# Alberta Biologics Pharmacosurveillance Program


FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

UNIVERSITY OF ALBERTA

# Alberta Biologics Pharmacosurveillance Program

Liam Martin MB, MRCPI, FRCPC
Rheumatologist, Department of Medicine
University of Calgary

# Objectives

- The Objectives of this talk are to address the AbioPharma from 3 perspectives
- 1. The Beginning – How it all started
- 2. The Middle – What we have achieved and how
- 3. The End – A new beginning as we move into a new and exciting future

# The Beginning

- Interest in biologic therapies from the beginning
- Involved in clinical trials of both infliximab and adalimumab
- Special Access Program for infliximab was developed through Schering
- SAP clinic was developed in our 2 sites
- Assessment process developed in keeping with clinical trials

# The Beginning

- Special Access Program 2000-2003
  - Infliximab – both sites
    - Etanercept and leflunomide as comparator groups – Edmonton only
  - Data collected at baseline, week 14 and q6 months
    - Patient demographics, disease duration, DMARD history
    - Tender and swollen joint counts, pain VAS, patient and physician global VAS, HAQ, ESR, X-rays
    - SF36, EuroQol
    - Adverse events and co-medications
    - If drug stopped, date of last dose and reason for stopping

# The Beginning

- Discussions with Alberta Blue Cross regarding approving infliximab and other TNFi's
- Infliximab and etanercept formulary listing on April 1, 2003 conditional on a province-wide pharmacosurveillance study funded by industry and with participation mandated for patients and rheumatologists
- Access criteria developed through discussions between Alberta Blue Cross and physicians at both sites
- Methotrexate, methotrexate combination with 1 other DMARD, and leflunomide failures
- Must meet pre-specified efficacy outcomes at week 12
  - ACR20 or DAS28 improvement of 1.2 units
  - HAQ improvement of ≥ 0.22 units
- Evaluated q6 months (q1 year in 2009)
- Now includes all biological therapies, rituximab, abatacept and tocilizumab

# The Beginning

- The plan for ABioPharm was developed
- Study protocol developed
- Ethics approval obtained in 2004 at both sites
- Funding given to AHW by companies (Schering and Amgen) to support program
- Project Council was put in place to monitor study progress and expenditures
  - Chaired by IHE, representatives include Minister of Health (representative), Alberta Health and Wellness, and 1 from each company
- Scientific Committee
  - Chaired by Dr. WM, Representatives from UofA and UofC

# Logistics

**Both sites developed a Biologic Clinic (Total patient numbers May 25, 2014: 3132 patients (Edmonton = 2268, Calgary = 864)**

- **Edmonton**
  - **2 nurse clinicians in Edmonton**
- **Calgary**
  - **1 coordinator in Calgary responsible for data management (funded through study funds)**
  - **1 nurse clinician and 1 RN and an administrative assistant, (funded by Alberta Health Services)**
- **Database hosted by EPICORE**
- **Study Funding**
  - **Alberta Health and Wellness (2004-2009)**
  - **Industry until December 2012**
- **Extension funding and grants beyond 2012**

# Data Collected

- Baseline demographics
  - patient characteristics (DOB, sex, ethnicity, years of education)
  - diagnosis and date
  - prior DMARDs or biologics
  - Self-Assessed Comorbidity Questionnaire (Sangha, A&R 2003)
- Each visit:
  - Height and weight
  - Smoking
  - Marital status

# Data Collected

- Patient-reported
  - HAQ
  - Patient Global
  - SF-36
  - EuroQol EQ-5D
  - Resource use: inpatient and outpatient services (physicians, allied health, diagnostic tests, surgeries), community services, investments)
  - Participation in activities of daily living
  - Illness-related employment history

# Data Collected

- Physician/Nurse Assessment
  - Tender and Swollen Joint Counts
  - Global VAS
  - ESR, CRP, ANA/ENA, X-Rays
  - Adverse events by OMERACT categorization
    - system involvement, severity, causality, outcome
  - Change in biologic and reason, co-medications

# Economic Aspects

- Economics Evaluation
  - Alberta Health and Wellness administrative data
    - Discharge Abstract Database
    - Physician Claims
    - Ambulatory Care Classification System
  - Cost estimates for healthcare utilization

# The Middle

- **What we have achieved and how**

# Aims of the study

- To investigate the patient safety and efficacy of the anti-TNF drugs (clinical study)
- To assess cost-effectiveness of anti-TNF medication in real world situation in Alberta

=> Connection between economic indicators and clinical indicators through economic analysis

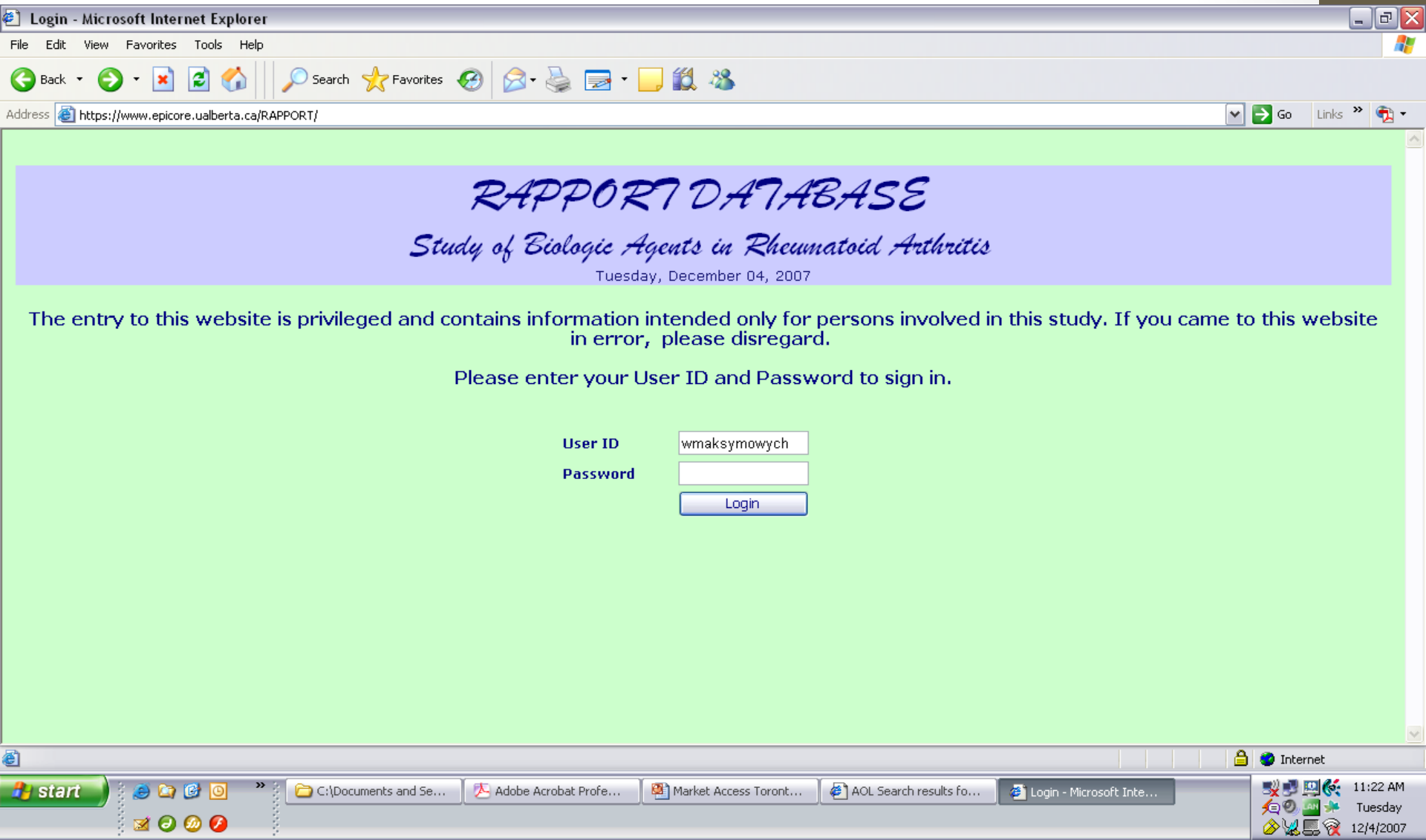
# ABioPharm Objectives

- Timely and appropriate *access* to advanced treatment
- Long-term *active/integrated/centralized patient care* monitoring effectiveness and safety in the context of a disease management program
- Evidence-based *targeting of treatment* (e.g. development of prediction models, evaluation of biomarkers)

