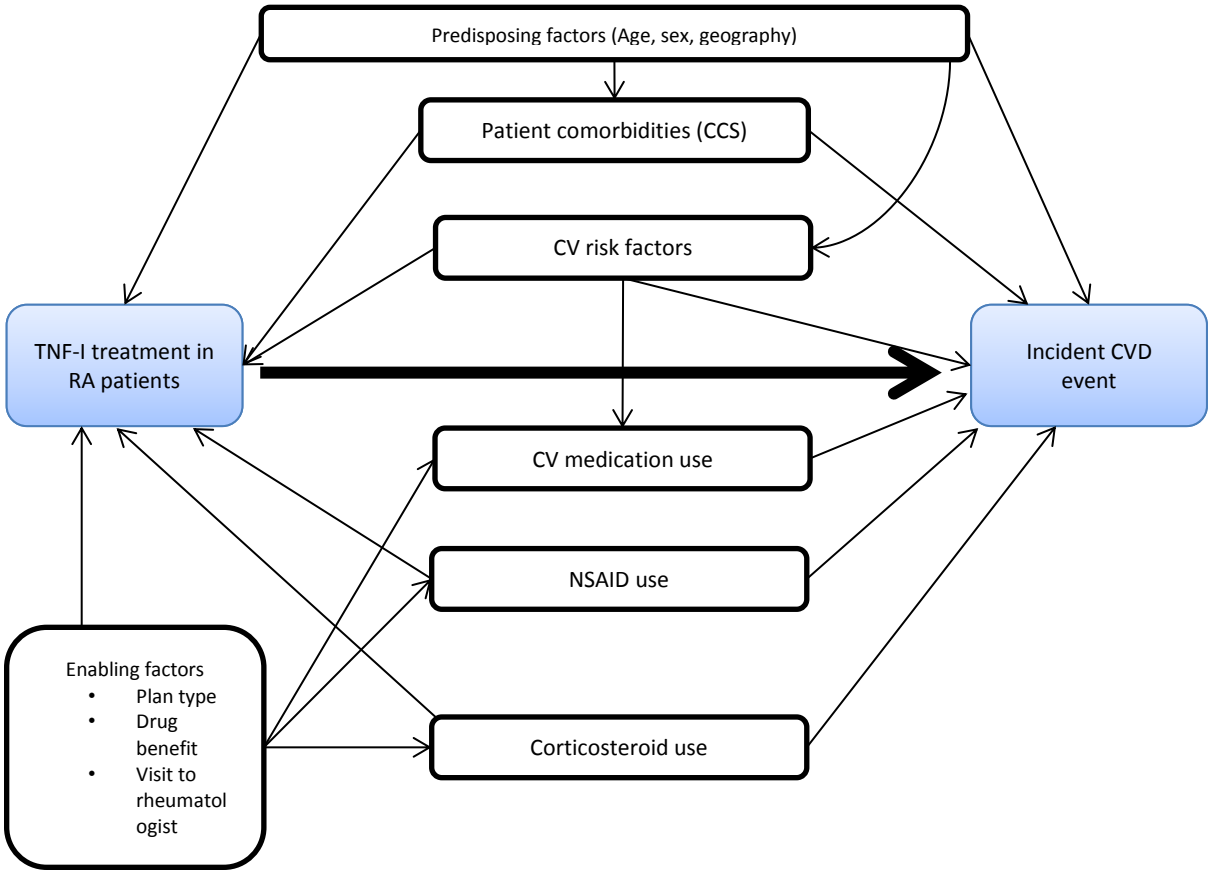
After identifying all the relevant variables in the Andersen model, it is equally important to consider their relation with the exposure and outcome of interest, as well as with one-another. In pharmacoepidemiology research, the biggest threat to the internal validity of any study is the issue of confounding. Confounding refers to a phenomenon where the relationship between the exposure and outcome of interest is due, completely or in part, to another variable that is associated independently with exposure and outcome. This variable is defined as the confounder (77).The theory of directed acyclic graphs (DAG) provides a

theoretical framework for identifying the potential confounders based on subject-matter knowledge (78-80).

In the past, various studies have successfully used the theory of DAG to identify relevant confounders and controlling for them through conditioning (81-83). Weng et al. (84) compared DAG with change-in-estimate method, in which the confounders are selected based on their impact on exposure-outcome association, for their performance in covariate selection in a simulation analysis. The performance was measured by standard error, bias, square root of the mean-squared error, and 95% confidence interval coverage. This study concluded that under correct specifications, DAG outperformed change-in-estimate method. More recently, Cox et al. (85) have recommended the use of DAGs in identifying confounders in design of nonrandomized studies of treatment effects using secondary data sources. Therefore, we used the theory of DAG to identify relevant confounders based on information from the literature.

A DAG is drawn as a network of exposure, outcome and all the other relevant variables that are associated with exposure and outcome independently. All the associations specified in the DAG must be directed, meaning the direction of the association between all the variables must be known. DAG must be acyclic, meaning there must not be any closed loops in the DAG. Any variable should not affect itself through other variables. Following all these rules, we constructed a DAG for the association between TNF-Is and CVD events (Figure 2.2). Within this framework, factors independently associated with TNF-Is (exposure) and CVD event (outcome) are shown along with the associations of interest, namely the association between TNF-I treatment and first CVD event.

Figure 2.2: Directed acyclic graph (DAG) for the association between TNF-I use and cardiovascular diseases



*CCS: Combined Comorbidity Score

** CVD risk factor includes diabetes mellitus, hyperlipidemia and hypertension

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Patient predisposing factors, age, sex and geogrpahic location, are considered as factors independently associated with exposure (TNF-I) and outcome (CVD events) in the DAG. This observation is supported by several studies in the literature. Bonafede et al. (62) reported that geographic location was associated with biologic medication initiation. Patient age has been consistently shown to be associated with prescription of biologic agents in RA

in the literature (63, 86-88). Older age is also directly associated to higher risk of CVD events as established by the Framingham heart study (89). Gender differences in the incidence of CVD have also been well established (90).

A number of clinical need factors including patients' comorbidities, CVD risk factors, use of NSAIDs and use of corticosteroids were postulated to be associated with both exposure and outcome independetly. Analysis of a registry data suggested that prior treatment with steroids were significantly associated with inititation of TNF-Is (63). Another study reported an association between NSAIDs use and initiation of biologic treatment (62). Both NSAIDs and steroids have been shown to be associated independently with CVD events (91, 92). Literature suggests that patient co-morbid conditions play an important role in initiation of biologic treatment in RA (62, 63). Comorbid conditions including diabetes, high blood pressure and hyperlipidemia have been consistantly reported to be associated with higher risk of CVD (93-95). We also must account for the causal effect of various classes of CV medications, including beta-blokers, inhibitors of renin angiotensin system, calcium channel blockers, and lipid lowering agents, on prevention of CVD events.

Finally, a set of enabling variables, including health plan type and patient co-pay are considered for their effect on the utilization of prescription medications including TNF-Is, NSAIDs, corticosteroids and CVD medications. Different plan types differ in their generosity of drug prescription coverage and the co-payments have been shown to be associated with prescription medication utilization (96). Therefore, it is important to consider impact of these variables on medication utilization while evaluating subsequent outcomes. Additionally, we also considered the impact of visit to rheumatologist on TNF-Is initiation because prior

research demonstrated higher likelihood of initiation of biologics if the patient visited a rheumatologist (62).

Thus, DAG provided us with a systematic framework of all the relavent variables that should be considered for confounding control while evaluating the effects of TNF-Is on the risk of CVD events. We evaluated all the causal and non-causal paths in our Figure 2.2 and identified a minimal sufficient adjustment set to control for confounding in a multivariate model for our Aims 2 and 3.

CHAPTER 3

METHODS

In section 3.1, the data source used for this dissertation is described. In section 3.2, methods used are described in detail by Specific Aims and finally in section 3.3, issues related to statistical power are discussed.

3.1 Data-source:

Data from the Truven's MarketScan Commercial Claims And Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (COB) were analyzed for this study. This database contains de-identified, person-specific health data including clinical utilization, expenditures, insurance enrollment/plan benefit, inpatient, outpatient, and outpatient prescription information. The data include private sector health data from approximately 100 payers, and can be linked to track detailed patient information across sites, types of providers, and over time (12). Over 35 million individuals were included in the 2008 CCAE, encompassing employees, their spouses, and their dependents. The Medicare Database contains the health care experiences of 2.5 million individuals annually with Medicare Supplemental insurance paid for by employers. Both the Medicare-covered portion of payment (represented as the COB amount) and the employer paid portion are included, as well as any out-of-pocket expenses to patients. These data have been used widely in health services research. Due to its substantial size, longitudinal integrity, and

unique data links, this database provides an ideal opportunity to conduct pharmacoepidemiology studies. For this particular analysis, data from inpatient services file, outpatient services file, outpatient drug claims file and enrollment file were merged using unique patient identifiers.

3.2 Methods by Specific Aim:

The plan for patient population, study design, measurement of variables and statistical analyses is detailed below by Specific Aim.

3.2.1 Specific Aim 1: To identify factors influencing biologic treatment initiation in RA patients

Patient population:

The total study period for our study was from Jan 1, 2007 to Dec 31, 2010. This time frame was selected because our dataset also contains Medicare enrollees and in 2006, Medicare part D was implemented extending drug benefit coverage to many beneficiaries. Therefore, it is likely that prescription medication utilization pattern may have changed between pre-2006 and post-2006. To avoid the threat of this history effect on our study's internal validity, we began our study period from Jan 1, 2007. To allow for 12 months of baseline period for everyone, the subject identification period started from Jan 1, 2008 and ended at Oct 1, 2010. All patients with a recorded diagnosis in this subject identification period were eligible for inclusion in our cohort. Diagnoses of RA was defined by ICD-9-CM) code of 714.0 in our data source. This ICD-9-CM code has been shown to be highly sensitive in detecting RA in previous studies (97, 98). However, concerns have been raised about the specificity of this code because of the high false positive rate observed by Singh et al. (97). To ensure specificity of our criteria, while maintaining high sensitivity, we required the

patients to have at least 2 outpatient claims (not on the same day), or 1 inpatient claim with this diagnosis code. The earliest of these diagnoses dates was defined as the index diagnosis date**.** Further, we required patients to fill a prescription of a DMARD in the study period after diagnosis of RA because as suggested by Singh et al. (97), this criterion reduces the high false positive rate of RA identification obtained by only using ICD-9 codes.

We excluded any patients with age <18 years at the time of their diagnoses because RA diagnosis under the age of 18 years is generally classified as juvenile rheumatoid arthritis (JRA), which differs systematically from RA in terms of disease progression and treatments used (99, 100). We further limited the inclusion to patients continuously enrolled in their health plan for at least 12 months prior to and 3 months after their index diagnosis date. This was done because intermittent enrollment may result in incompleteness of the data in our analytic dataset; which in turn could lead to misinterpretation of our effect estimates. The 12 months of continuous enrollment period prior to the index diagnosis date was defined as the baseline period. Figure 3.1 summarizes the inclusion and exclusion criteria for our RA cohort.

Study design:

We designed a retrospective cohort study to evaluate factors influencing biologic treatment initiation for this particular aim. Patients included in the RA cohort (See Figure 3.1) were followed for 3 months from the index diagnosis date for determining initiation of a biologic DMARD treatment. Figure 3.2 shows a schematic diagram of study design for Aim 1.

Figure 3.1: Inclusion and exclusion criteria for Aim 1 cohort

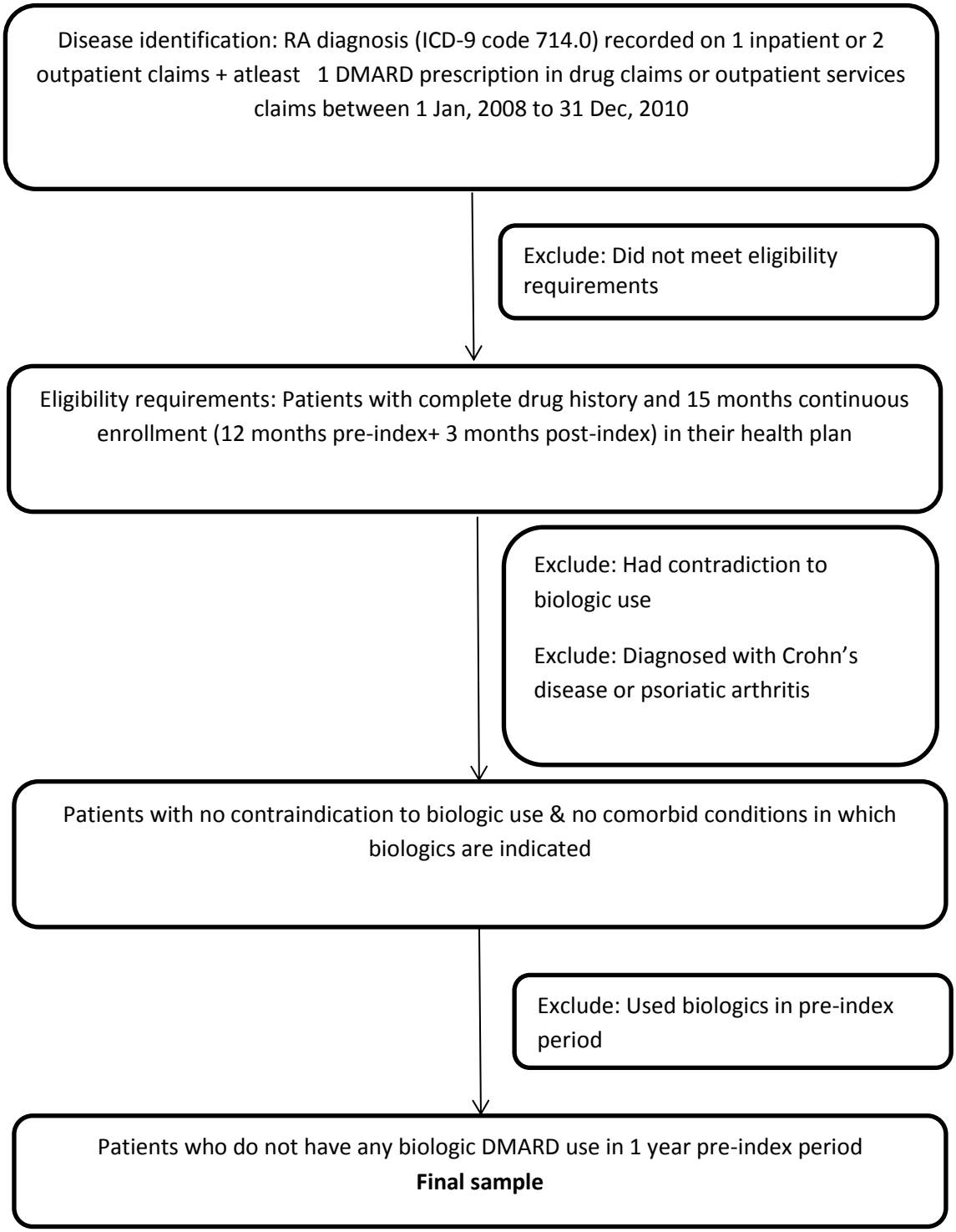
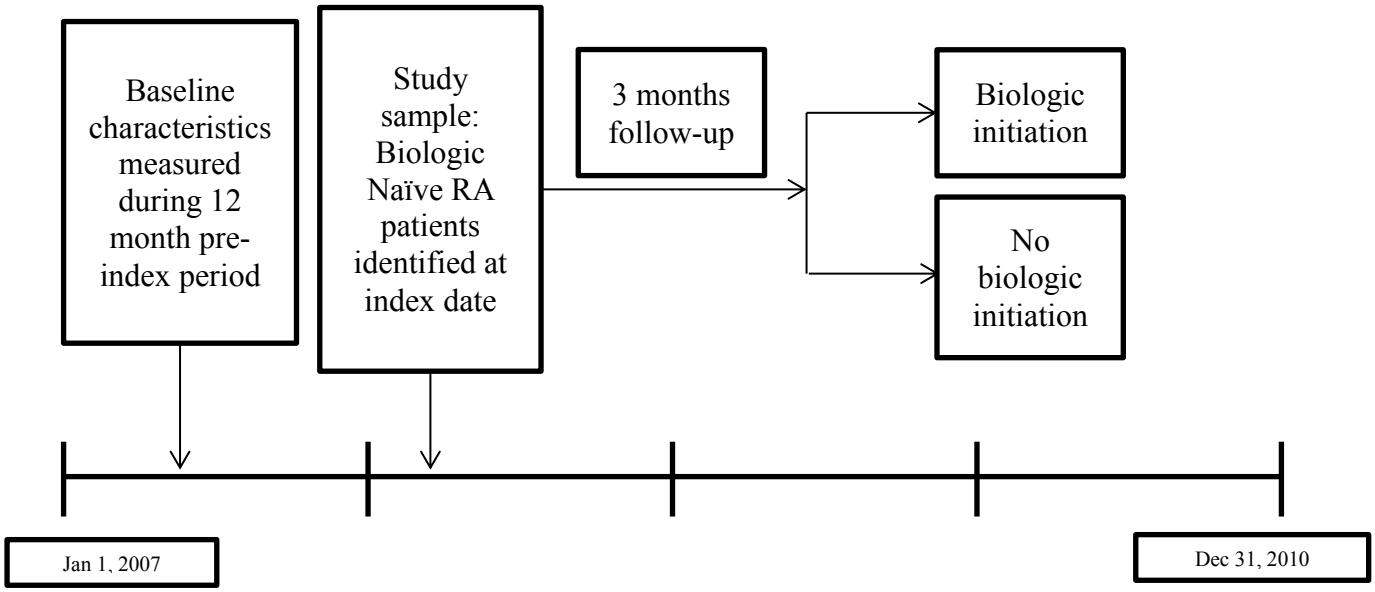


Figure 3.2: **Study design for Aim 1**



Measurement of variables:

Independent (Predictor) variables:

In this Specific Aim, we evaluated factors influencing biologic treatment initiation in RA patients. All the patient factors were independent variables of interest and were measured during the 12-month baseline period preceding their index diagnosis date. The details of variables to be measured are provided below,

1) **Predisposing factors:** Patients' age up to their index diagnosis date was measured as a continuous variable. Proportion of male and female patients in both the groups were reported. Two variables for the geographic location were included, 1) geographic

region, in which the patients were placed in one of the following groups based on US census region: Northeast, Midwest, South and West and 2) a metropolitan statistical area indicator.

2) **Clinical need factors:** We measured the risk factors for CVD, patients' comorbidity profile and severity of RA in the baseline period. Details for measurement are as follows,

    a. RA severity: To measure RA severity in our administrative claims data, we used the score developed by Ting et al. (101) This claims based index for rheumatoid arthritis severity (CIRAS) makes use of the information recorded in healthcare utilization claims to approximate RA severity through a composite score. CIRAS was calculated based on following information from administrative claims within past one year: patient age, gender, number of inflammatory marker tests ordered, rehabilitation visits, rheumatoid factor test, diagnosis of Felty's syndrome, number of chemistry panel ordered, number of platelet counts ordered, and number of rheumatology visits. CIRAS was measured as a continuous variable with higher score meaning worse disease.

    b. Use of co-medications: We measured the utilization of NSAIDs, steroids and number of oral DMARDs used in the baseline period. These products were identified using the national drug code (NDC) numbers from the outpatient pharmacy files and appropriate J codes from Healthcare Common Procedure Coding System (HCPCS) code set for injectable products.

c. Comorbidity profile: We measured patients' comprehensive comorbidity profile using the score proposed by Gagne et al., combined comorbidity score (CCS), which is reported to be superior in predicting mortality compared to the older scores (102). CCS was computed as a continuous variable using the algorithm proposed by these authors.

d. CVD risk factors: Diabetes, hypertension and hyperlipidemia have long been recognized as the major risk factors for CVD (94). In our RA cohort, we identified the proportion of patients with these risk factors. Identification of dibetes, hypertension and hyperlipidemia was based on an inpatient of outpatient diagnosis recorded using ICD-9-CM codes. Following codes were used: hypertension- 401.X–405.X; hyperlipidemia- 272.X; and diabetes mellitus-250.x.

3) **Enabling variables:** We included the following variables in this set: visit to a rheumatologist as a binary variable, health plan type as a binary variable indicating capitated plan (included HMO or capitated POS plans) or non-capitated plan (included Basic major medical, comprehensive, EPO, PPO, non-capitated POS, consumer driven health plan or high deductible health plan), type of insurance as a binary variable indicating either Medicare supplemental or commercial insurance and drug benefit generosity. Drug benefit generosity was approximated by creating a 'generosity index' using payment information from all the prescriptions filled by patients. Similar methods have been successfully used in prior studies (14). This index was calculated as a continuous variable in the range of 0-1 and was defined as the proportion of total drug cost paid by the patient out of pocket (OOP) as copay or

coinsurance. Based on this index, patients were classified into quartiles of drug benefit generosity to facilitate interpretation. The quartiles were termed as poor drug benefit generosity (highest OOP costs, 4th quartile), average drug benefit generosity (3rd quartile), above average drug benefit generosity (2nd quartile) and most generous drug benefit (lowest OOP costs, 1st quartile).

Dependent (Outcome) variable:

The outcome variable of interest was initiation of a biologic DMARD during the 90 days of follow up period beginning on the index diagnosis date. The following biologic agents were available during the study period and pooled for this analysis: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab. We did not categorize the biologics based on their mechanism of action because we assumed that due to similarities in costs and indications, the factors influencing treatment initiation might not differ across these classes and pooling them might give us better statistical power. The use of these agents was identified using both the NDC codes from outpatient pharmacy files for filled prescriptions and J codes using outpatient services files for injectable agents administered at physician's office.

Statistical analyses:

Descriptive statistics were used to summarize patient factors in biologic initiators and non-initiators. For dichotomous and categorical variables, the results were presented as numbers and proportions. For continuous variables, the results were presented as mean (± SD). The patient factors were then compared between biologic initiators and non-initiators using standardized differences (17). This method was used to avoid statistically significant

but clinically meaningless differences between our two groups owing to the large sample size. The equation for calculation of standardized difference can be given as follows,

$$d = \frac{100 \times (pT - pC)}{\sqrt{\frac{pT\ (1 - pT) + pC\ (1 - pC)}{2}}}$$

; pT= the prevalence of the binary variable in treated subjects.

pC = the prevalence of the binary variable in untreated subjects

To understand the impact of various predictors on the initiation of a biologic agent after controlling for other predictors in a multivariate manner, hierarchical logistic regression models were used in which the predictors were entered in 3 sets. The first model included only predisposing variables. The second model included predisposing and enabling variables. The final model included predisposing, enabling and need variables.

Following is the multiple logistic regression equation,

$$\text{Ln } (P/1\text{-}P) = \beta_0 + \beta_i X_{\text{Predisposing}} + \beta_j X_{\text{Enabling}} + \beta_k X_{\text{Need}} + \varepsilon$$

P= probability of outcome (biologic treatment initiation)

β=Regression co-efficient for the independent variables

ε= Error

The model fit was evaluated after entering each block using Akaike information criterion (AIC) and likelihood ratio tests.

3.2.2 Specific Aim 2: To compare the effect of TNF-Is on the risk of CVD events to other disease modifying anti rheumatic drugs (DMARDs) in RA patients.