# Patient Inclusion Criteria

- Data includes consecutive RA patients who have started their anti-TNF medication since April 2004 until March 2009
- To be eligible for the government funded program patients have to have failed 3 DMARDs and show improvement in the HAQ score by at least 0.22 and DAS score improvement of 1.2 at 12 weeks
- Patients were allowed to change their anti-TNF medication
- Comparison group from patients starting leflunomide (DMARD) collected from Edmonton

# Web-based Data Portal



# Methods

- Administrative data using Alberta government health data from April 2004 to March 2009
  - Hospitalizations, Emergency Room (ER) and other clinics, physician claims (GP and specialist)
  - Drug data was not available
  - Claims data changed to visits assuming that claims during one day are one visit
  - Clinical data includes, date of claim, procedures, LOS, diagnosis (ICD-9 or ICD-10), cost (or shadow price) using provincial cost estimates (2008 Dollars)

# Methods – Sub-group analysis

- **Study includes patients who started their first anti-TNF and either:**
  - **A) Use the first anti-TNF only (throughout follow up)**
  - **B) Switch to another anti-TNF (one or several changes) – either loss of efficacy or adverse events**
- **DMARD patients – leflunomide**
  - **C) Stayed on DMARD,**
  - **D) Switched to anti-TNF agent (failed leflunomide)**

# Methods – Sub-group analysis

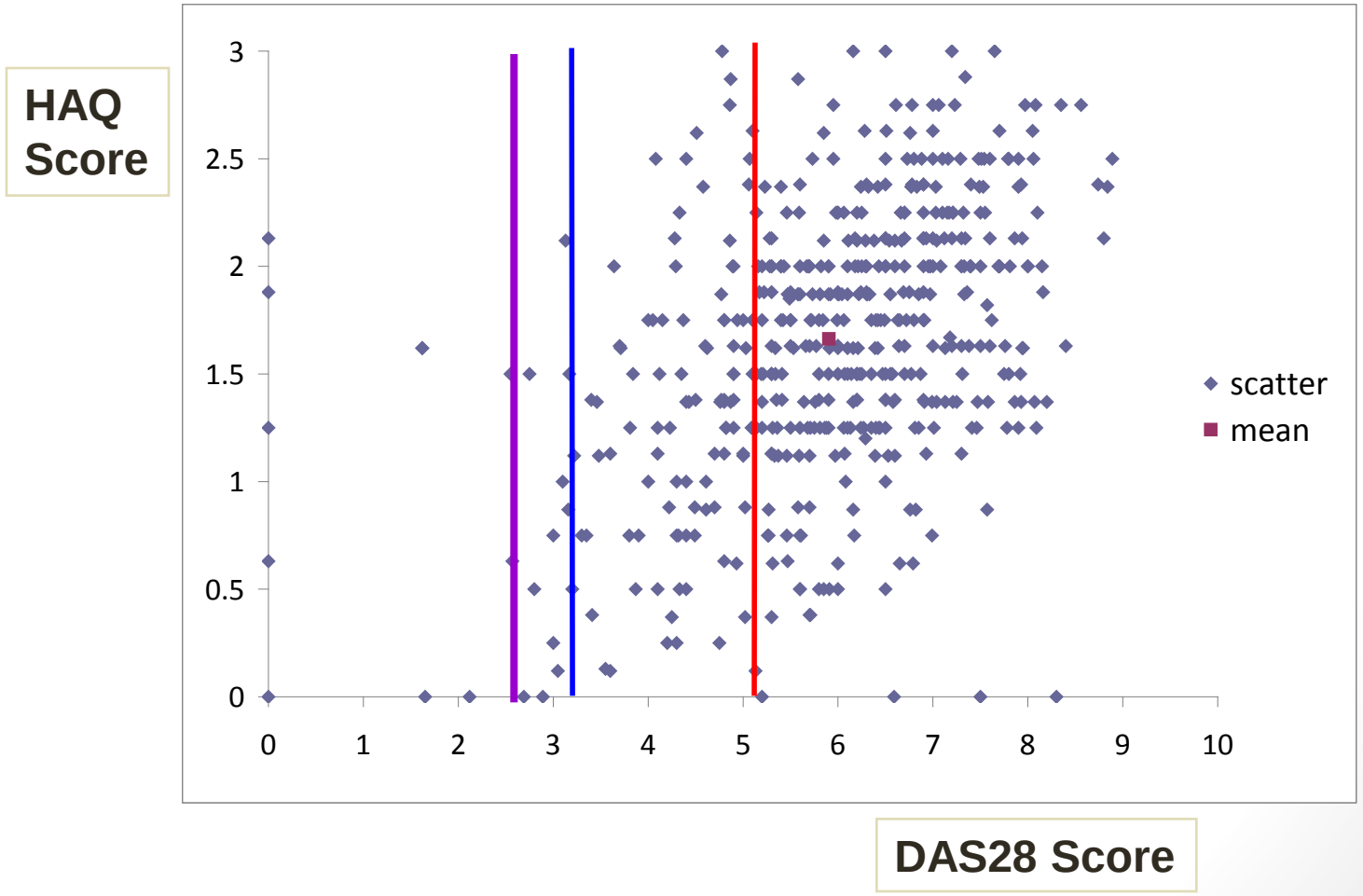
- Health care utilization and costs were divided into subgroups based on diagnostic categories developed by the consensus of a panel of four clinicians:
  - RA-related visits and costs:
    - RA diagnosis
    - Safety (infections, carcinoma, etc., shown or expected to be biologics related event)
    - Co-morbidities; diagnoses that are related to RA
  - Non-RA-related visits and cost
  - Total visits and costs
  - Propensity scoring used in all cost estimates

# ABR-Key Demographics

| | Total = 1222 |
|---|---|
| Age | 55 (13.5) |
| Females % | 72 |
| Symptom duration (pre-biologic) (years) | 14 (11.2) |
| Disease duration (pre-biologic) (years) | 12 (10.4) |
| Baseline HAQ | 1.5 (0.7) |
| Baseline DAS | 5.7 (1.5) |
| Baseline EQ-5D | 0.57 (0.23) |
| No of DMARDs | 3.3 (1.2) (0-9) |

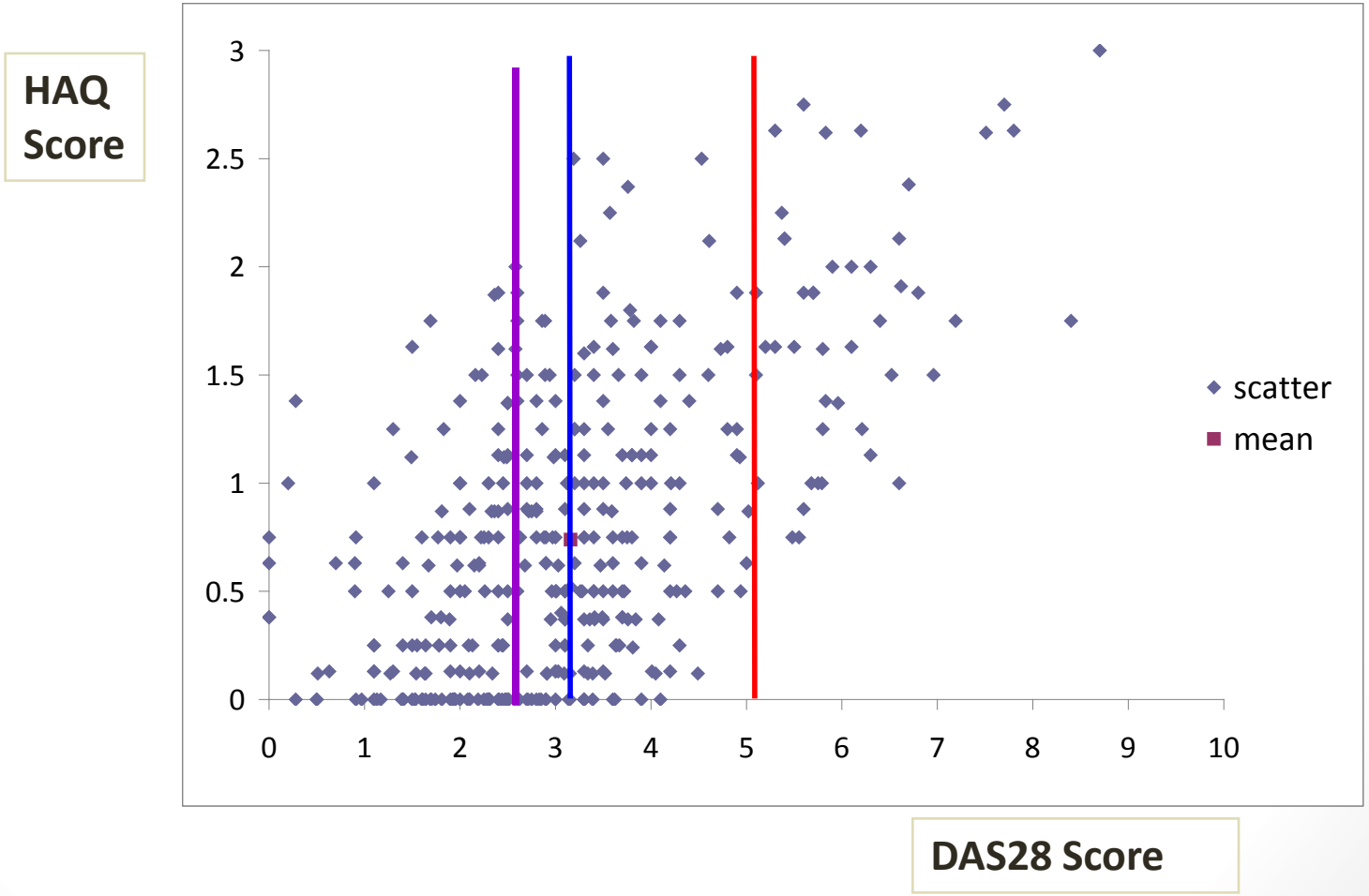
# Results - Outcomes

**Distribution of the HAQ and DAS 28 scores at baseline.**

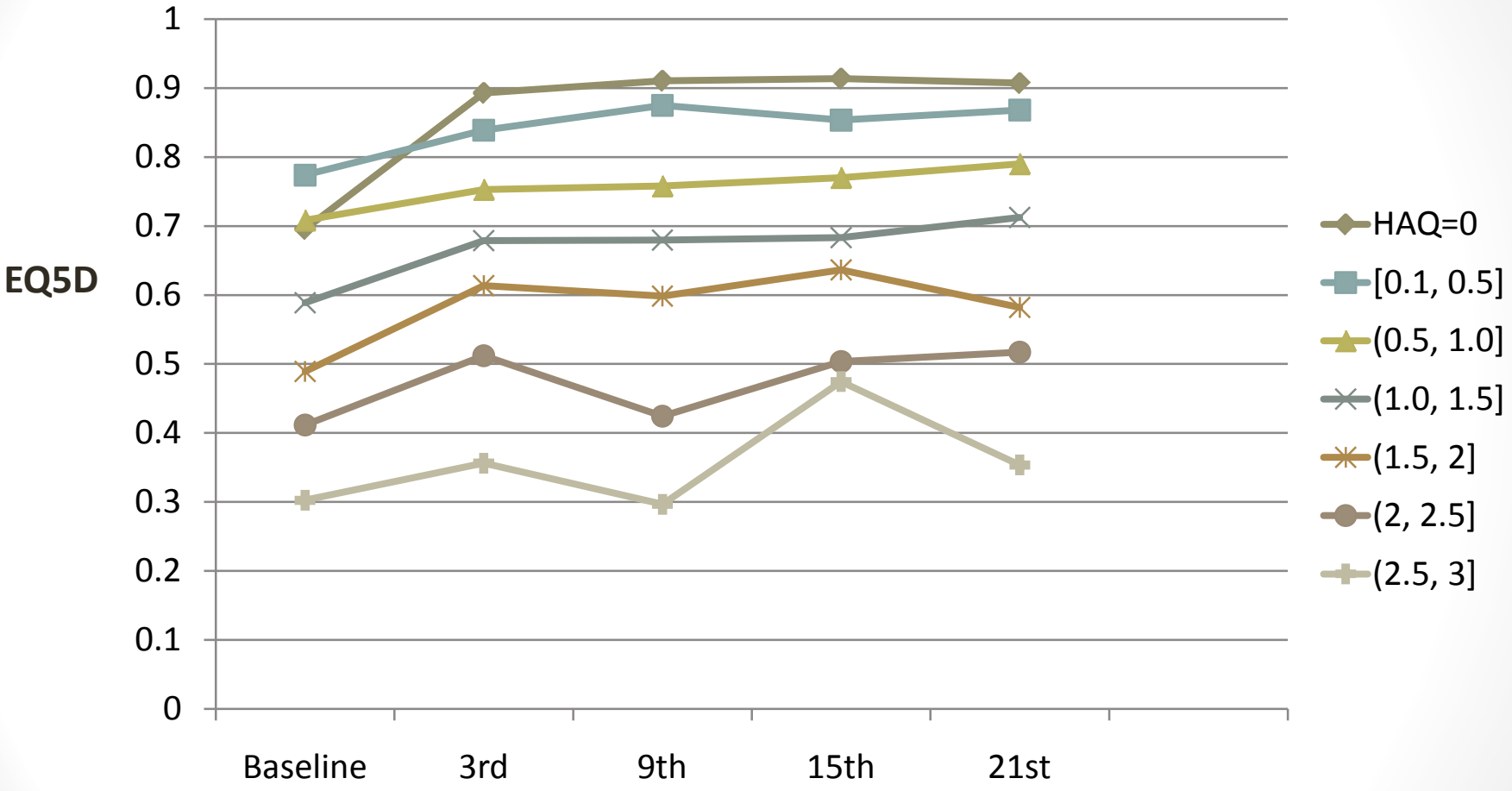


# Results - Outcomes

## Distribution of the HAQ and DAS 28 scores at 21 months



# Change in QOL by HAQ category




The DAS28 has minimal additional impact on HRQOL data categorized by the HAQ score and is therefore much less relevant for economic modelling than the HAQ. ⟹ **Formulary decisions**