Study design and patient population:

For this aim, we designed a ***nested case-control*** study within our RA cohort to study the effect of TNF-I use on the risk of CVD events. Nested case-control is an alternative study design to the cohort design that improves efficiency by matching only a fixed number of controls to cases in a defined cohort and comparing the exposure distribution in these two groups instead of analyzing person-time data for everyone in the cohort (77). The nested case-control study design uses special type of control sampling, known as *risk-set sampling* (103). A risk set at a given event date consists of the case (who observes the event at that time) and the remaining members of the cohort who are alive and being observed at that time point. From that risk set, a fixed number of controls are selected for each case. Since the cases and controls are matched on the event date in the sampling process by design, the nested case-control design can be used to model complex exposures that are time-varying (104). This study design has been shown to be a comparable alternative to survival analysis techniques that are computationally complex while studying time-dependent exposures (105). Matching on important covariates also allows control for potential confounders. In addition, it offers the classical advantage of the ability to study rare outcomes with sufficient power of the case-control study design. CVD events have been reported to have an incidence rate of 1.51 per 100 person years in RA patients in the US in previous research (106) . Therefore, to ensure sufficient power and to model our complex drug treatment appropriately over time, we selected the nested case-control study design to study the effect of TNF-α inhibitor use on CVD events.

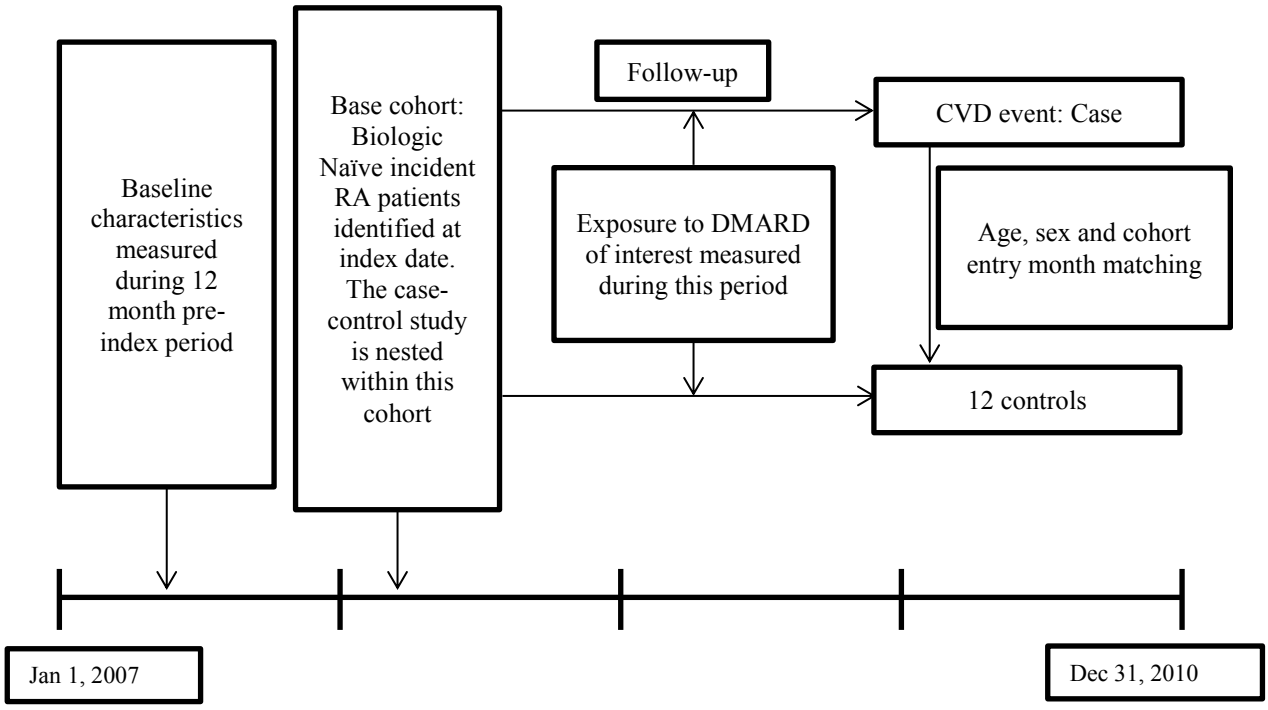
All the patients identified as the members of the RA cohort as shown in figure 3.1 comprised of the base cohort for Aim 2. Further, to be considered for our case-control sampling, patients in the base cohort had to meet the following inclusion criteria: 1) Continuous enrollment in their health plans during the 12 months of the baseline period to ensure completeness of data, 2) No diagnosis of RA in the baseline period to exclude prevalent RA cases, 3) No use of biologic agents in the baseline period because when the risk of outcome is altered with the course of treatment, the internal validity of the study is compromised if we fail to account for duration of the treatment. This problem can be circumvented by exclusion of prevalent drug users and constructing a clean cohort of only the incident drug users (107). 4) No history of tuberculosis (contraindication to biologics use) or psoriatic arthritis or Crohn's disease (both comorbid conditions in which some of the biologics are indicated) during the baseline period, and 5) No history of any CVD in the baseline period to ensure the selected patients are at risk for the outcome. Thus our patient population consisted of incident RA patients who had no history of biologic use, who were eligible to receive biologics in the future and who were at risk for an incident CVD event.

Nested case-control sampling:

All the patients identified as eligible for sampling from the base cohort were followed-up from their index date to the earliest of the following: the outcome (CVD diagnosis), disenrollment from their health plan, switch between biologic treatments or study end date (Dec 31, 2010). If patients experienced a CVD event, they were defined as cases and the date of CVD diagnosis was defined as the event date. Once the cases were identified, twelve age, sex and cohort entry month-matched controls were sampled using an incident density sampling procedure from the remaining patients of the base cohort who were being

followed-up at the event date and who were free from CVD at that time (Figure 3.3). The main purpose of matching in case-control studies is to balance the number of cases and controls across the levels of the selected matching variables. This balance can reduce the variance in the parameters of interest, which improves statistical efficiency. However, one must be extremely cautious because if the matching confounder is highly correlated to the exposure then matching forces the exposure distribution of the controls to be similar to the cases and hence may introduce a bias which is termed as 'control selection bias' in the literature (77). Since the follow-up began on the first ever RA diagnosis date for these patients, our sampling also ensured the matching of cases and controls on the duration of RA. Figure 5 depicts the schematic diagram for the study design for Aim 2.

Figure 3.3: **Study design for Aims 2 and 3**



Measurement of variables:

1. **Exposure:** Following three unique exposure definition schemes were used,
    a. Scheme 1 (Ever/Never): First, we considered a dichotomous definition of exposure: ever-treated with a TNF-I (Monotherapy or in combination with non-biologic DMARDs) vs never-treated with a TNF-I prior to the event date.
    b. Scheme 2 (Current use indicators for TNF-Is and other RA treatments): To take into account the timing of TNF-I use and also the use of other DMARDs, we defined exposure into following mutually exclusive categories, 1) Current use of TNF-Is (Monotherapy or in combination with non-biologic DMARDs), 2) Current use of other biologics (Monotherapy or in combination with non-biologic DMARDs), 3) Current use of only non-biologic DMARDs, 4) No current DMARD use. Drug use in the time period of 6-month prior to the event date was defined as 'current use'.
    c. Scheme 3 (Current and past use indicators for TNF-I and other RA treatments): In addition to the timing of TNF-I use and other DMARDs use, to account for the entire DMARD exposure history, we defined exposure into following mutually exclusive categories hierarchically: 1) No DMARD use, 2) Past use of only non-biologic DMARDs, 3) Current use of only non-biologic DMARDs, 4) Past use of TNF-Is (Monotherapy or in combination with non-biologic DMARDs), 5) Current use of TNF-Is (Monotherapy or in combination with non-biologic DMARDs), 6) Past use of other biologics (Monotherapy or in combination with non-biologic

DMARDs), and 7) Current use of other biologics (Monotherapy or in combination with non-biologic DMARDs). Drug use in the time period of 6-month prior to the event date was defined as 'current use' and any use before the time period of 6-months prior to the event date was defined as 'past use'.

TNF-Is included following agents: adalimumab, certolizumab, etanercept, golimumab and infliximab. Abatacept, anakinara, rituximab and tocilizumab were considered as 'other biologics'. Methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, cyclophosphamide and cyclosporine were defines as 'non-biologic DMARDs'. The use of these agents was identified using both the NDC codes from outpatient pharmacy files for filled prescriptions and J codes using outpatient services files for injectable/infusion agents administered at physician's office.

2. Measurement of duration of treatment:

Duration of treatment with TNF-I was defined as a continuous variable representing the cumulative days of TNF-I use for the patients who filled at least one TNF-I prescription in the exposure measurement period. Similarly, duration of treatment with non-biologic DMARDs and other biologics were also measured as continuous variables. Significance of a quadratic term was tested for the continuous variables representing cumulative use for each treatment to check for any evidence of non-linearity in the association between the duration and the risk of an incident CVD event.

3. **Outcome measurement:**

The outcome of interest was defined as a composite measure consisting of acute myocardial infarction (ICD-9 code 410), unstable angina (ICD-9 code 411), angina pectoris (ICD-9 code 413), chronic heart failure (ICD-9 codes 428.xx, 398.91, 402.01, 402.11, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93), other forms of chronic heart diseases (ICD-9 code 414), ischemic stroke (ICD-9 code s 433.x1, 434 [excluding 434.x0], or 436); and transient ischemic stroke (ICD-9 code 435).

4. **Covariates:**

We identified the following covariates during the baseline period: CVD risk factors including hypertension, hyperlipidemia, and diabetes mellitus, CVD drug use including lipid lowering agents, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and other CVD drugs, RA drug use including steroids, non-steroidal anti-inflammatory drugs and non-biologic DMARDs, and other comorbidities including chronic obstructive pulmonary disease and cancer.

Statistical analysis:

Descriptive statistics were used to summarize the patient characteristics for our cases and controls. Categorical variables were presented as numbers and percentages and continuous variables were presented as means (±standard deviations). The influence of the exposure definition on the absolute scale was assessed by calculating the estimates for the absolute risk of an incident CVD event during the 3 year follow-up period for all the three schemes using methods proposed by Langholz & Borgan (108). Based on this method, the

absolute risk of an incident CVD event at time t_j in the time interval (s,t] with a specified treatment history $X_0(u)$; $s< u\leq t$ is given by,

$$\hat{S}_1(s;t;X_0) = \prod_{s<t_j\leq t}\left(1-\hat{h}_1\left(t_j;X_0\right)\right)$$

; $\hat{h}_1\left(t_j;X_0\right)$ is a Kaplan-Mier type estimator of baseline hazard and given by following equation

$$\hat{h}_1\left(t_j;X_0\right) = \frac{r(\hat{\beta};\ X_0(t_j))}{\sum_{l\epsilon R(t_j)} r(\hat{\beta};\ X_l(t_j))\ w_l(t_j)} d_{1j}$$

$r(\hat{\beta};\ X_0(t_j))$ is a relative risk function for individual with treatment history X_0 at time t_j

$R(t_j)$ is the sampled risk set at time t_j

$r(\hat{\beta};\ X_l(t_j))$ is a relative risk function for individual l sampled in the risk set R with treatment history X_l at time t_j

$w_l(t_j)$ is sampling weights for individual l at time t_j calculated as the ratio of total patients sample at time t_j to total patients at risk set at time t_j

d_{1j}= 1 if occurrence of a CVD event is observed at t_j, 0 otherwise

For the relative risk estimation, our alternative hypothesis for this aim was following,

> H_a: TNF-Is reduce the risk of CV events compared to no use of DMARDs in newly diagnosed RA patients.

For this Specific Aim, a matched sampling technique (incidence density sampling) was used in which cases and controls are matched on person-time at risk by design. As a result, our final sample consisted of numerous groups, termed as risk sets, each with 1 case and 12 controls matched on person-time at risk, sex, age and cohort entry month and year. Matching presents a unique challenge in modeling because it divides the sample in to different strata, with the strata defined by potential confounder or sets of confounders (for instance, age, sex, cohort entry month and year and person-time at risk for CVD) represented by risk sets (77). These risk sets differ from one-another in terms of the baseline risk of the patients that are sampled within each set. If there are total 'n' risk sets then an unconditional logistic regression model would need (n-1) dummy variables to account for differences across those risk sets. Such model would be tremendously unstable because of the number of parameters that are needed to be estimated. The appropriate way to handle stratified data is the use of a conditional logistic regression (CLR) model, which is a model for stratum-specific regression. This model differs from unconditional model in which it conditions out the effects of each risk set instead of trying to model these effects. In other words, it does allow for the baseline risk to differ between the risk sets by fitting them as separate intercepts but does not estimate these baseline risks (or the nuisance parameters) (109).

Therefore, CLR methods were used to estimate crude and adjusted odds ratio (OR) for the effect of TNF-Is on the risk of CVD compared to no use of DMARDs only. The covariates discussed above were used for risk adjustment. Following is the CLR equation,

$$\text{logit}\,(\Theta_k) = \alpha_k + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 V$$

Θ_k = odds of CVD event given the exposure status and covariates

α_k= intercepts for n strata (for n risk sets)

$x_{1,..,} x_6$ = Exposure status indicators;

x_1=1 if past exposure to traditional DMARDs, 0 otherwise

x_2=1 if current exposure to traditional DMARDs, 0 otherwise

x_3=1 if past exposure to TNF-Is, 0 otherwise

x_4=1 if current exposure to TNF-Is, 0 otherwise

x_5=1 if past exposure to other biologics, 0 otherwise

x_6=1 if current exposure to other biologics, 0 otherwise

V= Vector of covariates

No use of DMARDs during the study period is the reference exposure category. Additionally, crude and adjusted estimates for the association between the duration of TNF-I use and incident CVD events were also estimated from separate CLR models.

3.2.3 *Specific Aim 3: To compare the effect of individual TNF-Is (adalimumab, etanercept, infliximab) on the risk of CVD events among RA patients.*

Study design:

For this Aim, we used the nested case-control study design as well. All the patients identified as the members of the RA cohort as shown in figure 3.1 comprised of the base cohort for Aim 3. For this Aim, we used similar exclusion criteria and sampling scheme used for Aim 2.

Measurement of variables:

1. **Exposure:**

We created 7 mutually exclusive categories for drug use based on at least one filled prescription of these agents during the study period. 1) Infliximab, 2) Etanercept, 3) Adalimumab, 4) Newer TNF-α inhibitors (golimumab and certolizumab) 5) Non-biologic DMARDs (including methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, cyclophosphamide and cyclosporine), 6) Other biologic agents (Abatacept, anakinara, rituximab and tocilizumab) and 7) No use of DMARD during the study period. The use of these agents was identified using both the NDC codes from outpatient pharmacy files for filled prescriptions and J codes using outpatient services files for injectable agents administered at physician's office.

Additionally, duration of treatment with these agents was defined as continuous variable representing the cumulative days of use for the patients who filled at least one prescription in the study period. Significance of a quadratic term was tested for the continuous variables representing cumulative use for each treatment to check for any evidence of non-linearity in the association between the duration and the risk of an incident CVD event.

2. **Outcome:**

The outcome of interest was defined as a composite measure consisting of acute myocardial infarction (ICD-9 code 410), unstable angina (ICD-9 code 411), angina pectoris (ICD-9 code 413), chronic heart failure (ICD-9 codes 428.xx, 398.91, 402.01,

402.11, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93), other forms of chronic heart diseases (ICD-9 code 414), ischemic stroke (ICD-9 code s 433.x1, 434 [excluding 434.x0], or 436); and transient ischemic stroke (ICD-9 code 435).

3. Covariates:

We identified following covariates during the baseline period: CVD risk factors including hypertension, hyperlipidemia, and diabetes mellitus, CVD drug use including lipid lowering agents, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and other CVD drugs, RA drug use including steroids, non-steroidal anti-inflammatory drugs and non-biologic DMARDs, and other comorbidities including chronic obstructive pulmonary disease and cancer.

Statistical analyses:

Descriptive statistics were used to summarize the patient characteristics for our cases and controls. Categorical variables were presented as numbers and percentages and continuous variables were presented as mean (±standard deviations).

To account for the matched sampling, we used conditional logistic regression (CLR) models for the estimations of incident rate ratios (IRRs). Results from both unadjusted and adjusted models were presented. The reference group was comprised of patients did not use any DMARD during the study period. Following is the CLR equation

$$\text{logit}(\Theta_k) = \alpha_k + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 V$$

Θ_k = odds of CVD event given the exposure status and covariates

α_k= intercepts for n strata (for n risk sets)

$x_{1,..,} x_6$ = Exposure status indicators;

x_1=1 if exposed to infliximab, 0 otherwise

x_2=1 if exposed to etanercept, 0 otherwise

x_3=1 if exposed to adalimumab, 0 otherwise

x_4=1 if exposed to newer TNF-Is, 0 otherwise

x_5=1 if exposed to non-biologic DMARDs, 0 otherwise

x_6=1 if exposed to other biologics, 0 otherwise

V= Vector of covariates

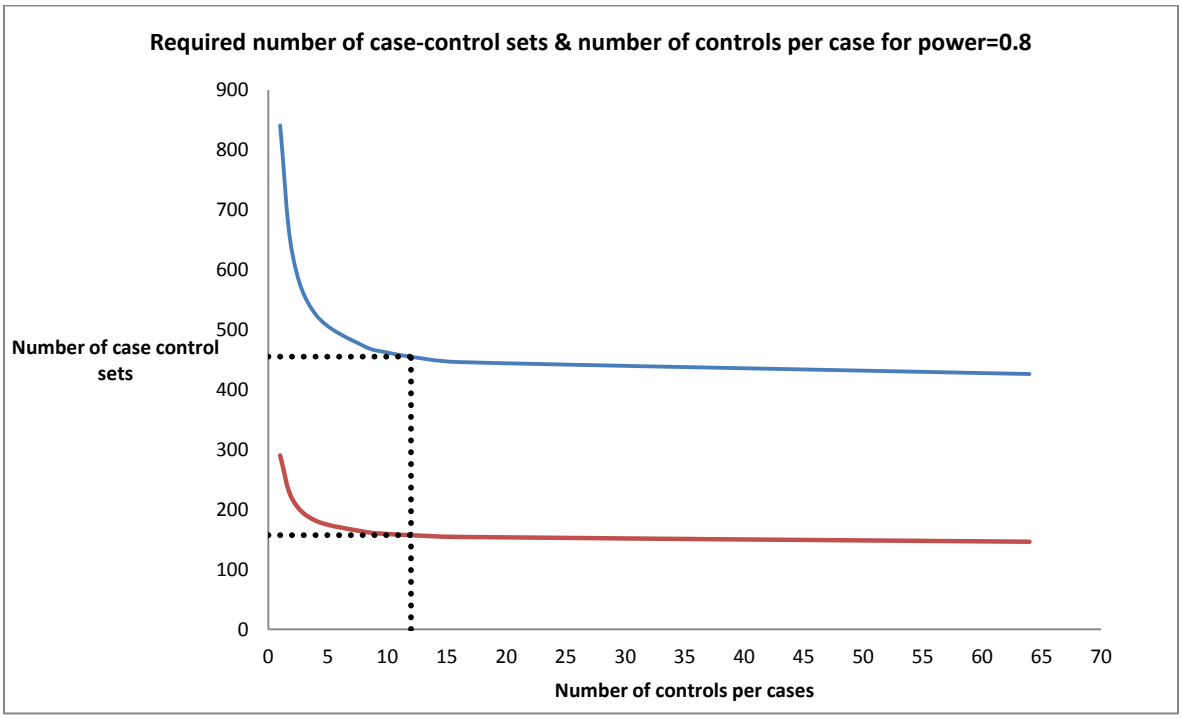
Additionally, crude and adjusted estimates for the association between the duration of infliximab, adalimumab and etanercept use and incident CVD events were also estimated from CLR. All analyses were conducted using SAS version 9.2 (SAS institute, Cary, NC).

3.3 Statistical power consideration:

Various authors have provided suggestions regarding the selection of number of controls per case in traditional case-control studies (110, 111) to achieve sufficient statistical power. The traditional dictum is to select four controls per case for traditional case-control analyses. Studies have shown that although the statistical power in case-control studies depends on exposure-outcome association strength, the gain in statistical power quickly diminishes after 4 controls per case (111). However, unlike the traditional case-control studies, nested case-control studies are conducted in a confined base cohort. Therefore, the

researchers have limited flexibility in the number of case-control pairs that can be selected. The maximum number of cases that can be selected in a nested case control study equals to the number of events observed in the base cohort. Therefore, the traditional dictum of four controls per case does not hold true in the case of nested case-control studies. Figure 3.4 is a chart representing approximate number of case-control sets needed to achieve 80% power with different effect size. As it can be seen, the curves platue after 12 controls per case. Therefore, we selected 12 matched control(s) per case. If the highest true odds ratio for disease in exposed subjects relative to unexposed subjects is 1.5, 455 case patients with 12 matched control(s) per case would be needed to be able to reject the null hypothesis that this odds ratio equals 1 with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

Figure 3.4: Statistical power consideration



CHAPTER 4

FACTORS INFLUENCING TREATMENT INITIATION WITH BIOLOGIC DISEASE MODIFYING ANTIRHEUMATIC AGENTS IN PATIENTS WITH RHEUMATOID ARTHRITIS

This chapter presents the first of three manuscript prepared from this dissertation. In this manuscript, we evaluated the factors influencing treatment initiation with biologics in rheumatoid arthritis patients using health insurance claims from Marketscan databases during the period of 2007 to 2010.

4.1 Overview

Background: Very little information is available in the literature specifically related to factors influencing treatment initiation with biologics in RA patients.

Objectives: To evaluate the predictors of treatment initiation with biologics in RA patients

Methods: A retrospective cohort study was designed using data for patients diagnosed with RA between Jan 1, 2008 and Oct 1, 2010 identified from Truven's MarketScan Commercial Claims And Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (COB). These patients were followed up for 3 months for the outcome of biologic initiation. The selection of predictors of biologic initiation was guided

by the Andersen Behavior Model. Predictors were measured during 12 month pre-index period and were grouped into three sets: predisposing, enabling or need factors. To

understand the impact of various predictors on the initiation of a biologic agent after controlling for other predictors in a multivariate manner, hierarchical logistic regression models were used in which the predictors were entered in three sets.

Results: Approximately 5% of the total sample (2,610 of 52,212) initiated treatment with a biologic agent during the 3-month follow-up period, of which 93.02% initiated treatment with an anti-TNF agent (n= 2,428). In our multivariate models, we observed that treatment initiation with biologics in RA patients was associated with predisposing factors patient age and region, enabling factors, health insurance type, and drug benefit generosity and need factors, RA severity, RA type, pre-index non-biologic DMARD and steroid use.

Conclusion: We observed that treatment initiation with biologics is influenced by a mix of predisposing, enabling and need factors. Our findings suggest that interventions such as more generous drug coverage could promote timely initiation of biologic treatment.

4.2 Introduction:

Rheumatoid arthritis (RA) is an autoimmune disease that affects approximately 1.3 million adults in the United States and is associated with substantial morbidity and mortality (2). The annual direct cost to treat patients with RA is estimated to be $9,519 per person (15), and the indirect costs of RA are approximately twice the direct costs associated with this condition (16). The average number of days absent from work due to RA has been reported to be in the range of 2.7 to 30 days annually (17).