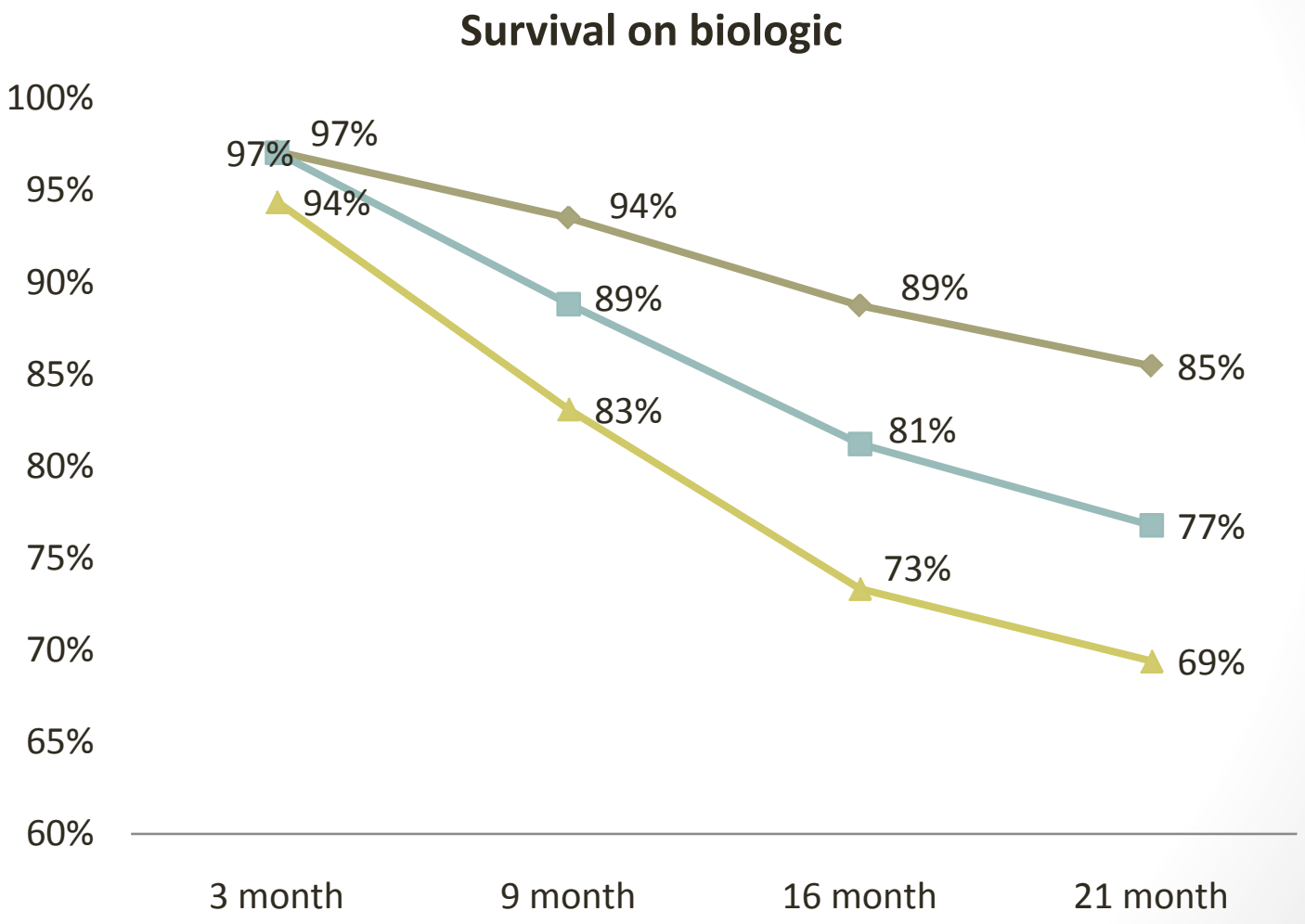
Ohinmaa et al. ACR 2009, 1206

# Results - Outcomes

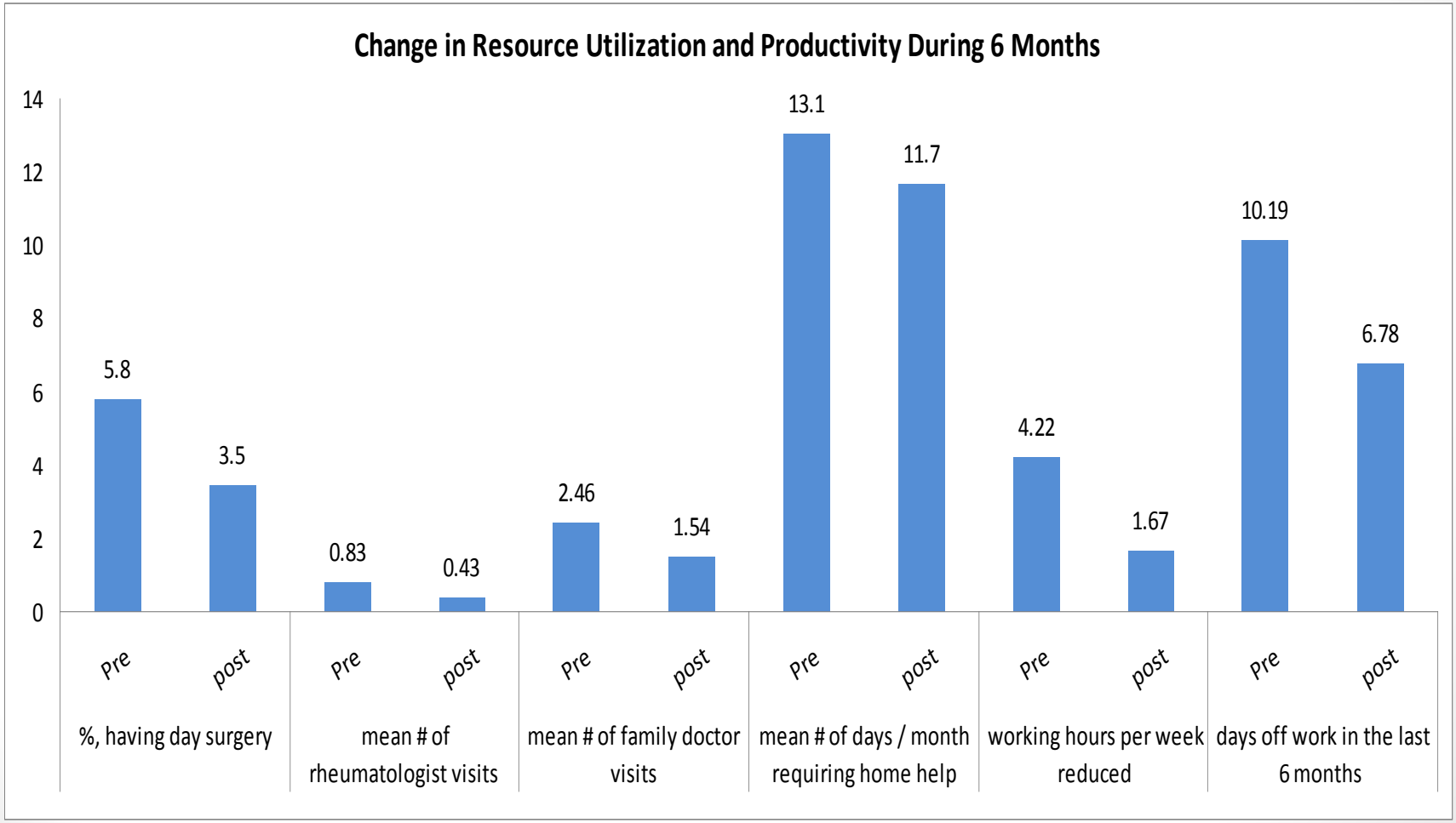
**Table 1. Remission status classified according to the DAS28 score.**

| | DAS28 Score | Duration | # of Patients |
|---|---|---|---|
| **Sustained Remission** | **≤ 2.6** | **> 6 months** | **n = 271 (26%)** |
| **Sustained Low Disease Activity** | **> 2.6 to ≤ 3.2** | **> 6 months** | **n = 87 (8%)** |
| **Brief Remission** | **≤ 2.6** | **≤ 6 months** | **n = 222 (21%)** |
| **No Remission** | **≥ 2.6** | **continuous** | **n = 470 (45%)** |

# Survival on First anti-TNF



# Resource utilization and change in working time pre- and post (15 months)-biologics

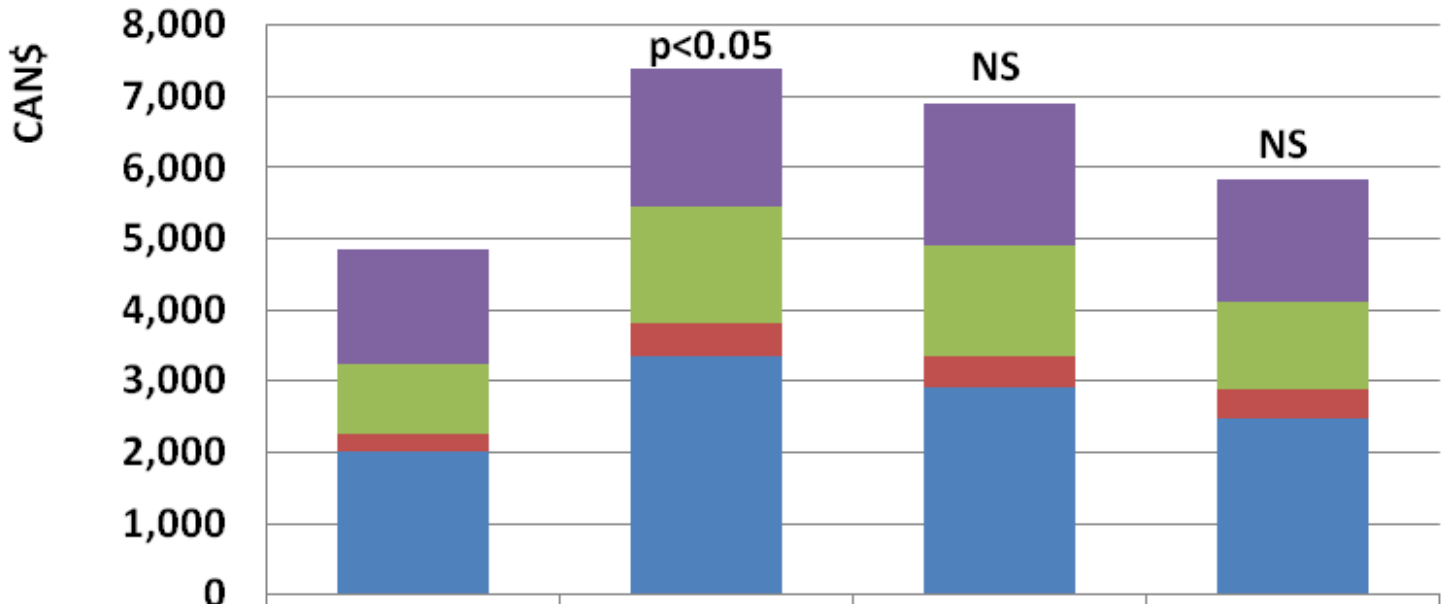



Maksymowych et al. ACR 2008, 1005

# Health Care Services and Their Costs

(Ohinmaa et al. Arthritis Care Research 2014 online)

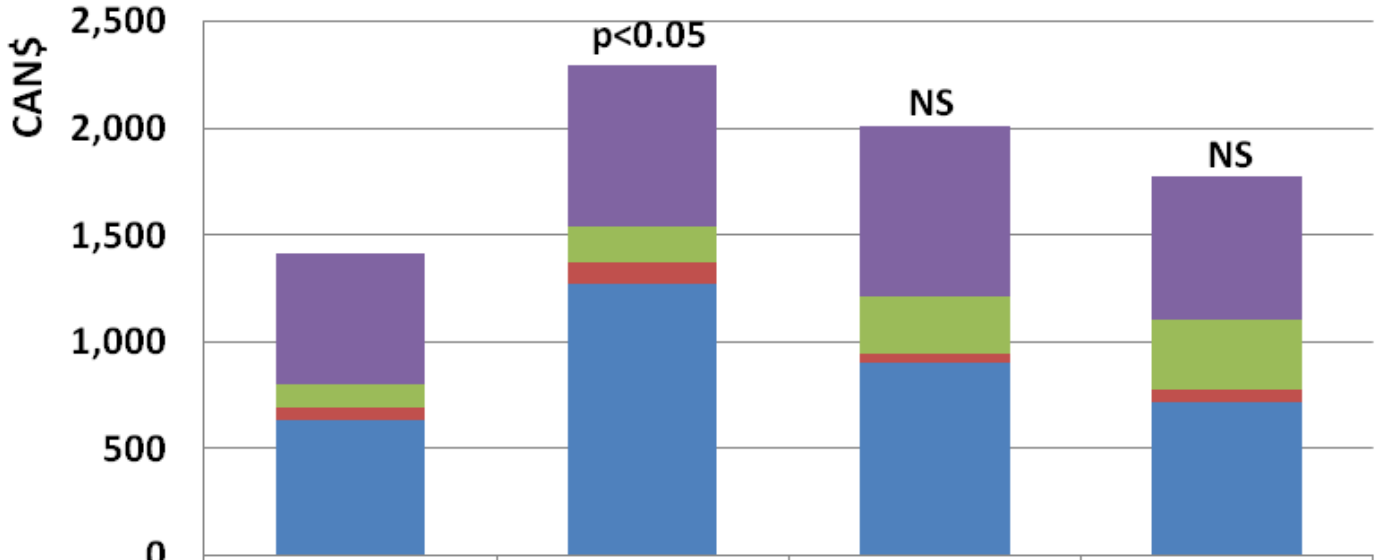
# Total health care costs by type of service in four treatment groups




| | Anti-TNF-only | Anti-TNF, switch | DMARD-only | DMARD switch |
|---|---|---|---|---|
| Physician cost | 1,617 | 1,936 | 1,997 | 1,722 |
| Outpatient clinic cost | 986 | 1,631 | 1,558 | 1,231 |
| Emergency room cost | 238 | 458 | 434 | 393 |
| Hospital cost | 2,008 | 3,349 | 2,909 | 2,486 |