Diseases modifying anti-rheumatic agents (DMARDs) form the cornerstone of pharmacologic treatment in RA by controlling inflammation and preventing joint damage. DMARDs are generally classified into non-biologic and biologic DMARDs. Non-biologic

DMARDs include agents, such as methotrexate, sulfasalazine, hydroxychloroquine, azathioprine, penicillamine and leflunomide. Although these medications halt the progression of the disease by suppressing inflammation, they do not interfere with the functioning of specific components of the immune system. On the other hand, biologic DMARDs (hereafter referred to as biologics) target specific components of the immune system, such as T cells, B cells, and cytokines (i.e., TNF- α and interleukins) that play an important role in the pathogenesis of RA (19). Currently, there are 10 biologics approved for the treatment of RA. Of these 10 agents, 5 are TNF-α inhibitors (e.g., adalimumab, etanercept), 2 are interleukin inhibitors (e.g., anakinra). The remaining agents include rituximab,an anti-CD20 antibody that causes depletion of B-cells, abatacept, a selective costimulation modulator that prevents full activation of T-cells, and tofacitinib, a janus kinase inhibitor.

The American College of Rheumatology (ACR) advocates the use of non-biologic DMARDs in all RA patients and the use of biologics in patients with moderate to high disease activity with features of poor prognosis or in patients who fail to respond to non-biologic DMARDs (112). Except for tofacitinib, the biologics are administered either subcutaneously or as an intravenous infusion, while most of the non-biologic agents are administered orally. The biologics are substantially more costly compared to non-biologic DMARDs. The mean annual direct costs for biologic treatment have been reported to be approximately five times greater than the annual direct costs for non-biologic DMARDs (15).

Treatment with biologics is efficacious in achieving ACR response rates in patients whose RA is not well controlled with conventional DMARDs (113). Uncontrolled RA decreases quality of life in patients and increases comorbidities, notably cardiovascular

diseases (114), which in turn can result in escalation of total healthcare costs. Timely initiation of biologics may be able to prevent these unfavorable consequences in RA patients.

Research surrounding the predictors of biologic treatment initiation is of special interest from a societal perspective because such research may provide an insight into potential strategies to improve access by identifying factors associated with lower likelihood of initiation of biologic agents. The current literature lacks studies that specifically evaluate the factors influencing biologic treatment initiation in RA. The 2 studies that examined this issue have important limitations. The study by Bonafede et al. (62) used insurance claims data to study the predictors of biologic and non-biologic DMARD treatment initiation in patients with newly diagnosed RA. This study provides limited information regarding biologics specifically since non-biologic and biologic DMARDs were pooled. It is well-understood that these two subgroups of DMARDs differ drastically in their mechanism of actions, indications and cost of treatment and therefore factors that influence the initiation of non-biologic DMARDs may differ from factors that influence the initiation of biologics. So, to study those as a single group may not give us estimates that are relevant to biologic agents. DeWitt et al. (63) evaluated specific predictors of biologic initiation in 1,545 RA patients in an observational database. This study used patient self-reported data for medication use, which is subject to numerous biases and did not consider important predictors such as patient cost-sharing. In addition to the limitations of a relatively small sample size and limited generalizability, this study used data up to 2006, at which point there were only 5 biologics compared to 10 which are available currently.

Therefore, we designed this study with the objective of evaluating the predictors of treatment initiation with biologics in RA patients. Our study adds new information to the

literature by evaluating factors specifically influencing biologic treatment initiation using a large nationally representative sample derived from health insurance claims. To systematically analyze the influence of sets of various population characteristics on biologic treatment initiation, we used Andersen's behavioral model (ABM) for health services use (73), a model that is helpful in understanding potential inequities in the use of healthcare services.

4.3 Methods:

Data source:

Data from the Truven's MarketScan Commercial Claims And Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (COB) were used for this study. This database contains de-identified, person-specific health data including clinical utilization, expenditures, insurance enrollment/plan benefit, inpatient, outpatient, and outpatient prescription information. The CCAE contains healthcare data for nearly 40 Million individuals, encompassing employees, their spouses, and their dependents. The COB data contains the health care experiences of 3.8 million Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. These data have been used widely in health services research due to its substantial size, longitudinal integrity, and unique data links (115). For this particular analysis, data from inpatient services file, outpatient services file, outpatient drug claims file and enrollment file were merged using unique patient identifiers.

Study design:

A retrospective cohort study was designed to evaluate factors influencing biologic treatment initiation in RA patients. The total study period was from Jan 1, 2007 to Dec 31,

2010. To allow for a 12-month baseline period for everyone in order to obtain stable baseline measurements and sufficient wash out period to identify prevalent biologic users, we began patient identification on Jan 1, 2008 and continued until Oct 1, 2010. All patients 18 years of age and older with recorded ICD-9-CM diagnosis code of 714.0 on at least 2 outpatient claims or 1 inpatient claim and at least 1 DMARD prescription in drug claims or outpatient services claims between Jan 1, 2008 and Dec 31, 2010 were identified as having RA. This algorithm has been validated for its use in identifying RA patients in electronic healthcare databases (97). The earliest diagnosis claim was defined as the index diagnosis. Patients who were not continuously enrolled in their health plan for 12 months pre-index and 3 months post-index or did not have complete drug history recorded in the database were excluded. We also excluded patients who had history of tuberculosis (contraindication to biologics use) or psoriatic arthritis or Crohn's disease (both comorbid conditions in which some biologic DMARDs are indicated) during the baseline period to ensure the included RA patients were eligible to receive biologics and the biologics initiated were for RA treatment. Finally, we excluded all the patients who used any biologic agent during the baseline period since we only were interested in incident users. Once the eligible RA patients were identified, they were followed for 3-months beginning from their index diagnosis for the initiation of a biologic agent (Figure 4.1).

Measures:

To evaluate factors influencing biologic treatment initiation in RA patients, we organized the patient factors into the following 3 distinct sets of predictors based on the ABM (73) 1) Predisposing factors 2) Enabling factors and 3) Need factors. ABM posits a process of health care use in which predisposing factors influence the ability (measured

through enabling factors) of a person to obtain health care which, when adding the need for treatment, predicts the use of health care services. We measured following sets of patient factors during the 12 month baseline period pre-index.

Predisposing factors:

Predisposing factors included the variables that may influence the likelihood of need for health services. Patients' age, gender and geographic location were included in this set. Age was defined as a continuous variable; gender was defined as a dichotomous variable and geographic location was defined as a categorical variable consisting of the following categories: Northeast, north central, west and south.

Enabling factors:

Enabling factors included variables suggesting patients' ability to secure healthcare services. We included the following variables in this set: visit to a rheumatologist as a binary variable, health plan type as a binary variable indicating capitated plan (included HMO or capitated POS plans) or non-capitated plan (included Basic major medical, comprehensive, EPO, PPO, non-capitated POS, consumer driven health plan or high deductible health plan), type of insurance as a binary variable indicating either Medicare supplemental or commercial insurance and drug benefit generosity. Drug benefit generosity was approximated by creating a 'generosity index' using payment information from all the prescriptions filled by patients. Similar methods have been successfully used in prior studies (116). This index was calculated as a continuous variable in the range of 0-1 and was defined as the proportion of total drug cost paid by the patient out of pocket (OOP) as copay or coinsurance. Based on this index, patients were classified into quartiles of drug benefit generosity to facilitate

interpretation. The quartiles were termed as poor drug benefit generosity (highest OOP costs, 4th quartile), average drug benefit generosity (3rd quartile), above average drug benefit generosity (2nd quartile) and most generous drug benefit (lowest OOP costs, 1st quartile).

Need factors:

Need factors included health conditions of patients that necessitate the utilization of health services. In this set, we included RA related factors such as RA type as a binary variable (incident or prevalent diagnosis) and RA severity as a continuous variable, calculated as a claims based index proposed and validated by Ting et al. (101). Other need factors included patients' comorbidity profile, which was calculated as a continuous score based on methods proposed by Gagne et al. (102), steroid use as a binary variable and use of non-biologic DMARDs as a categorical variable indicating whether patients used 0,1, 2 or more than 2 agents in the baseline period. Methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, cyclophosphamide and cyclosporine were included as non-biologic DMARDs.

The outcome variable of interest was initiation of a biologic DMARD during the 90 days of follow up period beginning on the index diagnosis date. The following biologic agents were available during the study period and pooled for this analysis: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab. We did not categorize the biologics based on their mechanism of action because we assumed that due to similarities in costs and indications, the factors influencing treatment initiation might not differ across these classes and pooling them might give us better statistical power. The use of these agents was identified using both the NDC codes from

outpatient pharmacy files for filled prescriptions and J codes using outpatient services files for injectable agents administered at physician's office.

Statistical analyses:

Descriptive statistics were used to summarize patient factors in biologic initiators and non-initiators. For dichotomous and categorical variables, the results were presented as numbers and proportions. For continuous variables, the results were presented as mean (± SD). The patient factors were then compared between biologic initiators and non-initiators using standardized differences (117). This method was used to avoid statistically significant but clinically meaningless differences between our two groups owing to the large sample size. The proportion of individual biologic agents initiated also was reported.

To understand the impact of various predictors on the initiation of a biologic agent after controlling for other predictors in a multivariate manner, hierarchical logistic regression models were used in which the predictors were entered in 3 sets. First only predisposing variables were added to the multivariate model, then enabling variables were added and finally need variables were added. All analyses were conducted using SAS version 9.2 (SAS institute, Cary, NC).

Sensitivity analyses:

To determine the robustness of our findings, we conducted several sensitivity analyses. First, we considered the initiation of biologic agents into two groups using two separate multivariate models, first model evaluating predictors of TNF-I initiation and second model evaluating predictors of other non-TNF-I biologics initiation. In another set of sensitivity analyses, we used follow-up periods for the length of 6 months and 12 months instead of the

original definition of 3 months. Finally, we conducted a stratified analysis based on the data source, commercial claims and Medicare supplemental claims, and reported findings.

4.4 Results:

A total of 52,212 patients were included in our cohort who were diagnosed with RA, had no history of biologic use, and could plausibly receive a biologic in the future (Figure 4.2). Approximately 5% of the total sample (2,610 of 52,212) initiated treatment with a biologic agent during the 3-month follow-up period. Table 4.1 compares the baseline characteristics of the biologic initiators and biologic non-initiators. Comparison of the predisposing variables suggested that the biologic initiators were more frequently younger (Mean age 51.6 years vs 59.2 years, *Standardized difference (SD)*=56.88), more likely to live in the south region (50.96% vs 41.40%, *Standardized difference=19.25*), less likely to live in the north central region (23.22% vs 30.30%, *Standardized difference=16.05*). For the enabling variables, type of insurance was less likely to be Medicare among the biologic initiators (12.07% vs 31.07%, *Sd=47.48).* Among need variables, the severity of RA was found to be significantly greater among biologic initiators (mean CIRAS 4.91 vs 4.10, *Sd*=16.05). Prevalence of certain comorbid conditions including any tumor (3.79% vs 6.99%, *SD=14.19*) and hypertension (32.61% vs 40.84%, *Sd=17.14*) was found to be lower in the biologic initiator group. Biologic initiators were more likely to use steroids (69.66% vs 61.46%, *SD=17.25*), more likely to have no use of any non-biologic DMARD (42.26% vs 30.77%, *SD=24.03*), while less likely to use only one non-biologic DMARD (37.01% vs 49.9%, *SD=26.22*) in the pre-index period.

Figure 4.3 shows the proportion of the 9 individual biologic agents that were initiated. Of 2,610 patients who initiated treatment with a biologic agent, most initiated treatment with

an anti-TNF agent (n= 2,428 or 93.02%). The patients most often initiated treatment with etanercept (47.32%) or adalimumab (37.47%), and initiated infliximab, golimumab, and certolizumab less frequently (5.48%, 1.76%, 1.00% respectively). Among other biologics, rituximab, abatacept, anakinara and tocilizumab were initiated by 3.95%, 2.34%, 0.61% and 0.08% of the patients, respectively.

The results of our multivariate model that evaluated the influence of various predictors on treatment initiation with biologics are presented in Table 4.2. The predisposing variables patient age and geographic region were found to be significant predictors of biologic initiation. Each year increase in age reduced the odds of biologic initiation by 2% (OR 0.98, 95% CI 0.97-0.98). Patients in the north central region had significantly lower likelihood of treatment initiation with biologics compared to patients in the south (OR 0.81, 95% CI 0.73-0.90).

Several of the enabling variables were found to be associated with biologic initiation. Medicare patients and patients with a capitated health plan had lower likelihood of biologic treatment initiation (Medicare vs commercial insurance OR 0.74, 95% CI 0.63-0.87, Capitated vs non-capitated health plan OR 0.81, 95% CI 0.71-0.91). On the other hand, 15% and 31% higher odds of biologic initiation were observed for above average and the most generous benefit generosity compared to poor benefit generosity (OR 1.15 95% CI 1.03-1.30 & OR 1.31 95% CI 1.17-1.47 respectively).

Among the need variables, RA severity, RA status, pre-index steroid and non-biologic DAMRD use were found to be significant predictors of biologic treatment initiation. With each unit increase in RA severity measure (CIRAS), the odds of biologic initiation

increased by 16% (OR 1.16 95% CI 1.12-1.21). Previous use of steroids raised the odds of biologic initiation by 51% (OR 1.51, 95% CI 1.38-1.66). Compared to no use of a non-biologic DMARD in the pre-index period, use of 1 non-biologic DMARD and 2 non-biologic DMARD decreased the odds of biologic initiation by 36% and 18% respectively (OR 0.64 95% CI 0.58-0.72 & OR 0.82 95% CI 0.72-0.93). Also, patients who had newly diagnosed RA at the index date had 34% greater odds of biologic initiation compared to those who had prevalent RA (OR 1.34 95% CI 1.16-1.56). Results and model fit statistics for our hierarchical models are reported in Appendix Table 4.1.

In our sensitivity analyses where we considered initiation of TNF-Is and other biologics as separate outcomes, findings similar to original model were observed for majority of the predictors but due to decreased power, some results were no longer statistically significant (Table 4.3). However, the need factor of patient comorbidity status (approximated by a combined comorbidity score (CCS)) was found to be a significant predictor of other biologic initiation but not TNF-I initiation. Each unit increase in CCS resulted in 25% increased odds of other biologic initiation (OR 1.25 95% CI 1.16-1.34). The results of other set of sensitivity analyses where follow-up periods were changed to 6 months and 12 months were very similar to the original results (Appendix Table 4.2). Finally, when we stratified our sample based on the data source into commercial and Medicare supplemental claims, we observed findings similar to our original results for all the variables except for the drug benefit generosity variable, which was a non-significant predictor among Medicare supplemental enrollees (Appendix Table 4.3).

4.5 Discussion:

In this nationally representative large sample of patients diagnosed with RA, we observed that treatment initiation with biologics is influenced by a mix of predisposing, enabling and need factors. When use of healthcare services is solely governed by patients' health related need factors, equity in healthcare use is demonstrated. However, when predisposing and enabling factors significantly explain the use of healthcare services independent of need factors, potential inequity in access of healthcare use is exhibited (75). In our analyses, in addition to the need factors such as RA severity, RA diagnosis type and pre-index use of non-biologic treatments for RA, the predisposing factor age, and the enabling factors of insurance type and drug benefit generosity were found to be significant predictors of treatment initiation with biologics suggesting potential issues with access to these agents.

The finding that age is inversely associated with biologic treatment initiation is consistent with a prior study by DeWitt et al. (63). A number of other studies have also reported a similar finding for DMARDs as a class and not only specific to biologics (62, 86, 87). Although there is no evidence in the literature suggesting differential efficacy of biologics in different age groups, evidence of their differential use is concerning because it may lead to less aggressive RA management and hence uncontrolled RA in older patients. One of the factors leading to less aggressive treatment in older RA patient may be physician preference (118). Future research should be conducted to examine the efficacy and safety of biologic agents in elderly patients to address physician concerns.

The significant association of higher RA severity score with biologic treatment initiation is an expected finding based on the ACR recommendations for the treatment of RA

(112). However, we also noted that incident RA cases were more likely than prevalent cases to initiate biologics and patients who used 1 or 2 non-biologic DMARDs in the pre-index period were less likely than patients who did not use any non-biologic DMARD to initiate biologics. These findings may seem counterintuitive at first glance. However, we postulate that this phenomenon may be attributed to the fact that combination therapy with biologics has been found to be superior to oral DMARD monotherapy for remission in early RA patients (119). Therefore physicians may start treatment with biologics at a very early stage of the disease to achieve remission in these patients.

We further observed that patients with drug benefit plans that had lower cost sharing were more likely to initiate treatment with biologics. Greater patient cost sharing has been known to delay or reduce the odds of initiation of treatments in a variety of disease conditions (120), including RA (121). The coverage of biologics under a higher or specialty formulary tier of pharmacy benefits has become increasingly common (122). Research suggests that this practice has substantially increased the OOP costs for biologics (122, 123). Insurers must be mindful of the fact that higher cost sharing may deter patients from initiation of timely pharmaceutical care, which may result in uncontrolled RA and eventual increase in total healthcare cost. Patients enrolled in capitated health plans were found to be less likely to initiate biologic treatment. However, since we did not have precise information about what services were capitated within these health plans, it is difficult to interpret this finding. We also found that Medicare supplemental enrollees were less likely to initiate biologics compared to the commercial enrollees, even after controlling for their age and other patient demographics. This may be attributed to differential patient and plan profiles between commercial and Medicare supplemental enrollees. To further examine this issue, we

conducted a stratified analysis in these two groups (Appendix Table 4.3). All the findings were found to be similar across the two data sources used, except for the drug benefit generosity. Among Medicare supplemental enrollees, drug benefit generosity did not significantly predict biologic initiation. We caution our readers trying to interpret this finding because our sample represents a special group of Medicare enrollees, those with employer sponsored health plans. These plans are seen as gold standards for drug benefits among all the Medicare patients.

Results from our sensitivity analyses, where we considered initiation of TNF-Is and other biologics as separate outcomes, suggested that patients with worse comorbidity profile were more likely to initiate non-TNF-I biologics (Table 4.3). This finding may reflect the fact that TNF-Is are contraindicated in a variety of comorbid conditions including congestive heart failure, multiple sclerosis, and lymphoproliferative diseases, while abatacept and rituximab are not (22). Therefore, it is likely that physicians may avoid TNF-I treatment in RA patients with a higher burden of comorbidities and hence sicker RA patients are channeled towards non TNF-I biologics. This finding is important for researchers evaluating associations between biologic treatments and various outcomes in RA patients in an observational setting. Appropriate measures should be taken to address this channeling bias in observational studies in order to ensure unbiased interpretation of the estimates.

This is the largest study of its kind to provide estimates on the influence of population characteristics on biologic treatment initiation. However, there are several limitations of this study that deserve discussion. As with any other study using administrative claims, we were not able to validate the diagnoses of the disease condition (RA) as well as co-morbid conditions. Further, the administrative claims contain very limited information on clinical

conditions of RA patients, such as disease activity and swollen joint count. Therefore, we were not able to capture the exact severity of RA in patients in our cohort. However, as a proxy, we used the validated claims-based index for getting an approximation of RA severity (101). We also did not have any specific information about the drug coverage criteria for our patients and therefore had to rely on a calculated generosity index that approximated the drug benefit generosity for the patients in our cohort. Next, because of the unavailability of information on patient race, our study cannot explain potential racial disparities in biologics initiation. Finally, the insurance claims data only represent employed individuals and their dependents and the Medicare supplemental data only represent retirees whose insurance are paid by their employers limiting generalizability.

4.6 Conclusion:

The results from our study suggest that treatment initiation with biologics in RA patients is associated with patient age, RA severity, RA type, pre-index non-biologic DMARD and steroid use, health insurance type, and drug benefit generosity. From a policy point of view, the finding that more generous drug coverage facilitated biologic initiation is of significance. Our findings also highlight potential age bias in the initiation of biologics.

Figure 4.1: Timeline of the study

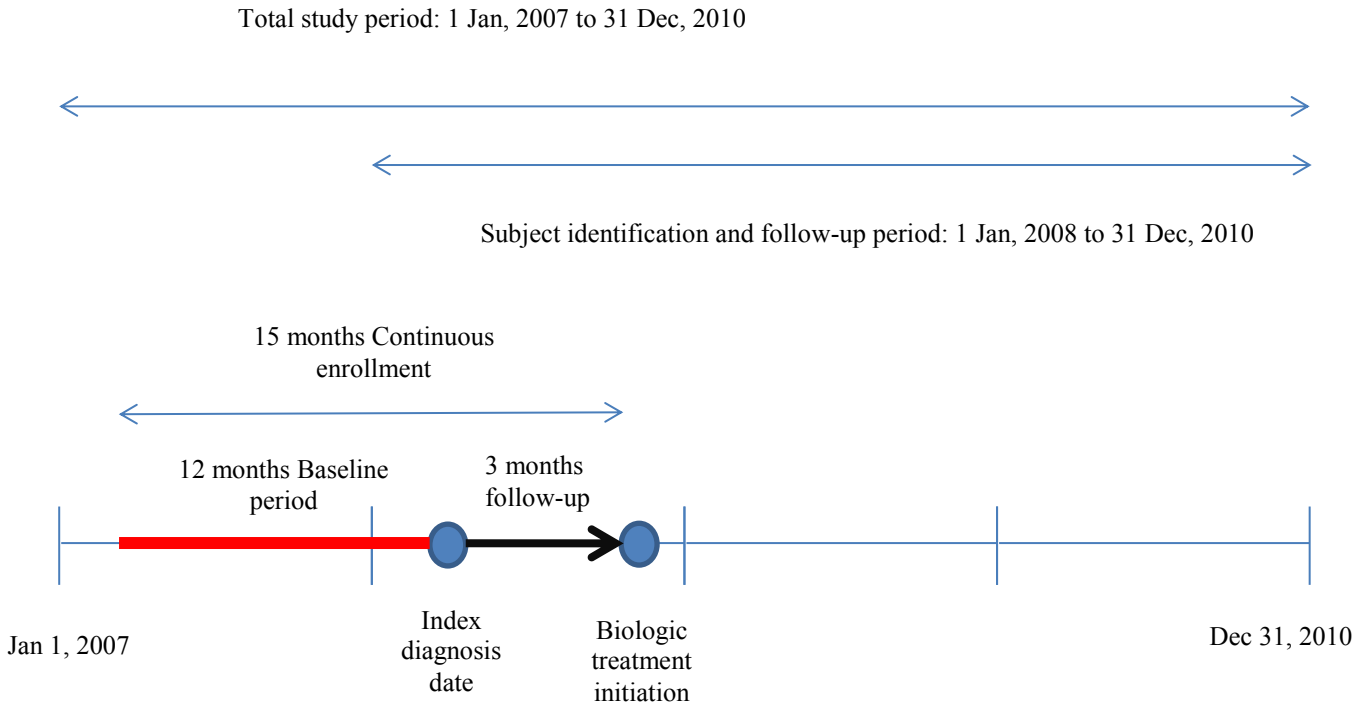
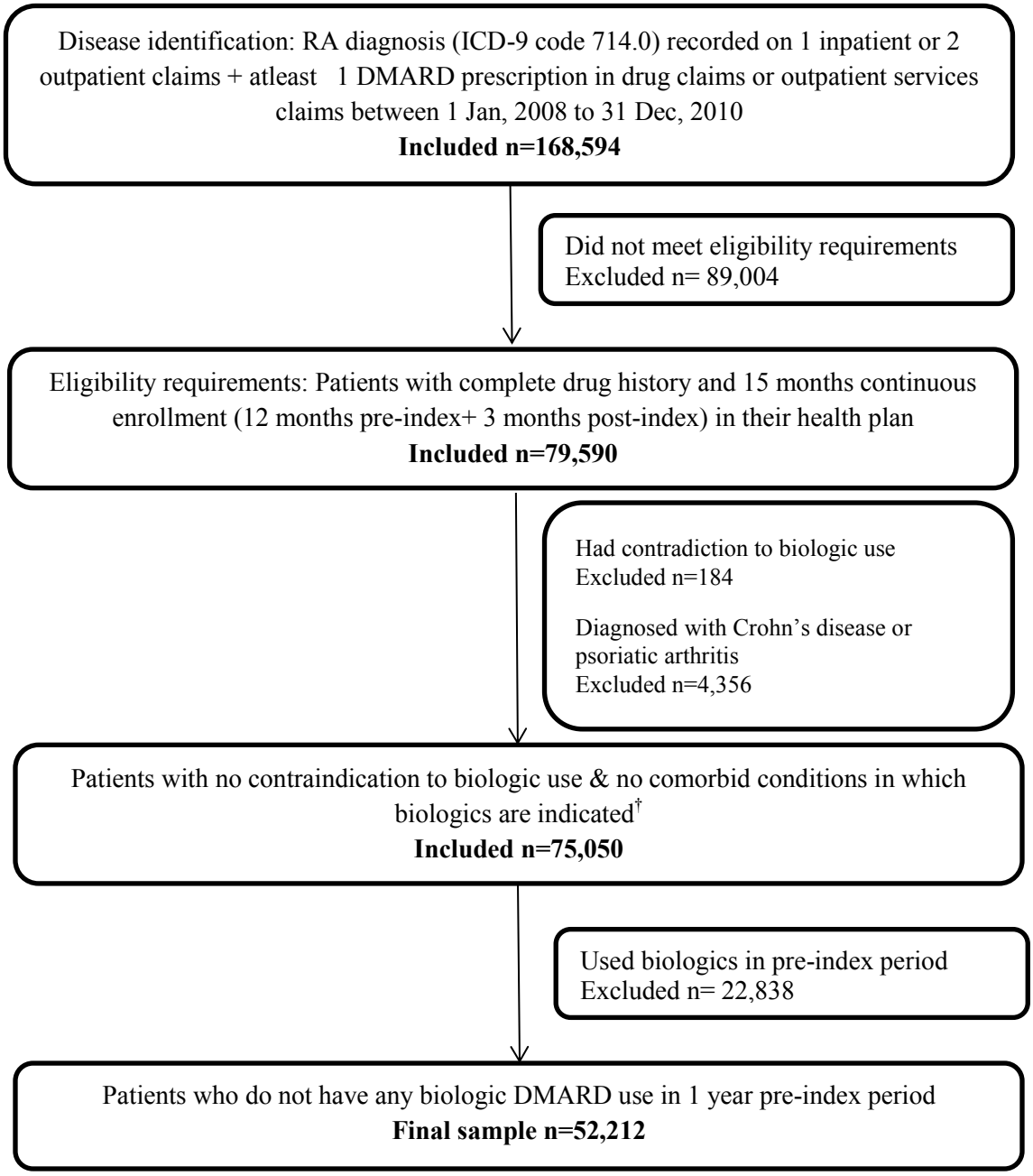