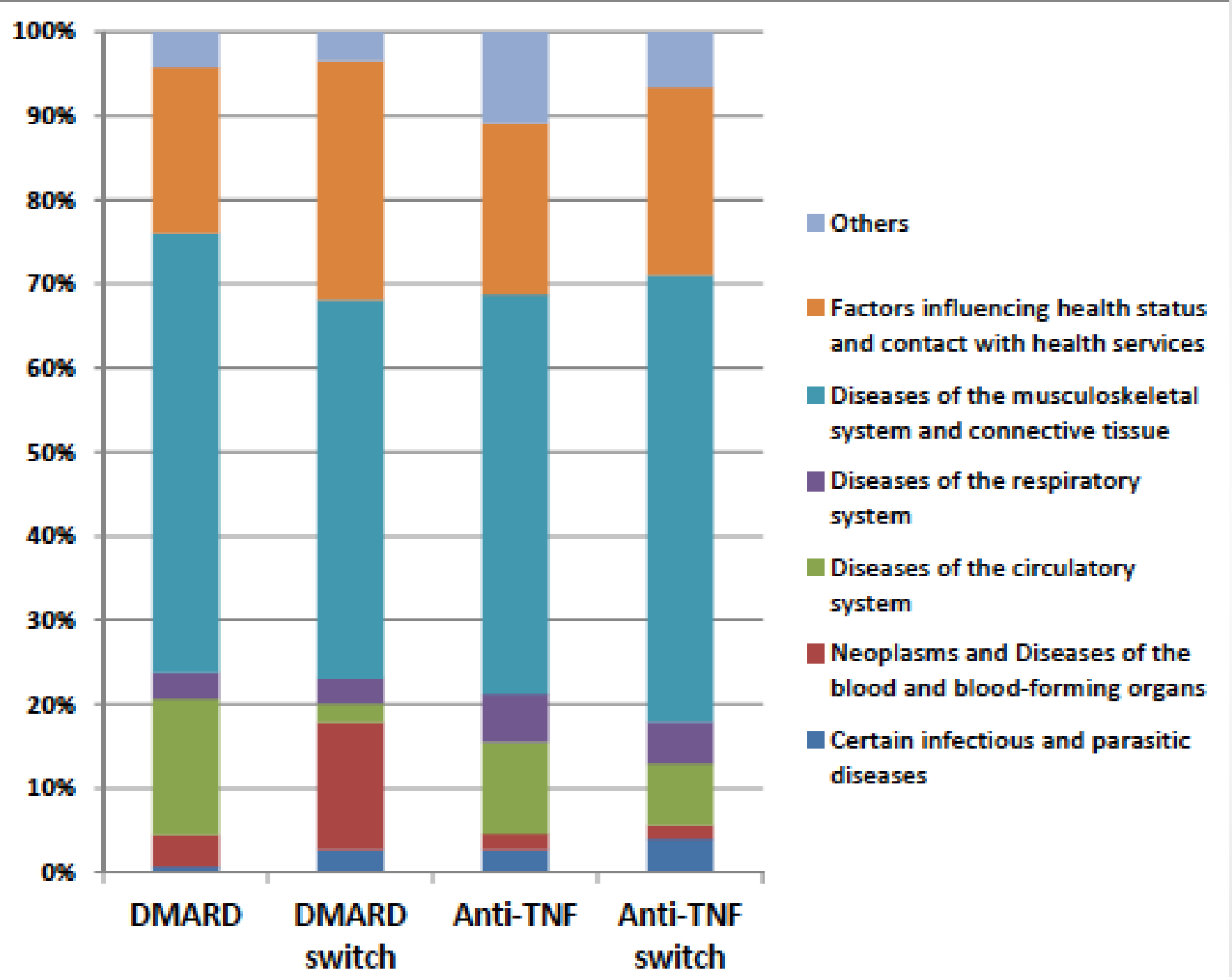
NS = Statistically not significant

# RA-related health care costs by type of service in four treatment groups

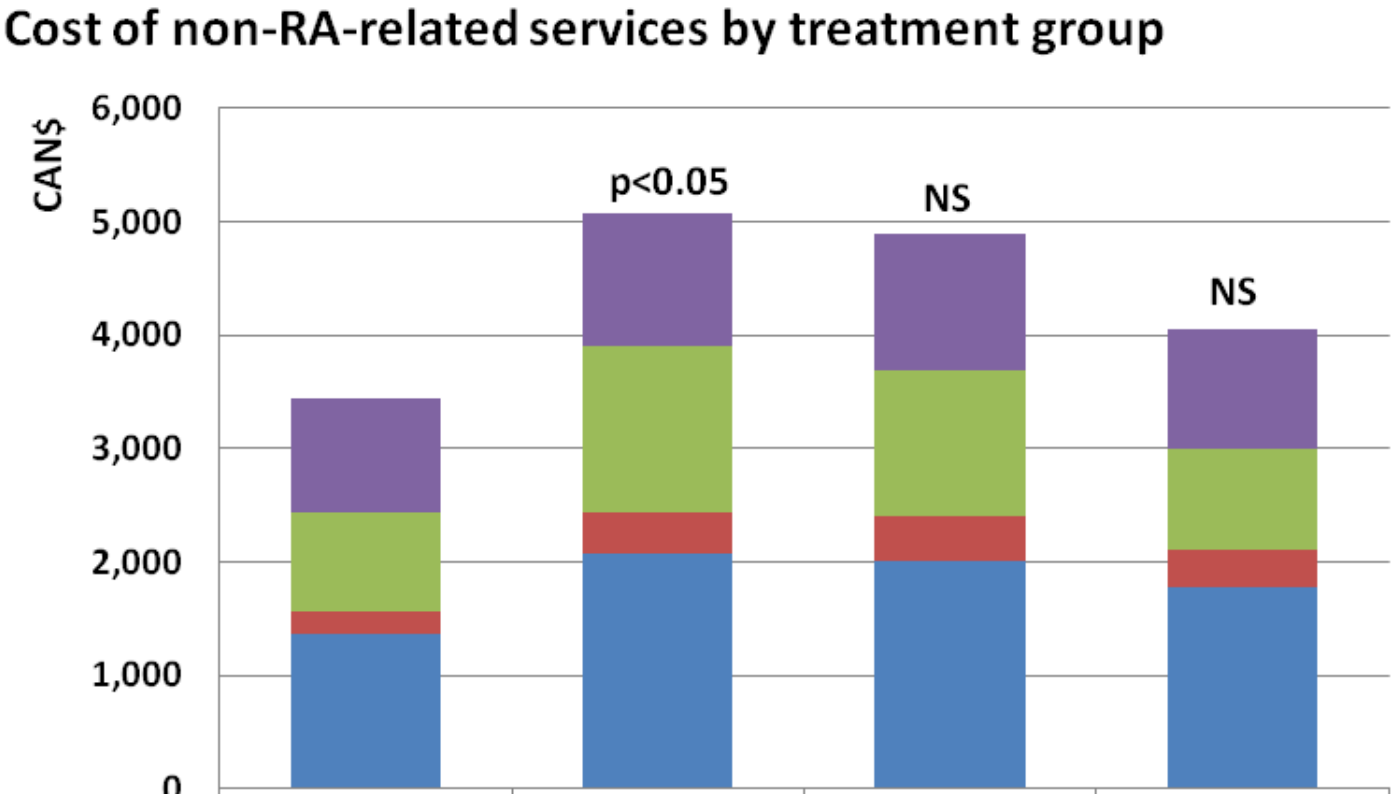



| | Anti-TNF-only | Anti-TNF, switch | DMARD-only | DMARD switch |
|---|---|---|---|---|
| Physician cost | 614 | 753 | 798 | 669 |
| Outpatient clinic cost | 108 | 172 | 263 | 329 |
| Emergency room cost | 53 | 102 | 43 | 60 |
| Hospital cost | 636 | 1,268 | 903 | 717 |

NS = Statistically not significant


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
DMARD
DMARD switch
Anti-TNF
Anti-TNF switch
Others
Factors influencing health status and contact with health services
Diseases of the musculoskeletal system and connective tissue
Diseases of the respiratory system
Diseases of the circulatory system
Neoplasms and Diseases of the blood and blood-forming organs
Certain infectious and parasitic diseases

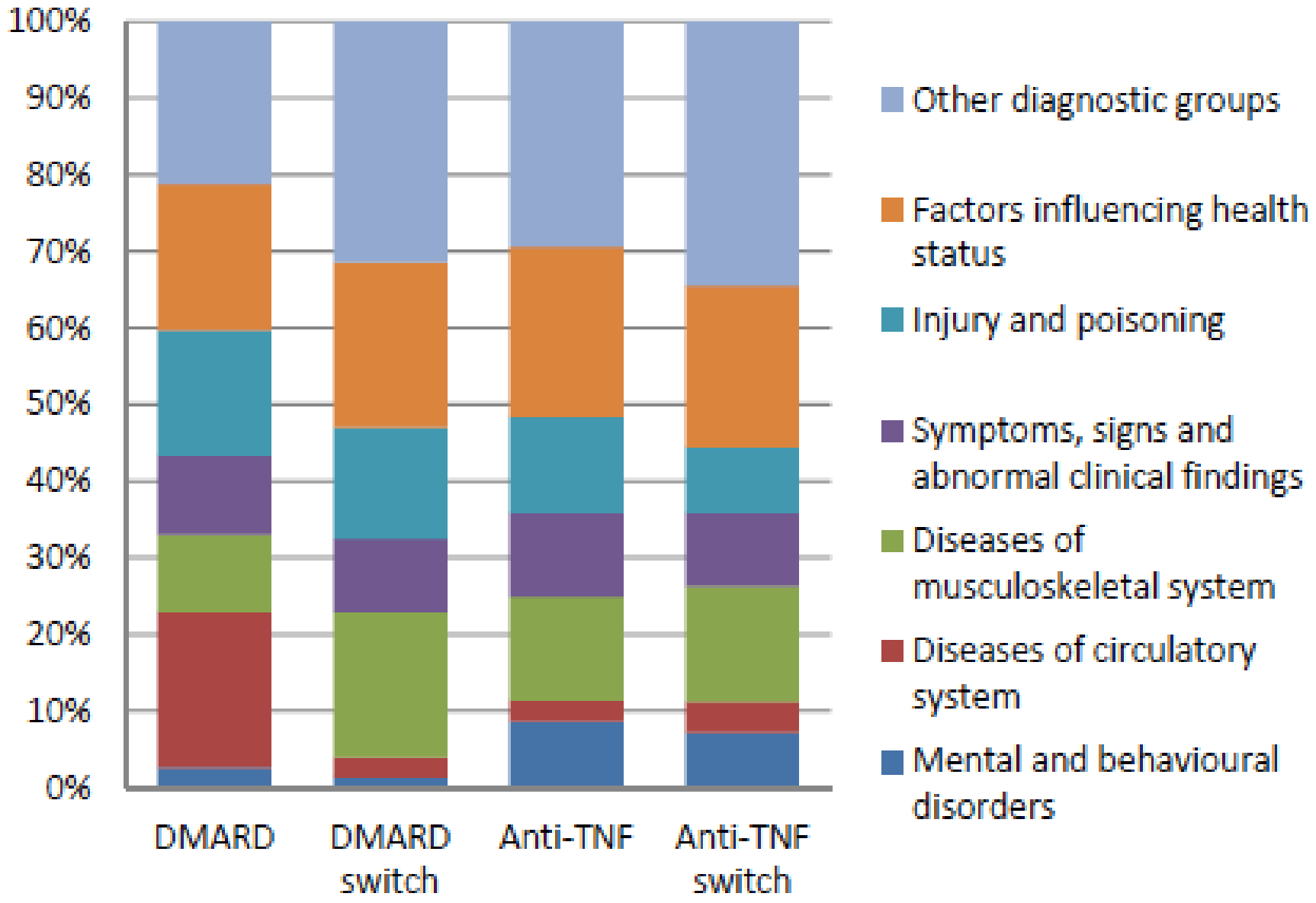
# Non-RA-related health care costs by type of service in four treatment groups



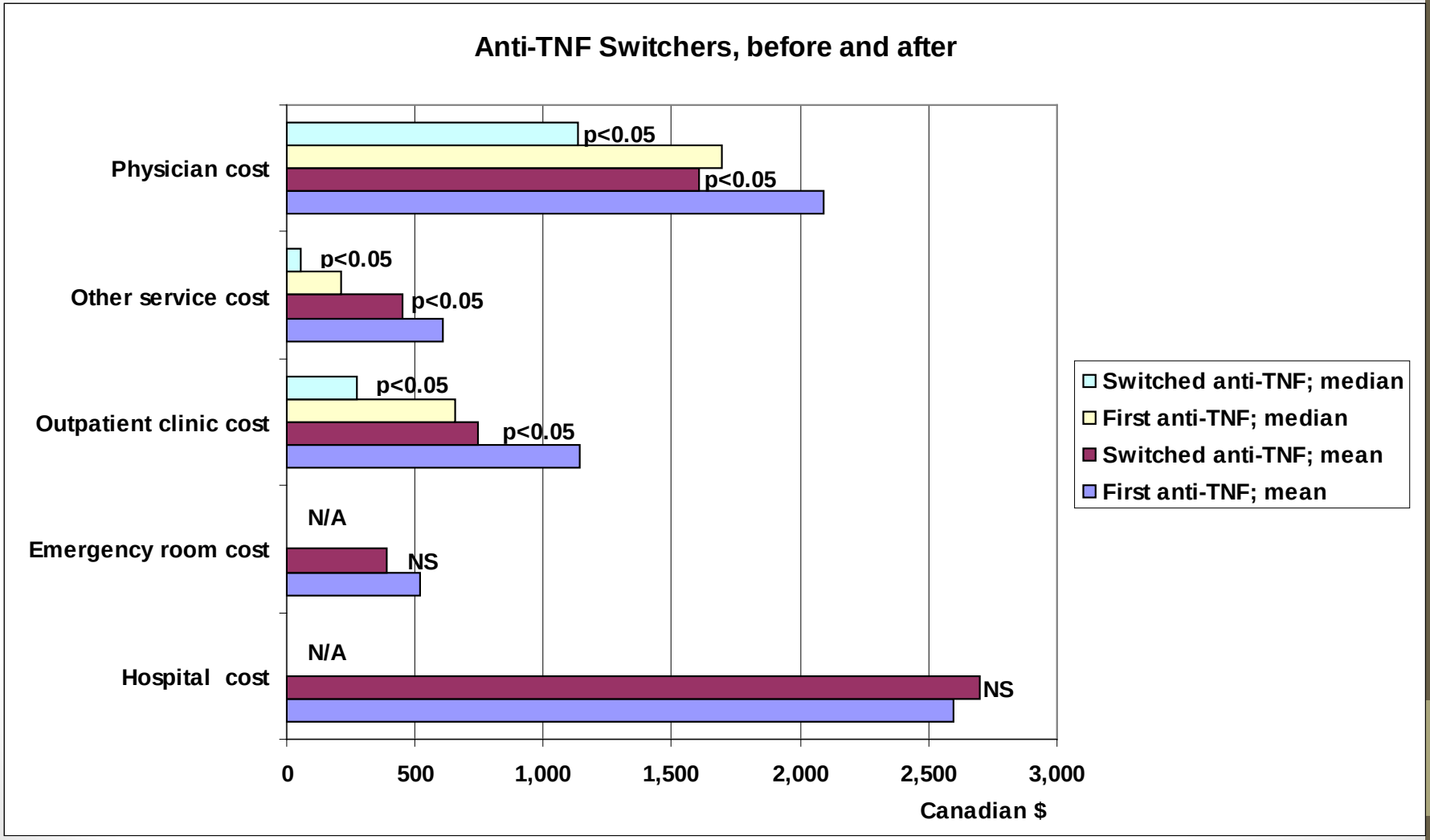

| | Anti-TNF-only | Anti-TNF, switch | DMARD-only | DMARD switch |
|---|---|---|---|---|
| Physician cost | 1,004 | 1,184 | 1,199 | 1,053 |
| Outpatient clinic cost | 877 | 1,459 | 1,295 | 902 |
| Emergency room cost | 185 | 356 | 390 | 332 |
| Hospital cost | 1,372 | 2,081 | 2,006 | 1,769 |

NS = Statistically not significant

# Distribution of non-RA related costs

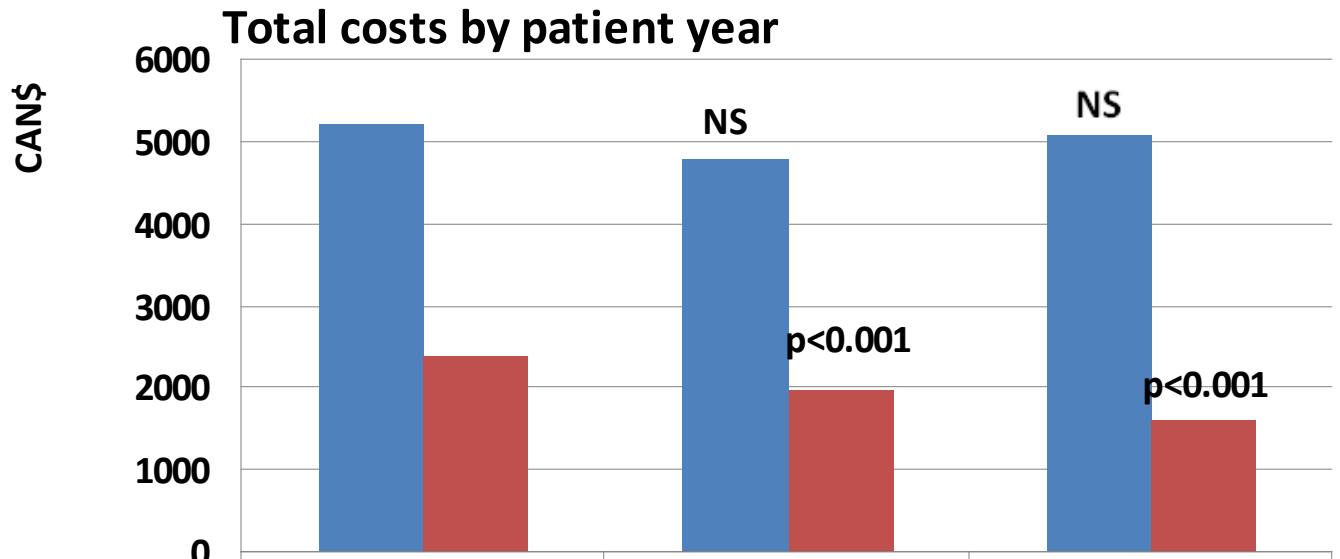


# Mean and median costs by service category for anti-TNF switchers during the first and following anti-TNF agents




NS = statistically not significant; N/A medians zero in both groups

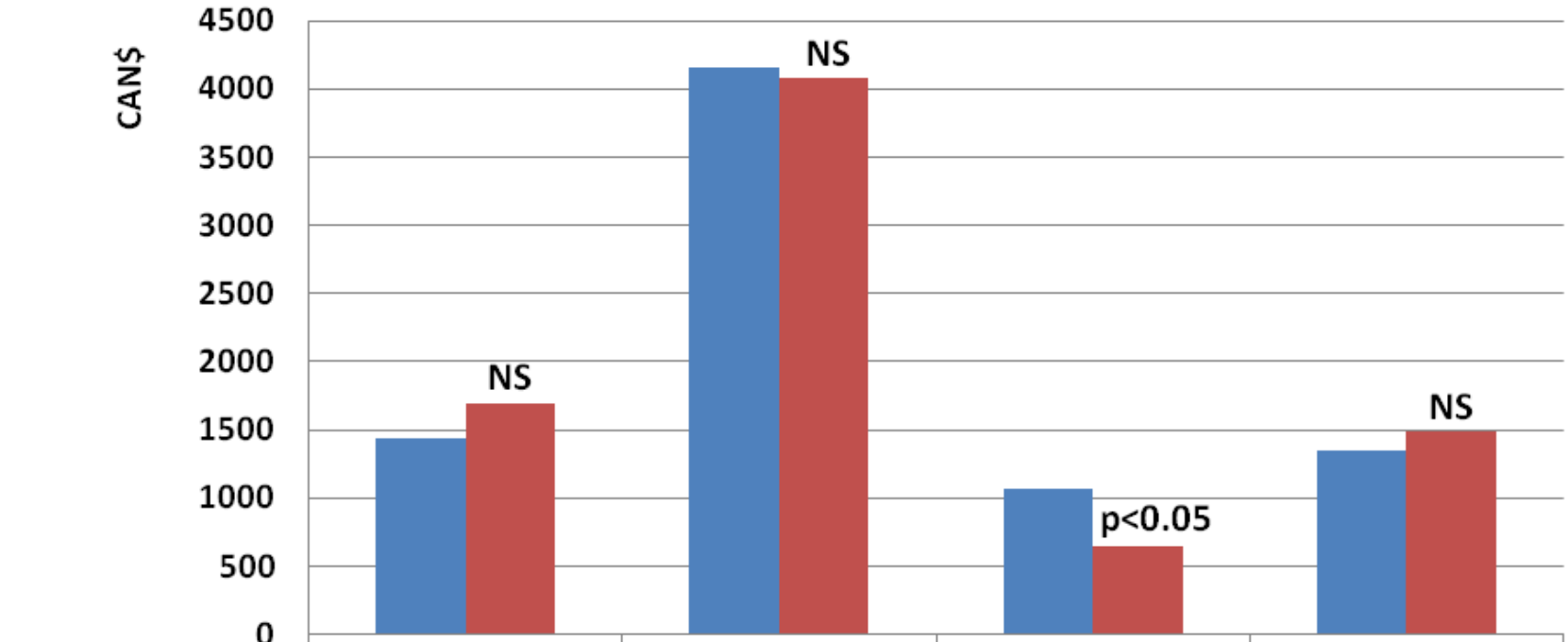
# First anti-TNF only mean and median total costs by the duration of treatment




| | First year | Second year | Third year |
|---|---|---|---|
| Mean cost / patient year | 5227 | 4797 | 5107 |
| Median cost / patient year | 2412 | 1964 | 1630 |