Figure 4.2: **Sample derivation flow-chart**



†The contraindications to biologic use considered were: Tuberculosis (ICD-9 codes: 010-018). The other conditions in which also biologics are indicated were Crohn's disease (ICD-9 code: 555) and Psoriatic arthritis (ICD-9 code: 696)

Table 4.1: Baseline characteristics of the biologic initiator and non-initiator patients with rheumatoid arthritis identified from Marketscan database, 2008-2010

Variable		*Biologic initiators (n=2,610)*	*Biologic non-initiators (n=49,602)*	*Standardized difference*[†]
		n(%)	n(%)	
Predisposing				
Patient age (Mean(SD))		51.63(12.8)	59.18(13.72)	56.88
Female		1985(76.05)	37182(74.96)	2.54
MSA		2121(81.55)	39997(81.01)	1.37
Region				
	Northeast Region	220(8.43)	4739(9.55)	3.93
	North Central Region	606(23.22)	15031(30.3)	16.05
	South Region	1330(50.96)	20537(41.4)	19.25
	West Region	442(16.93)	9045(18.24)	3.42
	Unknown region	12(0.46)	250(0.5)	0.64
Enabling				
Capitation				
	Non-capitated health plan	2193(86.14)	40966(84.38)	4.96
	Capitated health plan	353(13.86)	7585(15.62)	4.96
Seeing a rheumatologist		1281(49.98)	22688(46.1)	7.77
Payer type				
	Commercial	2295(87.93)	34190(68.93)	47.48
	Medicare	315(12.07)	15412(31.07)	

Drug benefit generosity‡			
Most generous drug benefit	687(26.32)	12338(24.87)	3.32
Better than average drug benefit	609(23.33)	12416(25.03)	3.97
Average drug benefit	603(23.1)	12423(25.05)	4.54
Below average drug benefit	685(26.25)	12340(24.88)	3.13
Need			
Incident RA	976(37.39)	16636(33.54)	8.07
CIRAS* (Mean(SD))	4.91(2.09)	4.10(1.92)	16.05
Combined comorbidity score (CCS or Gagne Score) (Mean(SD))	0.40(1.26)	0.48(1.42)	6.47
Individual comorbid conditions from CCS			
Metastatic cancer	6(0.23)	292(0.59)	5.62
Congestive heart failure	116(4.44)	2996(6.04)	7.16
Dementia	6(0.23)	297(0.6)	5.75
Renal failure	64(2.45)	1540(3.1)	3.97
Weight loss	10(0.38)	188(0.38)	0.07
Hemiplegia	7(0.27)	193(0.39)	2.11
Alcohol abuse	10(0.38)	171(0.34)	0.64
Any tumor	99(3.79)	3467(6.99)	14.19
Cardiac arrhythmias	150(5.75)	3874(7.81)	8.21
Chronic pulmonary disease	302(11.57)	7025(14.16)	7.75
Coagulopathy	46(1.76)	857(1.73)	0.26
Complicated diabetes	66(2.53)	1603(3.23)	4.2
Deficiency anemia	331(12.68)	6331(12.76)	0.24
Fluid and electrolyte disorders	129(4.94)	2983(6.01)	4.71

Liver disease	78(2.99)	905(1.82)	7.6
Peripheral vascular disorder	93(3.56)	2642(5.33)	8.56
Psychosis	129(4.94)	2156(4.35)	2.83
Pulmonary circulation disorders	20(0.77)	488(0.98)	2.34
HIV/AIDS	0(0)	36(0.07)	3.81
Hypertension	851(32.61)	20256(40.84)	17.14
Steroids use in pre-index period	1818(69.66)	30501(61.49)	17.25
Non-biologic DMARD use in pre-index period			
No use	1103(42.26)	15264(30.77)	24.03
Used 1 agent	966(37.01)	24750(49.9)	26.22
Used 2 agents	440(16.86)	8338(16.81)	0.13
Used more than 2 agents	101(3.87)	1250(2.52)	7.68

† A standardized difference of 10 (approximately equivalent to P<.05) indicates significant imbalance of a baseline covariate.

‡Drug benefit generosity was classified according to the quartiles of calculated generosity index. This index was calculated as a continuous variable and defined as the proportion of total drug cost paid by the patient out of pocket. The quartiles were termed as poor drug benefit generosity (highest out of pocket costs, 4th quartile), average drug benefit generosity (3rd quartile), above average drug benefit generosity (2nd quartile) and most generous drug benefit (lowest out of pocket costs, 1st quartile). Because of no prescription drug use, generosity index in 111 patients (26 and 85 respectively in biologic initiators and non-initiators) was missing.

*CIRAS: Claims based index of rheumatoid arthritis severity

Table 4.2: Multivariate predictors of treatment initiation with biologic agents in RA patients

Variables	OR (95% CI)
Predisposing	
Patient age	0.98 (0.97-0.98)
Region	
South region	1
North Central Region	0.81 (0.73-0.90)
Northeast Region	0.89 (0.76-1.03)
West Region	0.92 (0.82-1.04)
Metropolitan statistical area	
Non-MSA	1
MSA	1.04 (0.94-1.16)
Gender	
Female	1
Male	1.08 (0.98-1.19)
Enabling	
Capitation	
Non-capitated health plan	1
Capitated plan	0.81 (0.71-0.91)
Visit to rheumatologist in the pre-index period	
No visit	1
At least one visit	1.03 (0.94-1.13)

Drug benefit generosity†	
Poor	1
Average	1.00 (0.89-1.13)
Better than average	1.15 (1.03-1.30)
Most generous	1.31 (1.17-1.47)
Insurance type	
Commercial	1
Medicare	0.74 (0.63-0.87)
Need	
RA factors	
CIRAS‡	1.16 (1.12-1.21)
Prevalent RA	1
Incident RA	1.34 (1.16-1.56)
Medication use in the pre-index period	
No steroid use	1
Steroid use	1.51 (1.38-1.66)
No non-biologic DMARD use	1
1 non-biologic DMARD use	0.64 (0.58-0.72)
2 non-biologic DMARDs use	0.82 (0.72-0.93)
> 2 non-biologic DMARDs use	1.13 (0.90-1.41)
Combined comorbidity score	1.00 (0.97-1.04)

† Drug benefit generosity was classified according to the quartiles of calculated generosity index. This index was calculated as a continuous variable and defined as the proportion of total drug cost paid by the patient out of pocket. The quartiles were termed as poor drug benefit generosity (highest out of pocket costs, 4th quartile), average drug benefit generosity (3rd quartile), above average drug benefit generosity (2nd quartile) and most generous drug benefit (lowest out of pocket costs, 1st quartile).

‡ CIRAS: Claims based index of rheumatoid arthritis severity

Table 4.3: Sensitivity analyses: Multivariate predictors of treatment initiation with TNF-Inhibitors and other biologics in RA patients

Variables	OR (95% CI)	
	TNF-Inhibitors†	Other Biologics†
Predisposing		
Patient age	0.98 (0.97-0.98)	0.99 (0.97-1.01)
Region		
South region	1	1
North Central Region	0.80 (0.72-0.89)	0.94 (0.65-1.37)
Northeast Region	0.89 (0.76-1.04)	0.84 (0.47-1.5)
West Region	0.93 (0.82-1.05)	0.81 (0.5-1.31)
Metropolitan statistical area		
Non-MSA	1	1
MSA	1.05 (0.94-1.17)	0.96 (0.65-1.42)
Gender		
Female	1	1
Male	1.07 (0.97-1.18)	1.15 (0.81-1.64)
Enabling		
Capitation		
Non-capitated health plan	1	1
Capitated plan	0.83 (0.73-0.93)	0.47 (0.26-0.86)
Visit to rheumatologist in the pre-index period		

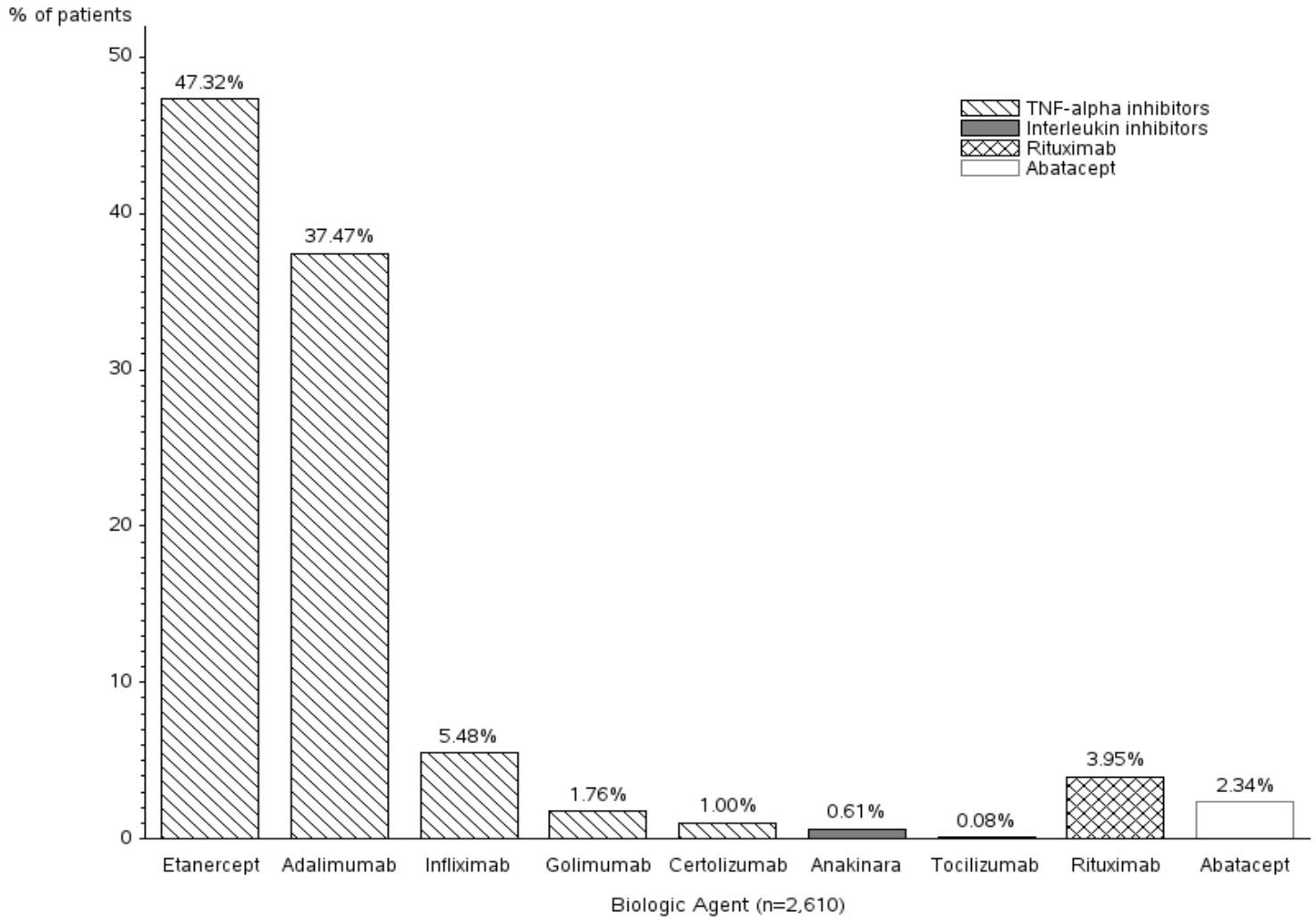
No visit	1	1
At least one visit	1.02 (0.92-1.12)	1.25 (0.89-1.76)
Drug benefit generosity[‡]		
Poor	1	1
Average	0.96 (0.85-1.09)	1.89 (1.17-3.05)
Better than average	1.13 (1.00-1.27)	1.72 (1.06-2.81)
Most generous	1.31 (1.17-1.48)	1.36 (0.82-2.25)
Insurance type		
Commercial	1	1
Medicare	0.67 (0.57-0.80)	0.66 (0.39-1.12)
Need		
RA factors		
CIRAS[*]	1.17 (1.12-1.22)	1.07 (0.92-1.24)
Prevalent RA	1	1
Incident RA	1.30 (1.12-1.52)	1.86 (1.07-3.2)
Medication use in the pre-index		
period		
No steroid use	1	1
Steroid use	1.50 (1.36-1.65)	1.66 (1.15-2.41)
No non-biologic DMARD use	1	1
1 non-biologic DMARD use	0.64 (0.58-0.72)	0.71 (0.48-1.06)
2 non-biologic DMARDs use	0.82 (0.71-0.93)	0.89 (0.54-1.46)
> 2 non-biologic DMARDs use	1.10 (0.87-1.39)	1.52 (0.70-3.30)
Combined comorbidity score	0.97 (0.94-1.00)	1.25 (1.16-1.34)

† For the other biologic model, the total number of events was 161(other biologic initiators) and for the TNF-Inhibitor model, the total number of events was 2,308 (TNF-inhibitor initiators). Other biologic agents include abatacept, anakinara, rituximab and tocilizumab and TNF-inhibitors include adalimumab, certolizumab, etanercept, golimumab and infliximab.

‡ Drug benefit generosity was classified according to the quartiles of calculated generosity index. This index was calculated as a continuous variable and defined as the proportion of total drug cost paid by the patient out of pocket. The quartiles were termed as poor drug benefit generosity (highest out of pocket costs, 4th quartile), average drug benefit generosity (3rd quartile), above average drug benefit generosity (2nd quartile) and most generous drug benefit (lowest out of pocket costs, 1st quartile).

*CIRAS: Claims based index of rheumatoid arthritis severity

Figure 4.3: **Proportion of individual biologics initiated in RA patients**



Appendix Table 4.1: **Results of hierarchical models for prediction initiation of biologics**

Variable	OR (95% CI)		
	Model 1 (Predisposing factors)	**Model 2 (Predisposing+ Enabling factors)**	**Model 3 (Predisposing+ Enabling+ Need factors)**
Patient age	0.96(0.96-0.97)	0.98(0.97-0.98)	0.98(0.97-0.98)
Region			
South region	1	1	1
North Central Region	0.74(0.67-0.81)	0.79(0.72-0.88)	0.81(0.73-0.90)
Northeast Region	0.79(0.68-0.91)	0.85(0.73-0.98)	0.89(0.76-1.03)
West Region	0.81(0.72-0.9)	0.88(0.79-0.99)	0.92(0.82-1.04)
Metropolitan statistical area			
Non-MSA	1	1	1
MSA	1.06(0.96-1.18)	1.05(0.94-1.16)	1.04(0.94-1.16)
Gender			
Female	1	1	1
Male	1.08(0.99-1.19)	1.06(0.96-1.16)	1.08(0.98-1.19)
Capitation			
Non-capitated health plan		1	1
Capitated plan		0.79(0.70-0.90)	0.81(0.71-0.91)
Visit to rheumatologist in the pre-index period			
No visit		1	1
At least one visit		1.13(1.04-1.23)	1.03(0.94-1.13)

Drug benefit generosity†			
Poor		1	1
Average		1.01(0.90-1.13)	1.00(0.89-1.13)
Better than average		1.15(1.02-1.29)	1.15(1.03-1.30)
Most generous		1.31(1.17-1.47)	1.31(1.17-1.47)
Insurance type			
Commercial		1	1
Medicare		0.66(0.56-0.77)	0.74(0.63-0.87)
RA factors			
CIRAS‡			1.16(1.12-1.21)
Prevalent RA			1
Incident RA			1.34(1.16-1.56)
Medication use in the pre-index period			
No steroid use			1
Steroid use			1.51(1.38-1.66)
No non-biologic DMARD use			1
1 non-biologic DMARD use			0.64(0.58-0.72)
2 non-biologic DMARDs use			0.82(0.72-0.93)
> 2 non-biologic DMARDs use			1.13(0.90-1.41)
Combined comorbidity score			1.00(0.97-1.04)
Model Fit statistics			
c-statistic	0.64	0.67	0.69
AIC	19856.7	18892.1	18654.7

† Drug benefit generosity was classified according to the quartiles of calculated generosity index. This index was calculated as a continuous variable and defined as the proportion of total drug cost paid by the patient out of pocket. The quartiles were

termed as poor drug benefit generosity (highest out of pocket costs, 4th quartile), average drug benefit generosity (3rd quartile), above average drug benefit generosity (2nd quartile) and most generous drug benefit (lowest out of pocket costs, 1st quartile).

‡ CIRAS: Claims based index of rheumatoid arthritis severity

Appendix Table 4.2: **Sensitivity analyses: Multivariate predictors of treatment initiation with biologics in RA patients, 6 months and 12 months follow-up period**

Variables	OR (95% CI)	
	6 month follow-up period†	12 month follow-up period†
Predisposing		
Patient age	0.98 (0.97-0.98)	0.98 (0.97-0.98)
Region		
South region	1	1
North Central Region	0.83 (0.76-0.9)	0.85 (0.78-0.92)
Northeast Region	0.89 (0.78-1.01)	0.85 (0.76-0.97)
West Region	0.99 (0.9-1.09)	0.93 (0.84-1.02)
Metropolitan statistical area		
Non-MSA	1	1
MSA	1.06 (0.97-1.16)	1.04 (0.95-1.13)
Gender		
Female	1	1
Male	1.07 (0.99-1.16)	1.03 (0.95-1.11)
Enabling		
Capitation		
Non-capitated health plan	1	1
Capitated plan	0.84 (0.76-0.92)	0.88 (0.81-0.97)
Visit to rheumatologist in the pre-index period		
No visit	1	1

At least one visit	1.01 (0.93-1.09)	0.94 (0.87-1.01)
Drug benefit generosity‡		
Poor	1	1
Average	1.03 (0.93-1.13)	1.01 (0.92-1.11)
Better than average	1.13 (1.03-1.25)	1.08 (0.99-1.19)
Most generous	1.29 (1.17-1.41)	1.21 (1.1-1.33)
Insurance type		
Commercial	1	1
Medicare	0.77 (0.68-0.88)	0.79 (0.7-0.89)
Need		
RA factors		
CIRAS*	1.18 (1.15-1.22)	1.19 (1.15-1.22)
Prevalent RA	1	1
Incident RA	1.5 (1.33-1.7)	1.52 (1.35-1.71)
Medication use in the pre-index period		
No steroid use	1	1
Steroid use	1.58 (1.46-1.7)	1.57 (1.46-1.69)
No non-biologic DMARD use	1	1
1 non-biologic DMARD use	0.54 (0.49-0.59)	0.48 (0.44-0.52)
2 non-biologic DMARDs use	0.68 (0.61-0.76)	0.6 (0.54-0.67)
> 2 non-biologic DMARDs use	0.89 (0.73-1.08)	0.8 (0.66-0.97)
Combined comorbidity score	0.98 (0.95-1)	0.97 (0.94-1)

† For the 6 month follow-up period model, the sample size was 45,901 total patients (3,821 biologic initiators) and for the 12 month follow-up period model, the sample size was 34,112 total patients (4,368 biologic initiators).

‡ Drug benefit generosity was classified according to the quartiles of calculated generosity index. This index was calculated as a continuous variable and defined as the proportion of total drug cost paid by the patient out of pocket. The quartiles were

termed as poor drug benefit generosity (highest out of pocket costs, 4th quartile), average drug benefit generosity (3rd quartile), above average drug benefit generosity (2nd quartile) and most generous drug benefit (lowest out of pocket costs, 1st quartile)

* CIRAS: Claims based index of rheumatoid arthritis severity

Appendix Table 4.3 Sensitivity analyses: Multivariate predictors of treatment initiation with biologics in RA patients, Medicare supplemental and commercial enrollees

Variable	OR (95% CI)		
	Combined data	**Medicare Supplemental†**	**Commercial†**
Predisposing			
Patient age	0.98(0.97-0.98)	0.95(0.93-0.97)	0.98(0.97-0.98)
Region			
South region	1	1	1
North Central Region	0.81(0.73-0.90)	0.77(0.58-1.03)	0.82(0.73-0.92)
Northeast Region	0.89(0.76-1.03)	1.20(0.81-1.76)	0.84(0.71-1.00)
West Region	0.92(0.82-1.04)	1.32(0.95-1.83)	0.87(0.77-0.99)
Metropolitan statistical area			
Non-MSA	1	1	1
MSA	1.04(0.94-1.16)	0.81(0.60-1.09)	1.08(0.97-1.22)
Gender			
Female	1	1	1
Male	1.08(0.98-1.19)	0.86(0.66-1.12)	1.12(1.00-1.24)
Enabling			
Capitation			
Non-capitated health plan	1	1	1
Capitated plan	0.81(0.71-0.91)	0.74(0.50-1.10)	0.81(0.70-0.93)
Visit to rheumatologist in the pre-index period			

No visit	1	1	1
At least one visit	1.03(0.94-1.13)	1.13(0.87-1.46)	1.02(0.92-1.13)
Drug benefit generosity‡			
Poor	1	1	1
Average	1.00(0.89-1.13)	0.98(0.67-1.42)	1.00(0.88-1.30)
Better than average	1.15(1.03-1.30)	0.86(0.60-1.24)	1.18(1.04-1.34)
Most generous	1.31(1.17-1.47)	0.97(0.68-1.38)	1.35(1.19-1.52)
Insurance type			
Commercial	1	-	-
Medicare	0.74(0.63-0.87)	-	-
Need			
RA factors			
CIRAS*	1.16(1.12-1.21)	1.13(1.01-1.27)	1.16(1.11-1.20)
Prevalent RA	1	1	1
Incident RA	1.34(1.16-1.56)	1.49(1.04-2.14)	1.29(1.09-1.52)
Medication use in the pre-index period			
No steroid use	1	1	1
Steroid use	1.51(1.38-1.66)	1.36(1.05-1.77)	1.53(1.39-1.59)
No non-biologic DMARD use	1	1	1
1 non-biologic DMARD use	0.64(0.58-0.72)	0.44(0.32-0.60)	0.68(0.61-0.76)
2 non-biologic DMARDs use	0.82(0.72-0.93)	0.70(0.49-1.01)	0.83(0.72-0.95)
> 2 non-biologic DMARDs use	1.13(0.90-1.41)	1.04(0.56-1.92)	1.13(0.88-1.44)
Combined comorbidity score	1.00(0.97-1.04)	1.05(0.98-1.11)	0.99(0.96-1.03)

† For the commercial model, the sample size was 35052 total patients (2,174 biologic initiators) and for the Medicare supplemental model, the sample size was 15,276 total patients (295 biologic initiators)

‡ Drug benefit generosity was classified according to the quartiles of calculated generosity index. This index was calculated as a continuous variable and defined as the proportion of total drug cost paid by the patient out of pocket. The quartiles were termed as poor drug benefit generosity (highest out of pocket costs, 4th quartile), average drug benefit generosity (3rd quartile), above average drug benefit generosity (2nd quartile) and most generous drug benefit (lowest out of pocket costs, 1st quartile).

* CIRAS: Claims based index of rheumatoid arthritis severity

CHAPTER 5

TNF-ALPHA INHIBITOR TREATMENT AND THE RISK OF INCIDENT CARDIOVASCULAR EVENTS IN PATIENTS NEWLY DIAGNOSED WITH RHEUMATOID ARTHRITIS

This chapter presents the second of three manuscripts prepared from this dissertation. In this manuscript, we evaluated the association between TNF-alpha inhibitor treatments and the risk of incident cardiovascular events in patients newly diagnosed with rheumatoid arthritis using health insurance claims from Marketscan databases during the period of 2007 to 2010.

5.1 Overview:

Objective: There is little evidence on the association between use of TNF-α inhibitors (TNF-Is) and the risk of CVD events in patients newly diagnosed with RA. Our study evaluated this association in this previously unstudied population.

Methods: A nested case-control study was designed using data for patients newly diagnosed with RA between Jan 1, 2008 and Dec 31, 2010 identified from the Marketscan claims database. These patients were followed up for the outcome of a composite cardiovascular disease (CVD) event. Patients who experienced the outcome were defined as cases on their event date and 12 age-, sex-, and cohort entry month-matched controls were selected on the same date. Exposure to TNF-I was defined using three unique definition schemes that

accounted for timing and use of other RA treatments. Duration of treatment was defined as a continuous variable representing cumulative days use. Conditional logistic regression (CLR) models were used to derive estimates for incidence rate ratios (IRR).

Results: Of the 15,951 patients of the base cohort, 466 cases of an incident CVD event were identified during follow-up, who were matched with 5,592 controls (12 cases per control) using incidence density sampling. In our multivariate CLR models, which adjusted for baseline factors as well as treatment history with other DMARDs, current use of TNF-I and current use of non-biologic DMARDs were found to be associated with a reduced risk of an incident CVD events compared to no DMARD use (IRR 0.62 95% CI 0.40-0.98 & IRR 0.66 95% CI 0.48-0.89 respectively). Duration of use for both TNF-I and non-biologic DMARDs was found to be associated with a reduced risk of CVD in a linear manner.

Conclusion: Treatment with TNF-Is and non-biologic DMARDs may help in reducing the risk of incident CVD events in patients newly diagnosed with RA compared to no treatment with DMARDs.

5.2 Introduction:

Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammation of the synovium, a membrane that lines the joint capsule and produces lubricating fluid in the joint, leading to disability (1). The association between RA and cardiovascular diseases (CVD) has been the focus of recent attention, primarily because of the increasing recognition of the major role that inflammation plays in the development of atherosclerosis (7, 23, 24). Several epidemiological studies indicate that RA patients have an increased risk of CVD-related morbidity and mortality compared to the general population (4, 5, 41). The

proinflammatory cytokine, TNF-α, may play an important role in the development and acceleration of atherosclerosis in RA patients (25). Therefore, it is plausible to hypothesize that treatment with TNF- α inhibitors (TNF-Is) in RA patients may slow the progression of atherosclerosis and reduce the risk of CVD events.

Several observational studies have evaluated the association between CVD and TNF-Is in established RA patients (49, 52, 53, 55-60), but few focus on incident RA cases (51, 61). This is important because structural damage to joints occur aggressively within first few years of RA diagnosis (8, 9), so it is possible that development of atherosclerosis may also accelerate during the early stages of RA. Two small studies indicate that atherogenic lipid profile and subclinical atherosclerosis are features of early RA (10, 11). The epidemiological evidence of the effect of TNF-Is on CVD events among early RA patients is limited to only two studies, one limited to modest sample size (198 CVD events) (61) and the second mixed treatment exposure with TNF-Is and other biologics, which could bias the results (51).

The primary objective of this study is to examine the effect of TNF-I treatment on incident CVD event among patients newly diagnosed with RA. We extend previous analyses by studying a large sample of patients with a new diagnosis of RA, isolating treatment exposure to only TNF-I biologic treatment, and by using several different definitions of treatment exposure to account for the timing and history of treatment with disease modifying anti-rheumatic agents (DMARDs). The results from this study should help better understand the potential benefits of TNF-I medication use on cardiovascular risk in patients with RA.

5.3 Methods:

Data source:

Data from the Truven's MarketScan Commercial Claims And Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (COB) was used for this study. This database contains de-identified, person-specific health data including clinical utilization, expenditures, insurance enrollment/plan benefit, inpatient, outpatient, and outpatient prescription information. The CCAE contains healthcare data for nearly 40 million individuals, encompassing employees, their spouses, and their dependents. The COB data contains the health care experiences of 3.8 million Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. These data have been used widely in health services research due to its substantial size, longitudinal integrity, and unique data links (12). For this particular analysis, data from inpatient services file, outpatient services file, outpatient drug claims file and enrollment file were merged using unique patient identifiers.

Study design and patient population:

The nested case-control study design was selected to evaluate the association between TNF-Is and CVD because of its ability to efficiently deal with time varying nature of exposures without substantial loss in power (104). Many researchers in the past have preferred this study design while evaluating treatment-outcome associations in RA patients (49, 52, 56, 124). From the Marketscan data files, a base cohort of RA patients 18 years and older who had at least 2 outpatient or 1 inpatient diagnosis of RA (ICD-9 code: 714.0) and at least one prescription record for a DMARD between Jan 1, 2008 and Dec 31, 2010 was identified. The earliest of these diagnoses was defined as the index diagnosis and the 12

month period pre-index was defined as the baseline period (Figure 5.1). To be considered for our case-control sampling, patients in the base cohort had to meet the following inclusion criteria during the 12-month baseline period: 1) continuous enrollment in their health plans, 2) no diagnosis of RA in the baseline period, 3) No use of biologic agents, 4) no history of tuberculosis (contraindication to biologics use) or psoriatic arthritis or Crohn's disease (inflammatory conditions for which biologic treatment is indicated), and 5) not diagnosed with the outcome of interest in the baseline period. Thus our sample consisted of patients with an incident diagnosis of RA who had no history of biologic use but were eligible to receive biologics in the future and at risk for an incident CVD event.

Nested case-control sampling:

All of the patients identified as eligible for sampling from the base cohort were followed from their index date to the earliest occurrence of the following events: the outcome (CVD diagnosis), disenrollment from their health plan, switch between biologic treatments, or the study end date (Dec 31, 2010). If patients experienced a CVD event, they were defined as "cases" and the date of CVD diagnosis was defined as the event date. Once the cases were identified, twelve age, sex and cohort entry month-matched controls were sampled using an incident density sampling procedure from the remaining patients of the base cohort at the event date who were free from CVD at that time (Figure 5.1) (77). Because the index diagnosis of RA was the starting point for follow-up of all patients in the base cohort, our sampling strategy also ensured the matching of cases and controls on the duration of RA.

Exposure definition schemes:

While evaluating treatment-outcome association in RA, a precise exposure definition, one that accounts for both timing and history of the treatment, is vital because patients are known to start, stop and switch treatments often. There are several approaches used for exposure measurement by studies conducted in the past to evaluate the association between CVD and TNF-Is. One previously used approach (51, 55) is to define the use of TNF-Is or biologic DMARDs as ever-treated vs never-treated, meaning once a patient begins therapy with TNF-Is he or she is considered to be treated for the entire follow-up period. Another approach used by several studies (49, 54, 56) is to classify the use of TNF-Is as 'current use' vs 'no current use' based on the use of medications within a certain time period prior to the event. In addition to using the two commonly used approaches, we developed a unique third approach that accounted for both the timing and the history of the treatment to measure antirheumatic medication use in RA patients. We evaluated the impact of three exposure definitions described below on the observed estimates:

1) **Scheme 1 (Ever/Never):** First, we considered a dichotomous definition of exposure: ever-treated with a TNF-I (Monotherapy or in combination with non-biologic DMARDs) vs never-treated with a TNF-I prior to the event date. This over-simplified definition of exposure into a binary variable leads to non-differential misclassification of exposure by ignoring the timing of exposure and use of other treatments during that time. Although, some authors argue that such non-differential misclassification of the exposure would produce a bias towards the null and hence provide a conservative estimate of the treatment-outcome association (47), there is also evidence in the literature suggesting that this may not be true under all circumstances (64).

2) **Scheme 2 (Current use indicators for TNF-Is and other RA treatments):** To take into account the timing of TNF-I use and also the use of other DMARDs, we defined exposure into the following mutually exclusive categories: 1) current use of TNF-Is (monotherapy or in combination with non-biologic DMARDs), 2) current use of other biologics (monotherapy or in combination with non-biologic DMARDs), 3) current use of only non-biologic DMARDs, 4) no current DMARD use. Drug use in the time period of 6-months prior to the event date was defined as 'current use'. Compared to Scheme 1, this approach addresses some of the misclassification by considering the timing of the exposure, which may be closely associated with the outcome.
3) **Scheme 3 (Current and past use indicators for TNF-I and other RA treatments):** In addition to the timing of TNF-I use and other DMARDs use, to account for the entire DMARD exposure history, we defined exposure into the following mutually exclusive categories hierarchically: 1) no DMARD use, 2) past use of only non-biologic DMARDs, 3) current use of only non-biologic DMARDs, 4) past use of TNF-Is (monotherapy or in combination with non-biologic DMARDs), 5) current use of TNF-Is (monotherapy or in combination with non-biologic DMARDs), 6) past use of other biologics (monotherapy or in combination with non-biologic DMARDs), and 7) current use of other biologics (monotherapy or in combination with non-biologic DMARDs). Drug use in the time period of 6-months prior to the event date was defined as 'current use' and any use before the time period of 6-months prior to the event date was defined as 'past use'. This definition is advantageous compared to Scheme 2 because if a patient has used the treatment in the past before discontinuing it and the reason for discontinuation is associated with the outcome, that patient

would not be classified as drug users and would be misclassified into the reference group (no current DMARD use) in Scheme 2, which ignores treatment history. So, we are likely to miss out on this important finding in Scheme 2. However, in Scheme 3, such patients would be classified into separate groups based on their past use of DMARDs and the reference group would only be comprised of patients not exposed to any DMARDs during the study period.

TNF-Is included the following agents: adalimumab, certolizumab, etanercept, golimumab and infliximab. Abatacept, anakinara, rituximab and tocilizumab were considered as 'other biologics'. Methotrexate, hydroxychloroquine, auranofin, injectable gold, penicillamine, minocycline, sulfasalazine, azathioprine, leflunamide, cyclophosphamide and cyclosporine were defined as 'non-biologic DMARDs'. The use of these agents was identified using both the NDC codes from outpatient pharmacy files for filled prescriptions and J codes using outpatient services files for injectable/infusion agents administered at physician's office.

Measurement of duration of treatment:

Duration of treatment with TNF-I was defined as a continuous variable representing the cumulative days of TNF-I use for the patients who filled at least one TNF-I prescription in the exposure measurement period. Similarly, duration of treatment with non-biologic DMARDs and other biologics were also measured as continuous variables. Significance of a quadratic term was tested for the continuous variables representing cumulative use for each treatment to check for any evidence of non-linearity in the dose response relationship between the duration and the risk of an incident CVD event (125).

Outcome measurement:

The outcome of interest was defined as a composite measure consisting of acute myocardial infarction (ICD-9 code 410), unstable angina (ICD-9 code 411), angina pectoris (ICD-9 code 413), chronic heart failure (ICD-9 codes 428.xx, 398.91, 402.01, 402.11, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93), other forms of chronic heart diseases (ICD-9 code 414), ischemic stroke (ICD-9 code s 433.x1, 434 [excluding 434.x0], or 436); and transient ischemic stroke (ICD-9 code 435).

Covariates:

In addition to matching with age and gender, we identified the following covariates during the baseline period and added them to our multivariate model for risk adjustment: CVD risk factors including hypertension, hyperlipidemia, and diabetes mellitus; CVD drug use including lipid lowering agents, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and other CVD drugs; RA drug use including steroids, non-steroidal anti-inflammatory drugs and non-biologic DMARDs; and other comorbidities including chronic obstructive pulmonary disease and cancer.

Statistical Analyses:

Descriptive statistics were used to summarize the patient characteristics for our cases and controls. Categorical variables were presented as numbers and percentages and continuous variables were presented as means (±standard deviations). The influence of the exposure definition on the absolute scale was assessed by calculating the estimates for the absolute risk of an incident CVD event during the 3 year follow-up period for all the three schemes using methods proposed by Langholz & Borgan (108). The influence of the

exposure definition on the relative scale was assessed by comparing incident rate ratios (IRRs) for the three schemes. The IRRs were estimated by odds ratios calculated from conditional logistic regression (CLR) models. Results from both crude and adjusted models were presented for the three schemes. Additionally, crude and adjusted estimates for the association between the duration of TNF-I use and incident CVD events were also estimated from CLR. All analyses were conducted using SAS version 9.2 (SAS institute, Cary, NC).

Sensitivity analyses:

Multiple sensitivity analyses were conducted to evaluate the robustness of the findings. First, we varied the definition of current use to 3 months and 12 months from the 6 months definition used in the original analysis. Second, we repeated the entire analysis in a subgroup of the patients who were not exposed to any non-biologic DMARDs in the pre-index period. Next, for the duration of treatments we considered the cumulative use only in those patients who used TNF-I continuously, without interruption in the treatment for more than three months. Finally, we created separate categories for the use of TNF-I as monotherapy or combination therapy with non-biologic DMARDs.

5.4 Results:

The base-cohort consisted of 15,951 patients who were incident RA cases, had no history of biologic use, were eligible to receive biologics in the future and were at risk for an incident CVD event. Figure 5.2 shows the sample derivation flow chart along with the exclusion criteria. Of the 15,951 patients of the base cohort, 466 cases of an incident CVD event were identified during follow-up. These cases were age, sex, and cohort entry month-matched with 5,592 controls (12 cases per control) using incidence density sampling. Table

5.1 compares the case and control patients' baseline characteristics. CVD cases and their matched controls were 61 years old at the index date and 79% of the cases and controls were females. The mean follow-up time was 246 days for the cases and controls. Cases had higher prevalence of CVD risk factors (hyperlipidemia, hypertension and diabetes mellitus), other comorbid conditions (COPD and cancer) and used CV medications more often in the pre-index period compared to controls.

Table 5.2 shows patient disposition into categorical exposure groups based on the exposure definition scheme used. Scheme 1, which considered a binary exposure definition, classified 586 patients into 'ever use of TNF-I' and 5,427 patients into 'never use of TNF-I' category. Scheme 2, which considered current use of TNF-Is and other DMARDs, reclassified patients from the 'never use of TNF-I' category of scheme 1 into three separate categories (current use of non-biologic DMARDs (n=4,181), current use of other biologics (n=71), or no current DMARD use (n=1,249)) based on their current use of other DMARDs. Scheme 3, that considered current use as well as past use of all the DMARDs, reclassified patients from the 'no current DMARD use' category of scheme 2 into 4 separate categories (past use of TNF-I (n=29), past use of non-biologic DMARDs (n=351), past use of other biologics (n=15), and no use of any DMARD (n=854) based on patients' history of DMARD use.

Table 5.3 shows the estimates for absolute risk of an incident CVD event by exposure classification schemes. Finer exposure definitions (schemes 2 & 3) that classified users based on the use and timing of each class of DMARD use led to a decrease in exposure misclassification and hence more accurate absolute risk estimates compared to the broad exposure definition (scheme 1) that lumped the users of all the non-TNF-I biologics and non-

DMARD users into a single category (never use of TNF-I). The estimates for the category of TNF-I use were found to be similar across all the 3 definitions.

Table 5.3 shows results from our multivariate analysis.. In scheme 1, we observed no statistically significant difference in the risk of incident CVD event between 'ever use of TNF-I' and 'never use of TNF-I' (IRR 0.86, 95% CI 0.60-1.21). Similarly, in scheme 2, the risk of an incident CVD event after 'current use of TNF-I' was found to be no different than 'no current DMARD use' (IRR 0.74 95% CI 0.49-1.10). However, compared to 'no current DMARD use', 'current use of a non-biologic DMARD' was found to be associated with a decreased risk (IRR 0.76 95% CI 0.59-0.97) and 'current use of other biologics' was found to be associated with an increased risk (IRR 2.22 95% CI 1.14-4.33) of an incident CVD event. In scheme 3, 'current use of TNF-I' and 'current use of non-biologic DMARDs' were found to be associated with a reduced risk of an incident CVD events compared to 'no DMARD use' (IRR 0.62 95% CI 0.40-0.98 & IRR 0.66 95% CI 0.48-0.89 respectively). No other drug groups were found to have a significantly different risk of an incident CVD event compared to 'no DMARD use'.

We also observed significant association between duration of treatment and incident CVD events (Table 5.4). Each additional month of TNF-I use was found to reduce the risk of an incident CVD event by 5% (IRR 0.95, 95% CI 0.90-1.00, p=0.048). Each additional month of non-biologic DMARD use was found to reduce the risk by 3% (IRR 0.97 95% CI 0.94-1.00, p=0.041). The cumulative use of other biologics was not found to be significantly associated with CVD events. The quadratic terms for all the treatments were not statistically significant (p>0.05), indicating that the duration of use was associated with the risk of incident CVD events in a linear fashion.

Estimates from our sensitivity analyses, in which we evaluated the impact of 'current use' definition, duration of treatment definition, excluding prevalent users of non-biologic DMARDs, and type of TNF-I therapy on our original results, were found to be consistent with the primary model (Appendix Tables 5.1 and 5.2). While estimates for some exposure categories were no longer statistically significant potentially due to loss of power with smaller sample size in those categories, the estimates trended in the direction of the original results.

5.5 Discussion:

In this observational study of incident RA patients, we observed that the risk of incident CVD event was significantly reduced by current treatment with TNF-Is and non-biologic DMARDs compared to no treatment with any DMARD. Further, we observed that this protective effect was found to be associated with the duration of TNF-I and non-biologic DMARD use in a linear manner.

This is the largest study to our knowledge evaluating the association between TNF-I use and risk of incident CVD event in patients newly diagnosed with RA. Our findings suggest that beginning treatment with TNF-Is or non-biologic DMARDs early in the course of RA may represent a potential strategy to reduce the risk of an incident CVD event. Our findings are supported by results from several previous studies conducted in a similar population (new RA patients) (10, 11, 51). Georgiadis et al. (10) demonstrated that treatment with methotrexate in early RA patients resulted in a statistically significant increase in the levels of high density lipoprotein-C (HDL-C or 'good cholesterol'), which is a marker of improvement in atherogenic profile. Another study showed a significant decrease in the common carotid artery intima-media thickness, which is an early indicator for

atherosclerosis, after treatment with methotrexate in early RA patients (11). Hochberg et al. (51) reported a statistically significant risk reduction in the risk of a composite CVD endpoint after treatment with methotrexate, but not with biologics in incident RA patients. Our study differs from theirs in that we separated the biologics into TNF-Is and other biologics while evaluating their association with CVD, which they did not. However, Ljung et al. (61) did not observe any statistically significant risk reduction in acute coronary syndrome (ACS) after TNF-I treatment in early RA patients. One reason for the difference between our results and results from Ljung et al. may be the lack of power in their study due to smaller sample size (198 ACS events).

Our findings also highlight the importance of a precise and time specific definition of exposure. As observed in our exposure definition schemes 1 (Ever/Never TNF-I use) & 2 (Current use indicators for TNF-Is and other RA treatments), broad definitions lead to non-differential misclassification of exposure and result in a reference group consisting of a heterogeneous mix of patients (Table 5.2). When relying on relative measures of associations, such misclassification may lead to masking of important differences in treatment-outcome associations (Table 5.3). In our case, scheme 1 lumped the users of all non-TNF DMARDs along with non-users of DMARDs into the reference category 'Never use of TNF-Is'. In scheme 2, users of other DMARDs were separated but past users of these DMARDs got classified into the reference category 'No current DMARD use'. This misclassification may lead to an inappropriate conclusion that TNF-I use has no impact on incident CVD events. In reality, as reflected in scheme 3, the appropriate inference would be that compared to 'No DMARD use', current use of TNF-Is may have a potential protective effect against incident CVD events in patients newly diagnosed with RA. However, since

non-biologic DMARDs also have a similar protective effect and schemes 1 and 2 fail to account for the treatment history with these agents, this important finding is masked in these two definition schemes. Although several authors have highlighted this problem in the past using examples of different drug classes,(65, 126) unfortunately this remains a largely ignored issue in pharmacoepidemiology studies.

Our study has some important limitations. As with any other study using administrative claims, we were not able to validate the diagnoses of the disease condition (RA) as well as the outcome. However, to address this limitation we used algorithms that have been validated for their use in identifying these conditions in electronic databases (97, 127, 128) Further, the administrative claims contain very limited information on clinical status of RA patients, such as disease activity and swollen joint count. Therefore, we were not able to capture and control for the exact severity of RA in our cohort of patients. However, our sampling technique matched cases and controls on the duration of RA, which is used as an approximation for severity of RA. Additionally, since the claims data do not have reliable information on patient vital status, our study is limited by the competing risk of death. Certain exposure categories in our scheme 3 had small numbers of patients, which may lead to limited power to detect differences between the groups. Finally, our database did not contain information on important variables such as tobacco use, which is a risk factor for both RA and CVD. We were also not able to capture the over-the-counter use of certain pain relievers, which are commonly used by RA patients. Therefore, there may be some residual confounding in our exposure-outcome association even after multivariate risk adjustment. We postulate that the widespread problem of channeling bias affecting observational studies may explain the higher trend for increased CVD risk in users of other biologics because

patients with a higher baseline cardiovascular risk may be preferentially treated with non TNF-α inhibitor biologic agents. We caution the readers to interpret our findings in light of these limitations.

5.6 Conclusion:

We observed that treatment with TNF-Is and non-biologic DMARDs may help in reducing the risk of incident CVD events in patients newly diagnosed with RA compared to no treatment with DMARDs. Early treatment with a non-biologic DMARD or a TNF-I agent may represent a beneficial strategy for clinicians trying to manage the increased CVD risk in RA. Accurate measurement of exposure is important while evaluating treatment outcome association in RA to avoid inappropriate conclusions owing to non-differential misclassification of the exposure.

Figure 5.1: **Timeline of the study**

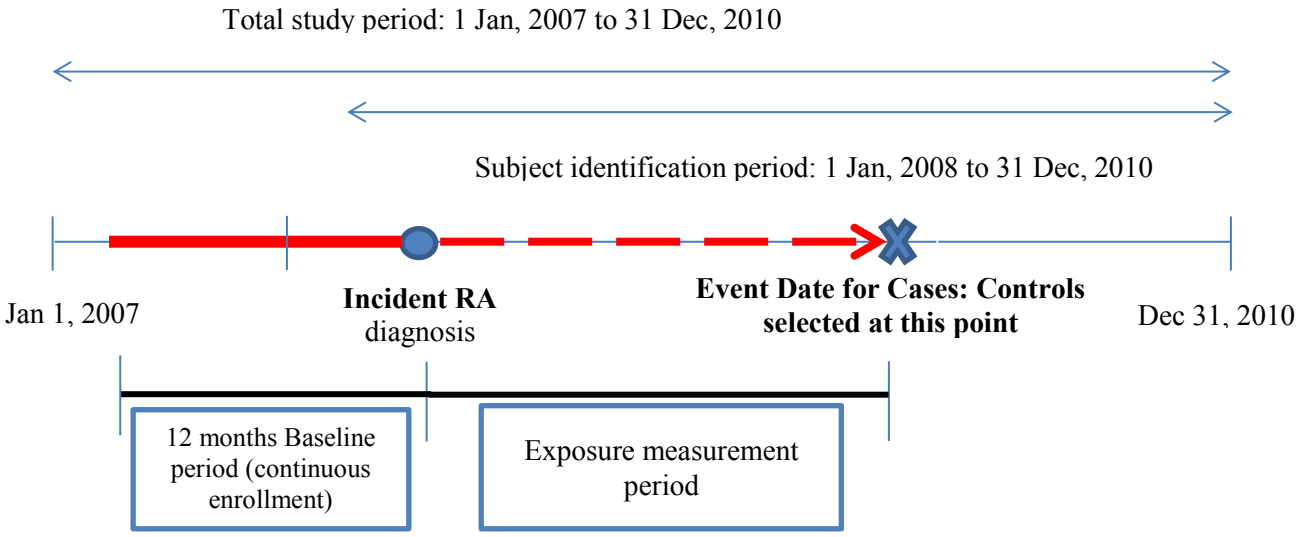


Figure 5.2: **Sample derivation flow chart**

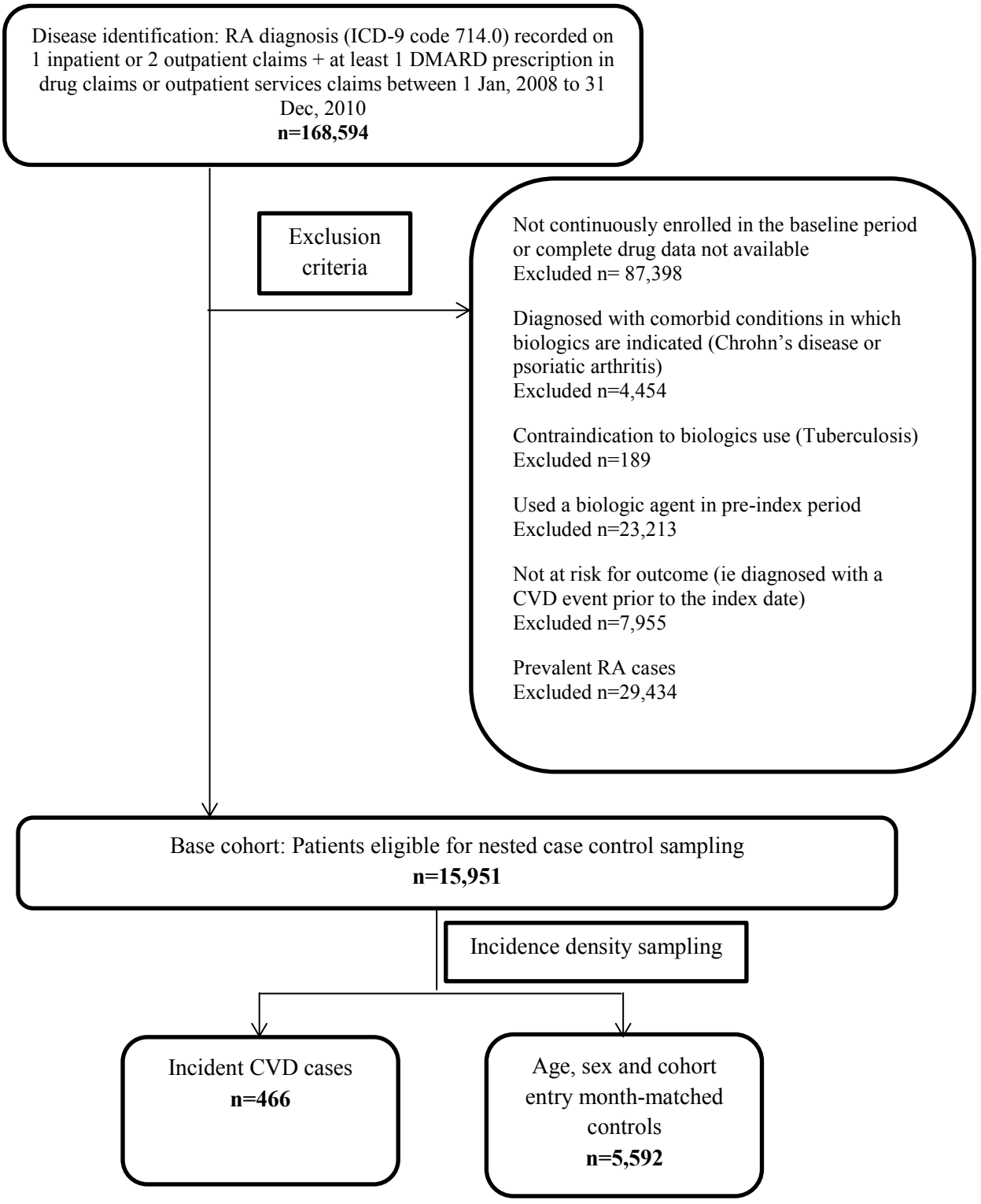


Table 5.1: **Baseline comparison of cases of incident cardiovascular diseases and controls sampled from a cohort of incident RA patients**

Variable	Cases[†] (n=466)		Controls (n=5,592)	
	n	%	n	%
Matching variables				
Patient age (Mean±SD)	61.21 ± 10.49		61.13 ± 10.46	
Mean duration of RA, days (Mean±SD)	249.61 ± 211.23		249.61 ± 211.02	
Female gender	368	78.97	4416	78.97
Cardiovascular risk factors				
Diabetes Mellitus	125	26.82	794	14.20
Hyperlipidemia	163	34.98	1674	29.94
Hypertension	264	56.65	2254	40.31
Other comorbid conditions				
Chronic obstructive pulmonary disease (COPD)	103	22.1	790	14.13
Cancer	36	7.73	340	6.08
RA medications in the pre-index period				
Coxib	51	10.94	590	10.55
NSAIDs	214	45.92	2507	44.83
Steroids	302	64.81	3128	55.94
Non-biologic DMARDs[‡]	204	43.78	2246	40.16
CV medications in the pre-index period				
ACE-Inhibitors	112	24.03	1047	18.72
Beta-blockers	144	30.9	1080	19.31
Lipid lowering agents	216	46.35	1797	32.14

Calcium channel blockers	121	25.97	892	15.95
Other CV drugs*	150	32.19	1166	20.85

† 466 cases included 23 patients with acute myocardial infarction (ICD-9 code 410), 16 patients with unstable angina (ICD-9 code 411), 43 patients with angina pectoris (ICD-9 code 413), 98 patients with chronic heart failure (ICD-9 codes 428.xx, 398.91, 402.01, 402.11, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93), 156 patients with other forms of chronic heart diseases (ICD-9 code 414), 98 patients with cerebrovascular accident (ischemic stroke, ICD-9 codes 433.x1, 434 [excluding 434.x0], or 436, and transient ischemic stroke, ICD-9 code 435), and 32 patients with multiple diagnoses from this list.

‡ Non-biologic DMARDs include methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, minocycline, cyclophosphamide and cyclosporine

*Other CV drugs include cardiac glycosides, antiarrhythmic agents, hypotensive agents, vasodilating agents and phosphodiesterase inhibitors

Table 5.2: **Patient disposition into categorical exposure groups based on the exposure definition scheme used**

Exposure definition Scheme	**Number of patients classified in exposure categories**[†]						
Scheme 1	Ever use of TNF-I[‡]	Never use of TNF-I					
	N=586	**N=5,427**					
Scheme 2	Current use of TNF-I[‡]	Current use of non-biologic DMARDs[‡]	Current use of other biologics[‡]	No current DMARD use			
	N=557	**N=4,181**	**N=71**	**N=1,249**			
Scheme 3	Current use of TNF-I[‡]	Current use of non-biologic DMARDs[‡]	Current use of other biologics[‡]	Past use of TNF-I	Past use of non-biologic DMARDs	Past use of other biologics	No use of any DMARD
	N=557	**N=4,181**	**N=71**	**N=29**	**N=351**	**N=15**	**N=854**

†Total number of patients in the cohort=6,058

‡TNF-inhibitors include infliximab, etanercept, adalimumab, certolizumab and golimumab. Non-biologic DMARDs include methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, minocycline, cyclophosphamide and cyclosporine. Other biologic agents include abatacept, anakinara, rituximab and tocilizumab.

Table 5.3: **Absolute CVD risk & relative measures of association of an incident CVD event by exposure status**

Exposure[†]	n (cases)	n (controls)	Absolute CVD risk estimates for 3 year period (95% CI)	Unadjusted IRR (95% CI)	Adjusted[‡] IRR (95% CI)
Scheme 1					
TNF-use never	426	5046	0.012 (0.011-0.014)	Ref.	Ref.
TNF-use ever	40	546	0.010 (0.0071-0.014)	0.86 (0.61-1.22)	0.86 (0.60-1.21)
Scheme 2					
No current DMARD	111	1138	0.014 (0.011-0.017)	Ref.	Ref.
Current TNF-I	39	518	0.011 (0.0072-0.014)	0.75 (0.51-1.11)	0.74 (0.49-1.10)
Current non-biologic DMARD	302	3879	0.011 (0.0095-0.013)	0.78 (0.61-0.99)	0.76 (0.59-0.97)
Current other biologic	14	57	0.033 (0.014-0.051)	2.48 (1.33-4.65)	2.22 (1.14-4.33)
Scheme 3					
No DMARD use	79	775	0.015 (0.011-0.020)	Ref.	Ref.

Current TNF-I	39	518	0.011 (0.0072-0.014)	0.68 (0.44-1.05)	0.62 (0.4-0.98)
Current non-biologic DMARD	302	3879	0.011 (0.0096-0.013)	0.71 (0.53-0.96)	0.66 (0.48-0.89)
Current other biologic	14	57	0.034 (0.015-0.052)	2.28 (1.19-4.39)	1.93 (0.96-3.87)
Past TNF-I	1	28	0.0051 (0-0.015)	0.32 (0.04-2.43)	0.24 (0.03-1.85)
Past non-biologic DMARD	28	323	0.012 (0.0074-0.017)	0.78 (0.47-1.28)	0.68 (0.4-1.13)
Past other biologic	3	12	0.035 (0-0.076)	2.31 (0.63-8.44)	2.32 (0.61-8.84)

† TNF-inhibitors include infliximab, etanercept, adalimumab, certolizumab and golimumab. Non-biologic DMARDs include methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, minocycline, cyclophosphamide and cyclosporine. Other biologic agents include abatacept, anakinara, rituximab and tocilizumab.

‡Adjusted for pre-index NSAID use, steroid use, non-biologic DMARD use, cardiovascular medication use, Diabetes, Hypertension, Hyperlipidemia, chronic obstructive pulmonary disease and cancer in addition to matching with age, gender, duration of RA and cohort entry month and year. Unadjusted associations are estimated in age, gender, duration of RA and cohort entry month and year matched sample

Table 5.4: **Association between duration of RA treatments and incident CVD event**

Exposure[†]	Adjusted[‡] IRR (95% CI)	p-values
Each additional month of cumulative TNF-I use	0.95 (0.90-1.00)	0.048
Each additional month of cumulative non-biologic DMARD use	0.97 (0.94-1.00)	0.041
Each additional month of cumulative other biologics use	1.06 (0.99-1.13)	0.12

†TNF-inhibitors include infliximab, etanercept, adalimumab, certolizumab and golimumab. non-biologic DMARDs include methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, minocycline, cyclophosphamide and cyclosporine, & Other biologic agents include abatacept, anakinara, rituximab and tocilizumab

‡Adjusted for pre-index NSAID use, steroid use, non-biologic DMARD use, cardiovascular medication use, Diabetes, Hypertension, Hyperlipidemia, chronic obstructive pulmonary disease and cancer in addition to matching with age, gender, duration of RA and cohort entry month and year. Unadjusted associations are estimated in age, gender, duration of RA and cohort entry month and year matched sample

Appendix Table 5.1: **Sensitivity analyses set 1**

Exposure[†]	Original results Adjusted[‡] IRR (95% CI)	Sensitivity analysis 1* Adjusted[‡] IRR (95% CI)	Sensitivity analysis 2** Adjusted[‡] IRR (95% CI)	Sensitivity analysis 3[§] Adjusted[‡] IRR (95% CI)	Sensitivity analysis 4[¶] Adjusted[‡] IRR (95% CI)
Scheme 1					
TNF-I use never	1.0	-	-	1.0	-
TNF-I use ever	0.86 (0.60-1.21)			0.80 (0.50-1.26)	
Scheme 2					
No current DMARD	1.0	1.0	1.0	1.0	-
Current TNF-I	0.74 (0.49-1.1)	0.65 (0.43-0.97)	0.66 (0.43-1.01)	0.69 (0.41-1.17)	
Current nbDMARD	0.76 (0.59-0.97)	0.70 (0.56-0.87)	0.69 (0.52-0.92)	0.74 (0.53-1.02)	
Current other biologic	2.22 (1.14-4.33)	2.23 (1.08-4.59)	2.14 (1.14- 4.02)	1.86 (0.79-4.37)	
Scheme 3					
No DMARD use ever	1.0	1.0	1.0	1.0	-
Current TNF-I	0.62 (0.40-0.98)	0.61 (0.38-0.98)	0.62 (0.39-0.98)	0.57 (0.31-1.03)	
Current nbDMARD	0.66 (0.48-0.89)	0.67 (0.49-0.90)	0.66 (0.49-0.90)	0.62 (0.42-0.93)	

Current other biologic	1.93 (0.96-3.87)	2.14 (1.01-4.54)	2.04 (1.07-3.87)	1.56 (0.64-3.81)	
Past TNF-I	0.24 (0.03-1.85)	0.78 (0.33-1.83)	0.81 (0.09-6.83)	0.27 (0.0-2.25)	
Past nbDMARD	0.68 (0.40-1.13)	0.88 (0.58-1.32)	0.68 (0.31-1.52)	0.67 (0.35-1.26)	
Past other biologic	2.32 (0.61-8.84)	3.08 (1.11-8.56)	3.06 (0.32-29.46)	2.50 (0.44-14.09)	
Duration of TNF-I use					
Each additional month of TNF-I use	0.95 (0.9-1.00)	-	-		0.96 (0.91-1.01)

† TNF-inhibitors include infliximab, etanercept, adalimumab, certolizumab and golimumab. Non-biologic (nb) DMARDs include methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, minocycline, cyclophosphamide and cyclosporine. Other biologic agents include abatacept, anakinara, rituximab and tocilizumab.

‡Adjusted for pre-index NSAID use, steroid use, non-biologic DMARD use, cardiovascular medication use, Diabetes, Hypertension, Hyperlipidemia, chronic obstructive pulmonary disease and cancer in addition to matching with age, gender, duration of RA and cohort entry month and year. Unadjusted associations are estimated in age, gender, duration of RA and cohort entry month and year matched sample

*Sensitivity analysis 1: Current use defined as any use in past 3 months

** Sensitivity analysis 2: Current use defined as any use in past 12 months

§ Sensitivity analysis 3: Excluded all the patients who used a non-biologic DMARD in the pre-index period

¶ Sensitivity analysis 4: Cumulative use considered only in patients who use biologic agents without any interruption of >3 months since starting the therapy

Appendix Table 5.2: Sensitivity analysis set 2, TNF-I monotherapy and combination therapy considered separately

Exposure[†]	Adjusted[‡] IRR (95% CI)
Definition 1	
TNF-I use never	-
TNF-I use ever	
Definition 2	
No current DMARD	1.0
Current TNF-I Monotherapy	0.88 (0.47-1.63)
Current TNF-I combination therapy*	0.68 (0.43-1.09)
Current non-biologic DMARD	0.76 (0.59-0.97)
Current other biologic	2.23 (1.14-4.34)
Definition 3	
No DMARD use ever	1.0
Current TNF-I monotherapy	0.76 (0.40-1.45)
Current TNF-I combination therapy	0.57 (0.34-0.95)
Current non-biologic DMARD	0.65 (0.48-0.89)
Current other biologic	1.93 (0.97-3.88)
Past TNF-I monotherapy**	-
Past TNF-I combination therapy	0.41 (0.05-3.27)
Past non-biologic DMARD	0.67 (0.40-1.13)
Past other biologic	2.35 (0.62-8.96)
Duration of TNF-I treatment	
Each additional month of TNF-I monotherapy	0.91 (0.80-1.04)
Each additional month of TNF-I combination	0.96 (0.90-1.01)

† TNF-inhibitors include infliximab, etanercept, adalimumab, certolizumab and golimumab. Non-biologic DMARDs include methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, minocycline, cyclophosphamide and cyclosporine. Other biologic agents include abatacept, anakinara, rituximab and tocilizumab.

‡Adjusted for pre-index NSAID use, steroid use, non-biologic DMARD use, cardiovascular medication use, Diabetes, Hypertension, Hyperlipidemia, chronic obstructive pulmonary disease and cancer in addition to matching with age, gender,

duration of RA and cohort entry month and year. Unadjusted associations are estimated in age, gender, duration of RA and cohort entry month and year matched sample

* Patients who begin TNF-inhibitor therapy within 30 days of beginning any non-biologic DMARD therapy or whose prescription at hand for these two classes overlap for more than 30 days were defined as using TNF-inhibitor combination therapy.

**Unable to provide estimates because none of the cases were classified as 'Past TNF-I monotherapy' users.

CHAPTER 6

ASSESSMENT OF INDEPENDENT EFFECT OF INFLIXIMAB, ETANERCEPT AND ADALIMUMAB ON THE RISK OF INCIDENT CARDIOVASCULAR EVENTS IN PATIENTS NEWLY DIAGNOSED WITH RHEUMATOID ARTHRITIS

This chapter presents the last of three manuscripts prepared from this dissertation. In this manuscript, we evaluated the association between individual TNF-alpha inhibitor treatments, infliximab, adalimumab and etanercpet, and the risk of incident cardiovascular events in patients newly diagnosed with rheumatoid arthritis using health insurance claims from Marketscan databases during the period of 2007 to 2010.

6.1 Overview:

Objective: No study in the past has evaluated the independent effects of individual TNF-α inhibitors (TNF-Is), etanercept, adalimumab and infliximab, and the risk of CVD events in patients newly diagnosed with RA. The objective of our study was to provide estimates of this association.

Methods: A nested case-control study was designed using data for patients newly diagnosed with RA between Jan 1, 2008 and Dec 31, 2010 identified from the Marketscan claims

database. These patients were followed up for the outcome of a composite cardiovascular disease (CVD) event. Patients who experienced the outcome were defined as cases on their event date and 12 age-, sex-, and cohort entry month-matched controls were selected on the same date. Following mutually exclusive exposure categories were created based on at least one filled prescription of these agents during the study period: 1) Infliximab, 2) Etanercept, 3) Adalimumab, 4) Newer TNF-Is (golimumab and certolizumab) 5) Non-biologic DMARDs, 6) Other biologic agents and 7) No use of DMARD during the study period. Conditional logistic regression (CLR) models were used to derive estimates for incidence rate ratios (IRR).

Results: Of the 15,951 patients of the base cohort, 466 cases of an incident CVD event were identified during follow-up, who were matched with 5,592 controls (12 cases per control) using incidence density sampling. In our multivariate CLR models, treatment with adalimumab (adjusted IRR 0.40, 95% CI 0.18-0.87) and non-biologic DMARDs (adjusted IRR 0.66, 95% CI 0.48-0.89) was found to be associated with a reduced risk of incident CVD events compared to no treatment with DMARDs. No differences were found between individual TNF-Is.

Conclusion: Treatment with adalimumab and non-biologic DMARDs may help in reducing the risk of incident CVD events in patients newly diagnosed with RA compared to no treatment with DMARDs

6.2 Introduction:

The association between rheumatoid arthritis (RA) and cardiovascular diseases (CVD) has been the recent focus of research because of the increasing recognition of atherosclerosis

as an inflammatory condition (7, 23, 24). The chronic systematic inflammatory process in RA may initiate or accelerate atherosclerosis (129). Several epidemiological studies have provided data that indicate an increased burden of CVD in RA patients compared to the general population (4, 5, 41). The disease modifying antirheumatic drugs (DMARDs) control inflammation in RA and therefore may help in reducing CV burden. Because of the role tumor necrosis factor (TNF)- α plays in the cascade of atherosclerotic events (25), TNF- α inhibitors (TNF-Is) are of special interest as the agents most likely to reduce CVD events in RA patients.

TNF- Is are a heterogeneous class of drugs. First TNF-I agent, infliximab, was approved for treating adults with RA in 1998; 4 additional agents have been approved since that time: etanercept (1998), adalimumab (2002), certolizumab pegol (2008), and golimumab (2009).These agents differ from each other in terms of their molecular structure, route of administration and pharmacokinetic parameters (20, 66). No randomized controlled trials (RCTs) have compared these agents head-to-head for their efficacy in RA. However, recent evidence from a mixed treatment comparison using data from RCTs suggests differences between these agents on efficacy endpoints in RA patients (130). The odds of achieving ACR50 response (American College of Rheumatology response criteria for 50% improvement in joint function) were found to be higher with etanercept compared to both infliximab and adalimumab (etanercept vs infliximab OR: 4.17, 95% Credible Interval (CrI) 2.00-11.17, etanercept vs adalimumab OR: 3.50, 95% CrI 1.37-7.63) (130). Individual TNF-Is also differ with respect to their effectiveness in treating other rheumatologic diseases. Unlike adalimumab and infliximab, etanercept lacks efficacy in treating other auto-immune diseases, such as Crohn's disease, Wegener's granulomatosis and sarcoidosis (69, 70).

Differences in the safety profiles of individual TNF-Is have also been reported. Infliximab, but not etanercept, is found to be associated with an increased risk of infections such as mycobacterium tuberculosis and histoplamosis (71). Evidence from indirect comparisons using withdrawals due to adverse events reported in randomized controlled trials as an outcome suggest that etanercept has a more favorable tolerability profile compared to infliximab and adalimumab in RA patients (etanercept versus infliximab OR:0.30, 95% CrI 0.16-0.62, etanercept versus adalimumab OR: 0.50, 95% CrI 0.25-0.91) (72).

Several observational studies have evaluated the association between CVD and TNF-Is in RA patients (49, 52, 53, 55-60), but no study has evaluated independent effects of individual TNF-I agents. Because these agents differ with respect to their pharmacological properties, effectiveness profiles in various rheumatologic diseases and tolerability, we believe that it is not appropriate to assume a class effect in terms of these agents' effect on the risk of CVD events in RA patients. Therefore, we designed this study to examine the effects of non-biologic and biologic DMARDs on the risk of CVD with a special focus on individual TNF-Is, infliximab, adalimumab and etanercept, in patients newly diagnosed with RA.

6.3 Methods:

Data source:

Data from the Truven's MarketScan Commercial Claims And Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (COB) was used for this study. This database contains de-identified, person-specific health data including clinical utilization,

expenditures, insurance enrollment/plan benefit, inpatient, outpatient, and outpatient prescription information. The CCAE contains healthcare data for nearly 40 million individuals, encompassing employees, their spouses, and their dependents. The COB data contains the health care experiences of 3.8 million Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. These data have been used widely in health services research due to its substantial size, longitudinal integrity, and unique data links (12). For this particular analysis, data from inpatient services file, outpatient services file, outpatient drug claims file and enrollment file were merged using unique patient identifiers.

Study design and patient population:

The nested case-control study design was selected to evaluate the association between individual TNF-inhibitors and CVD because of its ability to efficiently deal with the time varying nature of drug exposure. This study design has been used commonly to evaluate treatment-outcome associations in RA patients (49, 52, 56, 124). From the Marketscan data files, a base cohort of RA patients 18 years and older who had at least 2 outpatient or 1 inpatient diagnosis of RA (ICD-9 code: 714.0) and at least one prescription record for a DMARD between Jan 1, 2008 and Dec 31, 2010 was identified (97). The earliest of these diagnoses was defined as the index diagnosis and the 12 month period pre-index was defined as the baseline period (Figure 6.1). To be considered for our case-control sampling, patients in the base cohort had to meet the following inclusion criteria: 1) continuous enrollment in their health plans during the 12 month baseline period, 2) no diagnosis of RA in the baseline period, 3) no use of biologic agents in the baseline period, 4) no history of tuberculosis (which is a contraindication to biologics use), psoriatic arthritis or Crohn's disease (comorbid conditions in which some of the biologics are indicated) during the baseline period, and 5)

not diagnosed with the outcome of interest in the baseline period. Thus our patient population consisted of incident RA patients who had no history of biologic use, who were eligible to receive biologics in the future and who were at risk for an incident CVD event.

Nested case-control sampling:

All the patients identified as eligible for sampling from the base cohort were followed-up from their index date to the earliest of the following: the outcome (CVD diagnosis), disenrollment from their health plan, switch between biologic treatments or study end date (Dec 31, 2010). If patients experienced a CVD event, they were defined as cases and the date of CVD diagnosis was defined as the event date. Once the cases were identified, 12 age, sex and cohort entry month-matched controls were sampled from the remaining patients of the base cohort at the event date who were free from CVD at that time (Incidence density sampling) (Figure 6.1). Based on our power calculations, selecting more than 12 controls per case provided no benefit in statistical power. Therefore, we selected 12 controls per case. Since the follow-up began on the first ever RA diagnosis date for these patients, our sampling also ensured the matching of cases and controls on the duration of RA.

Measures:

1. Exposure measurement:

   To comprehensively categorize antirheumatic drug use, we considered exposure to both non-biologic and biologic DMARDs. Because of our special interest in individual TNF-I agents, biologic DMARDs were classified in the following categories: infliximab, etanercept, adalimumab, and newer TNF-Is (golimumab and certolizumab) or other biologic agents. As a result, the following mutually exclusive

categories were created based on at least one filled prescription of these agents during the study period: 1) Infliximab, 2) Etanercept, 3) Adalimumab, 4) Newer TNF-Is (golimumab and certolizumab) 5) Non-biologic DMARDs (including methotrexate, hydroxychloroquine, auranofin, injectable gold, penicillamine, sulfasalazine, minocycline, azathioprine, leflunamide, cyclophosphamide and cyclosporine), 6) Other biologic agents (Abatacept, anakinara, rituximab and tocilizumab) and 7) No use of DMARD during the study period. The use of these agents was identified using both the NDC codes from outpatient pharmacy files for filled prescriptions and J codes using outpatient services files for injectable agents administered at physician's office.

Additionally, duration of treatment with these agents was defined as a continuous variable representing the cumulative days of use for the patients who filled at least one prescription in the study period. Significance of a quadratic term was tested for the continuous variables representing cumulative use for each treatment to check for any evidence of non-linearity in the association between the duration and the risk of an incident CVD event.

2. Outcome:

The outcome of interest was defined as a composite measure consisting of acute myocardial infarction (ICD-9 code 410), unstable angina (ICD-9 code 411), angina pectoris (ICD-9 code 413), chronic heart failure (ICD-9 codes 428.xx, 398.91, 402.01, 402.11, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93), other forms of chronic heart diseases (ICD-9 code 414), ischemic stroke (ICD-9 code s 433.x1, 434 [excluding 434.x0], or 436); and transient ischemic stroke (ICD-9 code 435). A

patient was defined as a case if he/she experienced any one of these events during the follow-up period.

3. Covariates:

   We identified the following covariates during the baseline period: CVD risk factors including hypertension, hyperlipidemia, and diabetes mellitus; CVD drug use including lipid lowering agents, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and other CVD drugs; RA drug use including steroids, non-steroidal anti-inflammatory drugs and non-biologic DMARDs; and other comorbidities including chronic obstructive pulmonary disease and cancer.

Statistical analyses:

Descriptive statistics were used to summarize the patient characteristics for our cases and controls. Categorical variables were presented as numbers and percentages and continuous variables were presented as means (±standard deviations). To account for the matched sampling, we used conditional logistic regression (CLR) models for the estimations of incident rate ratios (IRRs). Results from both unadjusted and adjusted models were presented. We used two distinct reference groups for this analysis. Firstly, to estimate the effectiveness of various agents, we used all the patients who did not use any DMARD in the study period as the reference group. Next, to estimate the comparative effectiveness, we used the users of etanercept as the reference group.

Additionally, crude and adjusted estimates for the association between the duration of infliximab, adalimumab and etanercept use and incident CVD events were also estimated from CLR. All analyses were conducted using SAS version 9.2 (SAS institute, Cary, NC).

6.4 Results:

The base-cohort consisted of 15,951 patients who were incident RA cases, had no history of biologic use, were eligible to receive biologics in the future and were at risk for an incident CVD event. Figure 6.2 shows the sample derivation flow chart along with the exclusion criteria. Of the 15,951 patients of the base cohort, 466 cases of an incident CVD event were identified during follow-up. These cases were age, sex, and cohort entry month-matched with 5,592 controls (12 cases per control) using incidence density sampling. Table 6.1 compares the case and control patients' baseline characteristics. CVD cases and their matched controls were 61 years old at the index date and 79% of the cases and controls were females. The mean follow-up time was 246 days for the cases and controls. Cases had higher prevalence of CVD risk factors (hyperlipidemia, hypertension and diabetes mellitus), other comorbid conditions (COPD and cancer) and used CV medications more often in the pre-index period compared to controls.

A total of 40 cases (8.58%) and 518 controls (9.26%) were exposed to a TNF-α inhibitor. Of those, 12 cases and 160 controls were exposed to infliximab, 8 cases and 167 controls were exposed to adalimumab and 20 cases and 191 controls were exposed to etanercept treatment. Because 27 controls but none of the cases were exposed to the newer TNF- α inhibitors (golimumab and certolizumab), this drug category was not further

analyzed. Appendix Tables 6.1 and 6.2 summarize covariate distribution by exposure to various DMARDs for our sample.

Table 6.2 shows the crude and adjusted estimates of the associations between the use of various DMARDs and CVD events. Compared to no DMARD use, adalimumab treatment significantly reduced the risk of incident CVD event (adjusted IRR 0.40, 95% CI 0.18-0.87). Other TNF- α inhibitors, infliximab and etanercept were not found to be significantly associated with a similar risk reduction. However, the use of non-biologic DMARDs was also found to be associated with a reduced risk of an incident CVD event compared to no DMARD use (adjusted IRR 0.66, 95% CI 0.48-0.89). On the other hand, the use of other biologic treatment was found to be associated with a significantly increased risk of an incident CVD event compared to no DMARD use (adjusted IRR 2.01, 95% CI 1.06-3.82).

Compared to etanercept, use of adalimumab showed a trend towards a lower cardiovascular risk, which was not statistically significant (adjusted IRR 0.45, 95% CI 0.29-1.06). Treatment with infliximab and non-biologic DMARDs were found to be no different in reducing the risk of CVD events compared to etanercept. Treatment with other biologics was found to be associated with a higher risk of CVD events compared to etanercept (adjusted IRR 2.27 95% CI 1.08-4.76).

When exposure to DMARDs was defined as cumulative exposure duration in number of days, use of each additional month of adalimumab therapy was found to significantly reduce the risk of an incident CVD event by 15% (adjusted IRR 0.85 95% CI 0.73-1.00, p=0.048). Cumulative use of none of the other treatments was found to be associated with a

reduction in incidence of CVD events. Table 6.3 summarizes the association between duration of DMARD treatments and the risk of incident CVD events.

6.5 Discussion:

In this observational study of incident RA patients, treatment with adalimumab and non-biologic DMARDs was found to be associated with a reduced risk of incident CVD events compared to no treatment with DMARDs. We also observed that each additional month of treatment with adalimumab resulted in 15% reduction in the risk of an incident CVD event. Comparing adalimumab and infliximab head to head with etanercept, we did not observe any statistically significant differences between these agents.

Given the cost and clinical consequences of high CVD burden in RA patients, proper CV risk management is extremely important. This is the first study to our knowledge that estimates the independent effects of individual TNF-α inhibitors on the risk of incident CVD events using clinical endpoints. Several previous studies have evaluated the impact of these agents on subclinical endpoints. For instance, other studies estimated the associations between use of TNF-α inhibitors with endpoints such as carotid intima media thickness (cIMT), flow mediated dilation (FMD) and pulse wave velocity (PWV) (131, 132). A recent review summarizing these studies concluded that treatment with adalimumab, infliximab and etanercept generally results in improvement in vasodilating functions, endothelial functions and arterial stiffness (131). However, no study examined if these agents differed with respect to their effects on the aforementioned subclinical endpoints. Some studies have also evaluated the effects of these agents on atherogenic index, which is a strong predictor of CV events, in RA patients. A review summarizing these studies concluded that treatment with

adalimumab and etanercept, but not infliximab, may result in favorable changes in patients' atherogenic index (132). Our study provides further evidence, specifically in favor of adalimumab and non-biologic DMARDs, for their potential protective effects on the risk of CVD events compared to no DMARD use. For the head to head comparison, we did observe a trend favoring adalimumab compared to etanercept but this trend was statistically non-significant. Because of the limited sample size, our study may be underpowered to detect these differences. We call for future studies with more conclusive sample sizes to compare differences between these agents for their cardiovascular outcomes.

The finding that the use of other biologics is associated with an increased risk of incident CVD events compared to no DMARD use is puzzling. We postulate that the widespread problem of channeling bias affecting observational studies may explain this finding because patients with a higher baseline cardiovascular risk may be preferentially treated with non TNF-α inhibitor biologic agents. The fact that TNF-α inhibitors are contraindicated in New York Heart Association class III and IV CHF patients may deter physicians from prescribing these agents in patients with a higher cardiovascular risk profile altogether. We were not able to adequately control for this because of the unavailability of RA-specific cardiovascular risk factors such as smoking, obesity and RA disease activity in our data. Further studies that account for these differences are necessary to understand the impact of other biologic treatments on the risk of CVD events.

There are several other limitations that deserve mention. We were not able to validate the diagnoses of the disease condition (RA) as well as the outcome. However, to address this limitation we used algorithms for detection of RA and CVD events that were validated previously for their sensitivity and specificity (97, 127, 128). Additionally, since the claims

data do not have reliable information on patient vital status, our study is limited by the competing risk of death. In the definition of exposure, it is assumed that filling of prescription equates with the use of medication. This assumption is untestable. Our study had very small sample sizes for golimumab and certolizumab owing to their late market entry. Future studies that have sufficient data on the use of these agents should be planned to evaluate their effects on CVD. We caution the readers to interpret our findings in light of these limitations.

Our study also has several unique strengths. Our sample represents the real world experiences of RA patients from the entire country. We conducted the study exclusively in incident RA patients and matched our cases and controls on the duration of the disease to reduce unmeasured confounding. Finally, we used a study design that is known to account for the time varying nature of RA treatments (104).

6.6 Conclusion:

Early treatment with adalimumab and non-biologic DMARDs may help in reducing the risk of incident CVD events in patients newly diagnosed with RA compared to no DMARD use. Our data should serve as hypothesis generating for further studies.

Figure 6.1: **Timeline of the study**

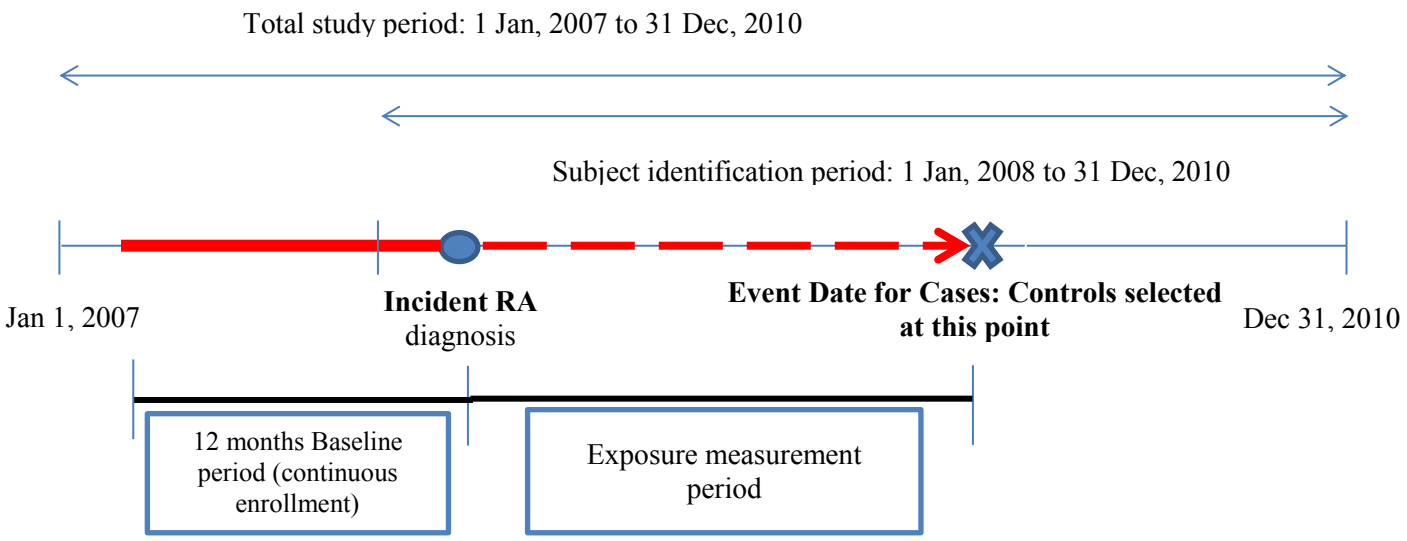


Figure 6.2: **Sample derivation flow chart**

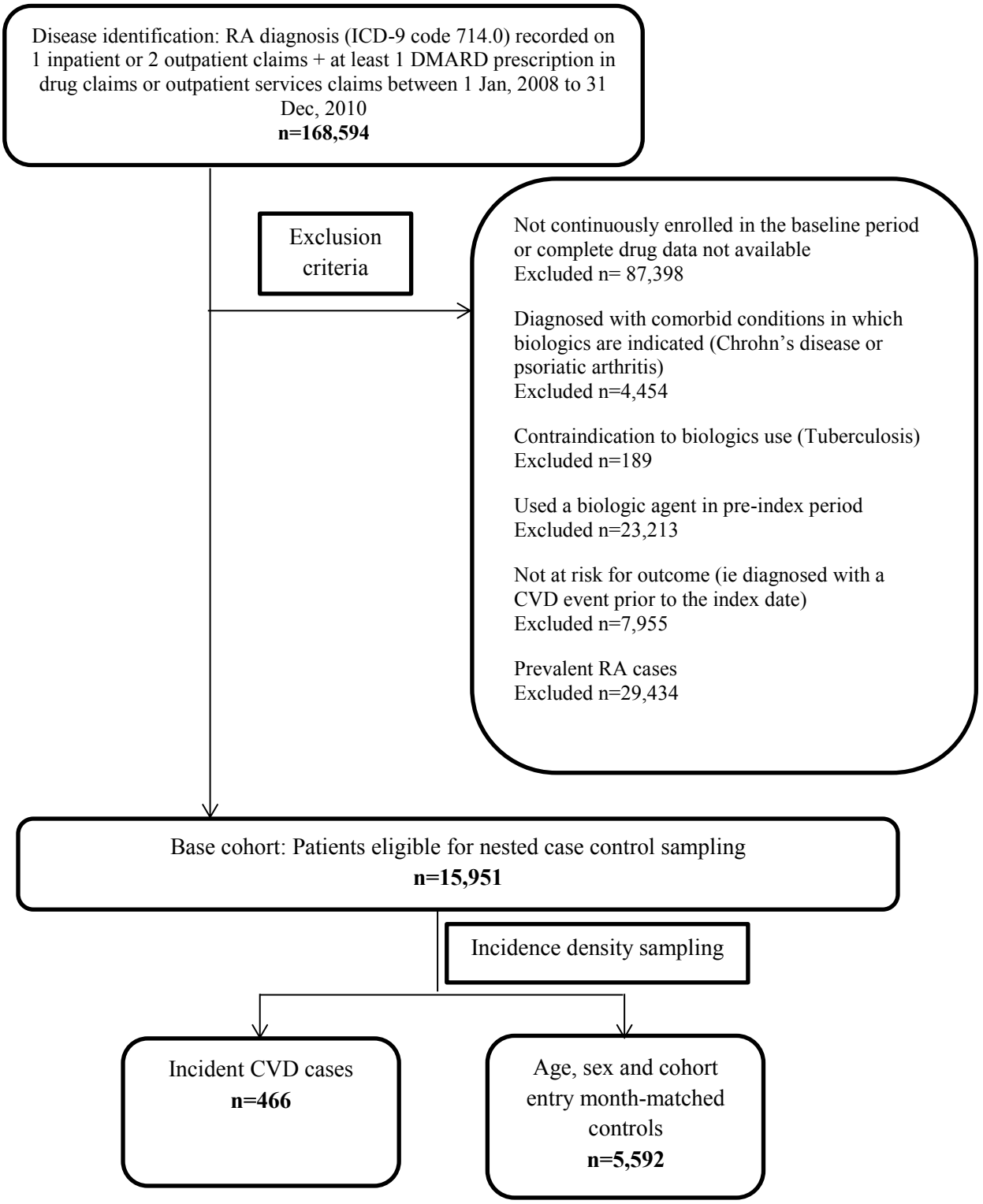


Table 6.1: **Baseline comparison of cases of incident cardiovascular diseases and controls sampled from a cohort of incident RA patients**

Variable	Cases[†] (n=466)		Controls (n=5,592)	
	n	%	n	%
Matching variables				
Patient age (Mean±SD)	61.21 ± 10.49		61.13 ± 10.46	
Mean duration of RA, days (Mean±SD)	249.61 ± 211.23		249.61 ± 211.02	
Female gender	368	78.97	4416	78.97
Cardiovascular risk factors				
Diabetes Mellitus	125	26.82	794	14.2
Hyperlipidemia	163	34.98	1674	29.94
Hypertension	264	56.65	2254	40.31
Other comorbid conditions				
COPD	103	22.1	790	14.13
Cancer	36	7.73	340	6.08
RA medications in the pre-index period				
Coxib	51	10.94	590	10.55
NSAIDs	214	45.92	2507	44.83
Steroids	302	64.81	3128	55.94
Non-biologic DMARDs[‡]	204	43.78	2246	40.16
CV medications in the pre-index period				
ACE-Inhibitors	112	24.03	1047	18.72
Beta-blockers	144	30.9	1080	19.31
Lipid lowering agents	216	46.35	1797	32.14

Calcium channel blockers	121	25.97	892	15.95
Other CV drugs*	150	32.19	1166	20.85

† 466 cases included 23 patients with acute myocardial infarction (ICD-9 code 410), 16 patients with unstable angina (ICD-9 code 411), 43 patients with angina pectoris (ICD-9 code 413), 98 patients with chronic heart failure (ICD-9 codes 428.xx, 398.91, 402.01, 402.11, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93), 156 patients with other forms of chronic heart diseases (ICD-9 code 414), 98 patients with cerebrovascular accident (ischemic stroke, ICD-9 codes 433.x1, 434 [excluding 434.x0], or 436, and transient ischemic stroke, ICD-9 code 435), and 32 patients with multiple diagnoses from this list.

‡ Non-biologic DMARDs include methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, minocycline, cyclophosphamide and cyclosporine

* Other CV drugs include cardiac glycosides, antiarrhythmic agents, hypotensive agents, vasodilating agents and phosphodiesterase inhibitors

Table 6.2: **Estimates of the association between the use of individual TNF-Is, non-biologic DMARDs and other biologics and the risk of an incident CVD event compared to no DMARD use or etanercept use**

Exposure[†]	N (cases)	N (controls)	Unadjusted IRR (95% CI)	Adjusted[‡] IRR (95% CI)
No DMARD use	79	776	Reference	Reference
Infliximab	12	160	0.68 (0.35-1.30)	0.61 (0.31-1.20)
Adalimumab	8	167	0.43 (0.20-0.93)	0.40 (0.18-0.87)
Etanercept	20	191	0.94 (0.55-1.63)	0.89 (0.50-1.56)
Other biologics*	17	69	2.27 (1.24-4.18)	2.01 (1.06-3.82)
Non-biologic DMARDs*	330	4,202	0.71 (0.53-0.96)	0.66 (0.48-0.89)
Etanercept	20	191	Reference	Reference
Infliximab	12	160	0.72 (0.34-1.52)	0.69 (0.32-1.50)
Adalimumab	8	167	0.46 (0.20-1.06)	0.45 (0.29-1.06)
Other biologics[‡]	17	69	2.41 (1.19-4.91)	2.27 (1.08-4.76)
Non-biologic DMARDs[‡]	330	4,202	0.76 (0.47-1.22)	0.74 (0.45-1.22)

† 27 controls but none of the cases were exposed to newer TNF-inhibitors (certolizumab and golimumab). Therefore we were not able to estimate the association between the use of these agents and an incident CVD event

‡ Adjusted for pre-index NSAID use, steroid use, non-biologic DMARD use, cardiovascular medication use, Diabetes, Hypertension, Hyperlipidemia, chronic obstructive pulmonary disease and cancer in addition to matching with age, gender, duration of RA and cohort entry month and year. Unadjusted associations are estimated in age, gender, duration of RA and cohort entry month and year matched sample

*Non-biologic DMARDs include methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, minocycline, cyclophosphamide and cyclosporine, & Other biologic agents include abatacept, anakinara, rituximab and tocilizumab

Table 6.3: **Association between duration of RA treatments and incident CVD event**

Exposure	Adjusted† IRR (95% CI)	p-value
Each additional month of cumulative infliximab use	0.97 (0.89-1.04)	0.37
Each additional month of cumulative adalimumab use	0.85 (0.73-1.00)	0.048
Each additional month of cumulative etanercept use	0.99 (0.93-1.07)	0.86
Each additional month of cumulative other biologics use‡	1.06 (0.99-1.14)	0.099
Each additional month of cumulative non-biologic DMARD use‡	0.97 (0.95-1.00)	0.092

† Adjusted for pre-index NSAID use, steroid use, non-biologic DMARD use, cardiovascular medication use, Diabetes, Hypertension, Hyperlipidemia, chronic obstructive pulmonary disease and cancer in addition to matching with age, gender, duration of RA and cohort entry month and year. Unadjusted associations are estimated in age, gender, duration of RA and cohort entry month and year matched sample Non-biologic

‡ DMARDs include methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, minocycline, cyclophosphamide and cyclosporine, & Other biologic agents include abatacept, anakinara, rituximab and tocilizumab

Appendix Table 6.1 Distribution of covariates by DMARD use status

Variable	No DMARDs		TNF-Is†		Other biologics†		Non-Biologic DMARDs †	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Females	694	81.17	432	73.72	68	79.07	3590	79.21
Age (Mean (SD))	61.41	10.52	58.25	9.49	62.29	9.21	61.44	10.53
CVD risk factors								
Diabetes Mellitus	112	13.10	108	18.43	12	13.95	687	15.16
Hyperlipidemia	278	32.51	145	24.74	22	25.58	1392	30.71
Hypertension	369	43.16	207	35.32	50	58.14	1892	41.75
Other comorbidties								
COPD	147	17.19	79	13.48	18	20.93	649	14.32
Cancer	67	7.84	19	3.24	16	18.60	274	6.05
RA medications in the pre-index period								
Coxib	69	8.07	80	13.65	14	16.28	478	10.55
NSAIDs	305	35.67	269	45.90	27	31.40	2120	46.78
Steroids	477	55.79	352	60.07	45	52.33	2556	56.40
Did not use nbDMARD	584	68.30	387	66.04	61	70.93	2576	56.84
Used 1 nbDMARD	243	28.42	153	26.11	18	20.93	1580	34.86
Used 2 nbDMARDs	26	3.04	38	6.48	3	3.49	346	7.63
Used more than 2 nbDMARDs	2	0.23	7	1.19	4	4.65	30	0.66
CV medications in the pre-index period								

Beta-blocker use	193	22.57	96	16.38	16	18.60	919	20.28
Lipid lowering agents use	274	32.05	173	29.52	26	30.23	1540	33.98
Calcium channel blockers use	129	15.09	81	13.82	17	19.77	786	17.34
Other CV drug use‡	181	21.17	108	18.43	26	30.23	1001	22.09
ACE-I use	151	17.66	99	16.89	12	13.95	897	19.79

†TNF-inhibitors include infliximab, etanercept, adalimumab, certolizumab and golimumab. Non-biologic (nb) DMARDs (nbDMARDs) include methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, minocycline, cyclophosphamide and cyclosporine. Other biologic agents include abatacept, anakinara, rituximab and tocilizumab

‡ Other CV drugs include cardiac glycosides, antiarrhythmic agents, hypotensive agents, vasodilating agents and phosphodiesterase inhibitors

Appendix Table 6.2 Distribution of covariates among users of individual TNF-inhibitors

Variable	*Infliximab*		*Adalimumab*		*Etanercept*	
	N	*%*	*N*	*%*	*N*	*%*
Females	126	73.26	130	74.29	161	76.30
Age (Mean (SD))	62.69	10.33	56.26	8.62	55.94	8.23
CVD risk factors						
Diabetes Mellitus	46	26.74	29	16.57	31	14.69
Hyperlipidemia	27	15.70	48	27.43	56	26.54
Hypertension	48	27.91	62	35.43	84	39.81
Other comorbidties						
COPD	31	18.02	11	6.29	28	13.27
Cancer	8	4.65	6	3.43	5	2.37
RA medications in the pre-index period						
Coxib	20	11.63	22	12.57	34	16.11
NSAIDs	49	28.49	102	58.29	111	52.61
Steroids	99	57.56	110	62.86	124	58.77
Did not use nbDMARD[†]	94	54.65	123	70.29	151	71.56
Used 1 nbDMARD	68	39.53	34	19.43	45	21.33
Used 2 nbDMARDs	9	5.23	14	8.00	13	6.16
Used more than 2 nbDMARDs	1	0.58	4	2.29	2	0.95
CV medications in						

the pre-index period						
Beta-blocker use	34	19.77	29	16.57	31	14.69
Lipid lowering agents use	55	31.98	49	28.00	58	27.49
Calcium channel blockers use	28	16.28	18	10.29	29	13.74
Other CV drug use‡	37	21.51	24	13.71	39	18.48
ACE-I use	35	20.35	26	14.86	35	16.59

† non-biologic DMARDs (nbDMARDs) include methotrexate, hydroxychloroquin, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunamide, minocycline, cyclophosphamide and cyclosporine,

‡ Other CV drugs include cardiac glycosides, antiarrhythmic agents, hypotensive agents, vasodilating agents and phosphodiesterase inhibitors

CHAPTER 7

SUMMARY

7.1 Key Findings:

This dissertation research focused on the determinants of use of biologic treatments, including TNF- α inhibitors (TNF-Is), and the cardiovascular (CV) outcomes of the use of TNF-I treatment in patients with rheumatoid arthritis (RA). In specific Aim 1, we evaluated the predictors of treatment initiation with biologics in RA patients. This study added new information to the literature by evaluating factors specifically influencing biologic treatment initiation using a large nationally representative sample derived from health insurance claims. We used data up to 2010 for this study and systematically evaluated the impact of various population characteristics on biologic treatment initiation with Andersen's behavioral model (ABM) for health services use (73), a model that is helpful in understanding potential inequities in the use of healthcare services. We observed that treatment initiation with biologics was influenced by a mix of predisposing, enabling and need factors. In addition to the need factors such as RA severity, RA diagnosis type and pre-index use of non-biologic treatments for RA, the predisposing factor age, and the enabling factors of insurance type and drug benefit generosity were found to be significant predictors of treatment initiation with biologics. Neither the presence of cardiovascular risk factors, hypertension, hyperlipidemia

or diabetes nor the history of cardiovascular diseases, including acute myocardial infarction, chronic heart failure, stroke or other cardiovascular diseases (CVD), were found to be significantly associated with the initiation of biologic treatments.

The primary objective of Aim 2 was to examine the effect of TNF-I treatment on incident CVD event in patients newly diagnosed with RA. We assembled a large cohort that included cases with newly diagnosed RA that were not exposed to any biologic treatment prior to the onset of the disease. Thus, we assessed TNF-I exposure over the entire course of the disease. We used several different definitions of treatment exposure to account for the timing and history of treatment to gain a better understanding of prior medication use and length of treatment on CVD outcomes. We observed that the risk of incident CVD event was significantly reduced by current treatment with TNF-Is and non-biologic DMARDs compared to no treatment with any DMARD. Further, we observed that this protective effect was found to be associated with the duration of TNF-I and non-biologic DMARD use in a linear manner. Our findings also highlighted the importance of a precise and time specific definition of exposure by providing and comparing estimates of the risk of an incident CVD event using 3 unique exposure definitions with varying degrees of non-differential exposure misclassification.

Because the individual TNF-I agents differ with respect to their pharmacological properties, effectiveness profiles in various rheumatologic diseases and tolerability, we examined the independent effects of infliximab, adalimumab and etanercept on the risk of CVD in patients newly diagnosed with RA in our specific Aim 3. We observed that treatment with adalimumab, but not with infliximab and etanercept, and non-biologic DMARDs was found to be associated with a reduced risk of incident CV events compared to no treatment

with DMARDs. We also observed that each additional month of treatment with adalimumab resulted in 15% reduction in the risk of n an incident CVD event.

7.2 Implications:

We undertook this analysis to provide meaningful answer to the important clinical question related to the best strategies of reducing CVD risk in patients with RA. Because of the increased burden of CVD in RA patients, the potential of various antirheumatic treatments for CV benefits has been the focus of attention in recent years. Numerous observational studies have provided estimates for the associations between TNF-I treatment and the risk of CVD in RA patients. Most of these studies point towards potential beneficial effects of TNF-Is, however estimates from some studies lack statistical significance. A meta-analysis that pooled data form 11 observational studies, reported that the use of TNF-I was associated with a reduced risk of all CV events, MI and stroke (133). However, all of these 11 studies included patients with established RA, with disease duration ranging from 5 to 15 years, in their cohort. Because of recent reports suggesting an increased atherosclerosis in RA patients since very early stages of the disease (10, 11), we hypothesized that early treatment with TNF-Is may be able to translate into clinical benefits by hindering the acceleration of atherosclerosis. To test this hypothesis, we designed our study using insurance claims data that represented real-world early RA patients.

First, we evaluated the association between TNF-Is as a class and the incidence of cardiovascular events in early RA patients, while controlling for the use of other treatments including non-biologic DMARDs and other biologics as well as other relevant patient covariates. Our finding that treatments with TNF-Is as well as non-biologic DMARDs are associated with a statistically significant risk reduction of CVD events in early RA patients

compared to no treatment with any DMARD is an important clinical finding. In this previously unstudied patient population, our estimates provide new insights for the clinicians who face the challenge of managing increased CV risk in RA patients. The American College of Rheumatology (ACR) advocates the use of DMARDs, both non-biologic or TNF-Is, depending upon the duration of symptoms and features of prognosis in early RA patients as early as possible to maximize the chances of remission by arresting the disease progression. Our findings further highlight the importance of early DMARD treatment in RA patients by providing evidence for their potential CV benefit. Additionally, we also observed that the reduction in CVD risk with both TNF-I and non-biologic DMARD treatment is linearly duration dependent. Longer treatment with both agents appeared to be more beneficial for reducing the incidence of CVD events. This finding is important because it emphasizes the importance of treatment persistence with non-biologic DMARDs and TNF-I patients with early RA.

Further, we also undertook the evaluation of independent effects of the three most commonly used TNF-Is on incident CVD events in the same cohort. We observed that adalimumab treatment appears to be significantly beneficial in reducing the risk of incident CVD events in early RA patients. Ours is the first study to report this important finding. Because our results are generated in an observational setting with a limited sample size, we call for further research to confirm these findings. If specific DMARDs with superior CVD benefit could be identified, maximum benefits could be obtained by targeting treatment with these agents in patient subgroups of RA patients who are at a greater risk of CVD events.

In addition to these important clinical implications, our study also offers some policy implications. In our specific Aim 1, we observed that generous drug benefit was associated

with increased likelihood of biologic initiation. This finding supports the earlier observations by Karaca-Mandic et al. (121). The coverage of biologics under a higher or specialty formulary tier of pharmacy benefits has become increasingly common (25). Research suggests that this practice has substantially increased the out of pocket costs for biologics (25, 26). Insurers must be mindful of the fact that higher cost sharing may deter patients from initiation of timely pharmaceutical care, which may result in uncontrolled RA and eventual increase in RA-related healthcare cost. In addition, RA patients with co-morbid CVD have been known to incur higher overall costs than RA patients without co-morbid CVD (134). In our specific Aim 2, we observed that early treatment with TNF-Is and non-biologic DMARDs may be able to help in preventing incident CVD events in RA patients. Together these findings suggest that promoting early treatment with TNF-Is and non-biologic DMARDs by reducing patient cost sharing may result in ultimate cost savings for the insurers.

Finally, our study also has methodological implications. We used 3 unique definitions to evaluate the impact of exposure definition on the observed estimates in our specific Aim 2. As observed in our exposure definition schemes 1 (Ever/Never TNF-I use) & 2 (Current use indicators for TNF-Is and other RA treatments), broad definitions lead to non-differential misclassification of exposure and resulted in a reference group consisting of a heterogeneous mix of patients. When relying on relative measures of associations, such misclassification may lead to masking of important differences in treatment-outcome associations. In our case, scheme 1 lumped the users of all non-TNF DMARDs along with non-users of DMARDs into the reference category ‘Never use of TNF-Is’. In scheme 2, users of other DMARDs were separated but past users of these DMARDs got classified into the reference category ‘No

current DMARD use'. This misclassification may lead to an inappropriate conclusion that TNF-I use has no impact on incident CVD events. In reality, as reflected in scheme 3, the appropriate inference would be that compared to no DMARD use, current use of TNF-Is may have a potential protective effect against incident CVD events in patients newly diagnosed with RA. However, since non-biologic DMARDs also have a similar protective effect and schemes 1 and 2 fail to account for the treatment history with these agents, this important finding is masked in these two definition schemes. Although several authors have highlighted this problem in the past using examples of different drug classes,(65, 126) unfortunately this is still a largely ignored issue in pharmacoepidemiology studies. Based on our findings, we recommend that researchers evaluating treatment-outcome associations in RA patients should create exposure groups after considering patients' history of DMARD use. Based on the composition of the exposure group, the inference may change due to non-differential exposure misclassification.

Some authors (56) in the past have suggested that patients who do not receive DMARDs may not be the most appropriate reference group while evaluating impact of biologic treatments in CVD outcomes in RA because of the issues related to confounding by indication. Briefly, this phenomenon occurs if the reason behind prescribing biologics is related to the outcome (CVD in our case). However, based on our Aim 1 results, in which we observed that neither CVD risk factors nor CVD history was related to the initiation of biologic treatment, we believe that our results do not merely reflect confounding by indication. In addition, our reference group may be comprised of any combination of three clinically distinct types of patients, 1) Patients with less severe RA whose conditions do not require immediate DMARD initiation in their physician's opinion, 2) Patients not suitable for

DMARD initiation because of the concerns of adverse events from the use of these agents due to their generally poor health and 3) Patients similar to our comparator groups but who did not start timely DMARD therapy. If a large proportion of our reference group is comprised of patients type 1) discussed above, then arguably they should be at a lower risk of CVD events because severity of RA is associated with CVD risk. In that case, our estimates present a conservative estimate of the benefits of TNF-Is and non-biologic DMARDs. If a large proportion of our reference group is comprised of patients type 2) discussed above, then our findings may not represent the accurate estimates of benefits of TNF-Is and non-biologic DMARDs and may just be an artifact of the baseline CVD risk differences between the reference group and the comparator group. However, we strongly argue that this is unlikely because to be included in our cohort all the patients had to have at least one prescription of DMARDs during our study period. That means that the patients in our reference group represent the person-time experiences of new RA patients *prior to starting their DMARDs*. So clearly, these patients cannot be considered unsuitable for DMARD treatment. If a large proportion of our reference group is comprised of patients type 3) discussed above, then we think that our estimates present the most accurate relative risk estimates for the benefits of TNF-Is and non-biologic DMARDs. We believe that our findings should be interpreted as evidence in favor of using TNF-Is and non-biologic DMARDs for their CVD benefits compared to not using any DMARDs and should not be used to represent comparative differences between classes.

7.3 Strengths and Limitations:

Our study has several unique strengths. This is the largest study of its kind to provide the estimates of the association between TNF-Is and the risk of CVD events in newly

diagnosed RA patients. Our sample represents the real world experiences of RA patients from the entire country. We conducted the study exclusively in incident RA patients and matched our cases and controls on the duration of the disease to reduce unmeasured confounding. We used a study design that is known to account for the time varying nature of RA treatments (104). Additionally, we tested multiple definitions of exposure and provided estimates using the definition that accounted for the entire treatment history of the patients. Our specific Aim 3 is the only study to our knowledge that represents the estimates for the independent effects of individual TNF-Is on the risk of incident CVD events.

However, there are certain limitations of this study that deserve discussion. As with any other study using administrative claims, we were not able to validate the diagnoses of the disease condition (RA), outcomes as well as co-morbid conditions. Several issues in coding of disease diagnoses in administrative claims data, which are collected for reimbursement purposes, have been identified. One such issue is that of upcoding of claims, in which the recorded diagnosis codes are entered to reflect a more complex disease condition than the actual condition to maximize reimbursement (135). However, to address this limitation we used algorithms for detection of RA and CVD events that were validated previously for their sensitivity and specificity (97, 127, 128).

Further, the administrative claims contain very limited information on clinical conditions of RA patients, such as disease activity and swollen joint count. Therefore, we were not able to capture the exact severity of RA in patients of our cohort. However, as a proxy, we used the validated claims based index for getting an approximation of RA severity (101) for specific Aim 1. For specific Aims 2 and 3, our sampling technique matched cases and controls on the duration of RA, which is used as an approximation for severity of RA.

Additionally, since the claims data do not have reliable information on patient vital status, our Aims 2 and 3 are limited by the competing risk of death. To minimize that, we identified ICD-9 codes related to death (sudden death (798), instantaneous death (798.1), or death occurring in less than 24 hours from onset of symptoms, not otherwise explained (798.2)) and censored patients at their insurance disenrollment date.

Measurement of exposure also presents unique challenges in pharmacoepidemiology studies using administrative claims data. We had to rely on prescription refill records to estimate the exposure. In this definition of exposure, it has to be assumed that filling of prescription equates with the use of medication. This assumption is untestable. We would also like to acknowledge that our database did not contain information on important variables such as tobacco consumption of the patients, which is a risk factor for both RA and CVD. We were also not able to capture the over-the-counter use of certain pain relievers, which are commonly used by RA patients. Therefore, there may have been some residual confounding in our exposure-outcome association even after multivariate risk adjustment.

Because of the small number of patients using individual TNF-Is, our Aim 3 may be underpowered to detect the differences between these agents for the CVD outcomes. Some readers may argue that if conducting the study in a dataset that had information on healthcare experiences of over 35 Million unique individuals is unable to provide sufficient sample size for our research question, it may be difficult for future researchers to assemble a larger sample than ours. We acknowledge and share this concern. To gain a better understanding of this issue, it is imperative to discuss some of the major constraints limiting the sample size of our study. Firstly, our research interest of uncovering differences between individual TNF-Is led us to create exposure categories based on patients' use of adalimumab, etanercept or

infliximab instead of combining them as a single group in Aim 3. Secondly, very few patients who belong to the population of our interest (early RA patients) begin treatment with these agents. Finally, in order to improve the internal validity of the study, we excluded all the patients exposed to any biologics in the 12-months of pre-index period and conducted the study exclusively among the new users of these agents. Taken together, our exposure of interest, population of interest and the restrictions employed to improve the internal validity of the study resulted in small samples for the exposure groups of our Aim 3. If we were to relax some of these criteria, for example including prevalent users of these medications or defining the baseline period as a 6-month interval, we are likely to assemble a larger sample. However, in doing so the internal validity of the study may be compromised.

The finding that the use of other biologics is associated with an increased risk of incident CVD events compared to no DMARD use in our Aims 2 and 3 is puzzling. We postulate that the widespread problem of channeling bias affecting observational studies may explain this finding. It may be possible that patients with a higher baseline cardiovascular risk may be channeled towards the use of non TNF-I biologic agents. The fact that TNF-Is are contraindicated in New York Heart Association class III and IV CHF patients may deter physicians from prescribing these agents in patients with a higher cardiovascular risk profile altogether. The risk of CVD at baseline was found to be higher for these patients as evidenced by a higher IRR while defining the use of these agents categorically, but when the duration of use was accounted for this higher risk was no longer observed suggesting potential for channeling bias. We were not able to adequately control for this because of the unavailability of RA specific cardiovascular risk factors such as smoking, obesity and RA

disease activity in our data. Further studies that account for these differences are necessary to understand the impact of other biologic treatments on the risk of CVD events.

Additionally, since the claims data do not have reliable information on patient vital status, our study is limited by the competing risk of death. Patients who experience sudden cardiac death are likely to go unrecorded in our database. Therefore, the patients may either be censored because after their death, they would no longer be enrolled in the health plan or may still keep contributing person time to our study if somehow their health insurance enrollment is active after their death. Such patients should ideally be classified as cases, but because of unavailability of their data, our study could not accurately classify them as cases. We caution the readers to interpret our findings in light of these limitations.

7.4 Implication for future research:

Our study paves the way for future research in several meaningful ways. In our specific Aim 1, we observed that age was inversely associated with biologic initiation. We postulate that this finding may be explained by factors including but not limited to physician preference, patients' concerns related to the safety of biologics and patients' co-morbid conditions. Future research should be conducted to examine the efficacy and safety of biologic agents in elderly patients and patients with co-morbid conditions to address some of these issues. If safe and effective biologic agents are identified in this specific patient population, both patients and payers could be benefited. We also observed that lower patient cost sharing results in increased likelihood of biologic initiation. Further research examining whether this increased likelihood translates into improved outcomes and resultant cost savings should be conducted.

As discussed in section 7.3, our estimates from Aims 2 and 3 may suffer from residual confounding. Therefore, we call for future studies evaluating the association between TNF-Is and CVD events in this specific population using data sources that has sufficient covariate information to control for baseline CV risk. Additionally, because very limited data is available in the literature evaluating the associations between non TNF-I biologics including abatacept, rituximab, tocilizumab and certolizumab and CVD risk, future studies should be conducted with an exclusive focus on these agents to ensure sufficient power. Our study used a composite endpoint of all CVD events. Evaluation of association between TNF-I and separate cardiovascular endpoints should be planned to better understand the full potential of benefits of these treatments.

Cardiovascular risk reduction in RA patients after TNF-Is and non-biologic DMARDs as observed in our study involves complex biologic mechanisms. This risk reduction may be attributed either to the favorable changes in traditional cardiovascular risk factors, such as insulin resistance, blood pressure and atherogenic index, or to the favorable changes in inflammatory processes leading to acceleration of atherosclerosis. In order to maximize the treatment benefits in specific subpopulations of RA patients, an understanding of the mechanisms by which CV risk reduction occurs is very important. Studies conducted using subclinical endpoints such as high density lipoprotein levels and low density lipoprotein levels have their merits but provide little information related to the actual clinical benefits. Therefore, observational studies designed with clinical endpoints, such as development of diabetes, hyperlipidemia or hypertension, to evaluate the association between these treatments and traditional CVD risk factors are required. A recent evaluation using development of diabetes as an endpoint in RA or psoriasis patients after TNF-I treatment

presented encouraging findings that patients using these agents were nearly 40% less likely to develop diabetes than patients using certain non-biologic DMARDs (136). Further studies similar to this will provide very important insights in proper CV risk management in RA. The societal benefit of proper CV risk management is illustrated by the decline in CV mortality in patients with diabetes over last two decades (137). The medical community should strive for a similar decline in CV burden in RA patients and more research targeted towards understanding the potential role of antirheumatic agents in CV risk reduction represents a great opportunity to achieve this.

Finally, our Aim 3 finding of adalimumab showing a protective effect in terms of its CV risk reduction in new RA patients should be treated as hypothesis generating. No study in the literature has been conducted to evaluate independent CVD effects of individual TNF-Is. We call for more studies with larger sample size to confirm this finding.

7.5 Conclusion:

The results from this dissertation suggest that early treatment with TNF-Is and non-biologic DMARDs may help in reducing the risk of incident CVD events in patients newly diagnosed with RA. Among available TNF-Is, adalimumab showed the largest clinical benefit for CVD risk reduction. Future studies with larger sample size are recommended to confirm findings from our study.

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