NS = Statistically not significant

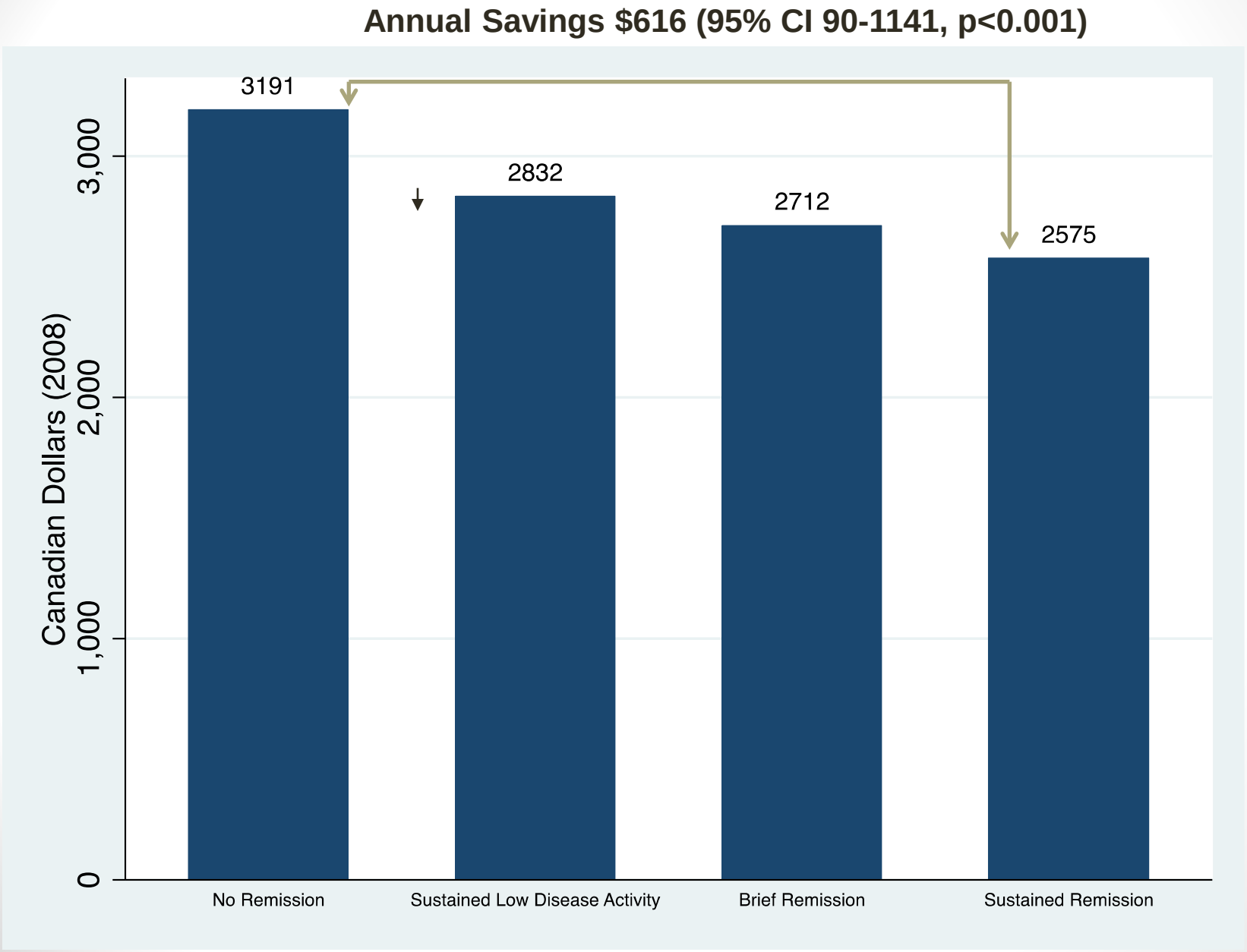
# Mean and median RA-related and non-RA-related costs for DMARD patients switching to anti-TNF




| | RA-related, Mean | Non-RA-related, Mean | RA-related, Median | Non-RA-related, Median |
|---|---|---|---|---|
| Before (DMARD) | 1441 | 4159 | 1069 | 1342 |
| After (Anti-TNF) | 1693 | 4084 | 644 | 1486 |

NS = Statistically not significant

# Median Annual Healthcare Costs, Stratified by Treatment Response and Duration of Response



# RA-related Costs by HAQ Categories

| HAQ-score categories | N | Mean Cost | RA-Related % |
|---|---|---|---|
| 1) HAQ-score from 0.0 to 0.5* | 421 | 4,300 | 32% |
| 1) HAQ-score from 0.6 to 1.0* | 149 | 5,300 | 27% |
| 1) HAQ-score from 1.0 to 1.5* | 126 | 5,900 | 33% |
| 1) HAQ-score from 1.6 to 2.0* | 61 | 10,300 | 28% |
| 1) HAQ-score from 2.1 to 3.0* | 27 | 14,800 | 30% |
| 6) Other | 137 | 7,200 | 27% |
| 7) Unknown | 165 | 5,500 | 30% |
| Total | 1086 | 5,765 | 30% |

* States have lasted at least 6 months

# Health Care Utilization

**Safety-related health care use by type of service and treatment group for 100 patient years.**

| | Anti-TNF-only | Anti-TNF, switch | DMARD-only | DMARD switch |
|---|---|---|---|---|
| Hospitalizations | 2.8 | 5.9 | 4.8 | 3.8 |
| Emergency room visits | 9.8 | 19.0* | 16.7 | 18.2 |
| Outpatient clinic visits | 8.9 | 12.1 | 18.1 | 9.7 |
| Physician visits | 186.3 | 242.5 | 291.2 | 141.1* |

* $p<0.05$; different from anti-TNF only group

# Conclusion

- 77% of the patients remained on their first anti-TNF agent
- Staying on the first anti-TNF significantly reduces utilization of health services compared to patients switching anti-TNF drugs.
- Due to small sample sizes, the comparison of patients remaining on DMARD and switching to an anti-TNF agent did not show significant differences.
- Those remaining on DMARD treatment had a tendency to have higher health care cost compared to patients with a successful first anti-TNF drug.
- Many patients who switched had beneficial long term effects both on health care utilization and HRQOL

# Conclusion

- RA-related service utilization and costs were less than one-third of total yearly patient costs
- Non-RA-related costs were significantly higher among anti-TNF switchers than in the group of the first anti-TNF only patients
- Within RA-related services and costs most of the variation between groups was in the category RA diagnosis
- Differences between safety and co-morbidity diagnosis related services between groups were small.

# Conclusion

- For a large proportion of RA patients, anti-TNF provided improvement in their health status, and a long term reduction in health care utilization and cost.
- However, the mean health care cost data was skewed by several patients with a very high service utilization, especially for non-RA-related diagnosis.
- Long term follow-up will provide better understanding of the relationship between RA treatment outcomes and service utilization and costs.

# Operational Lessons Learned

- **Patients: >95% participation (public/private plans)**
  - Education/reassurance
  - adherence to Tx (especially co-therapy)
  - Immediate access to diverse spectrum of arthritis care
- **Rheumatologists: initial skepticism ⟶ expectation**
  - Simplicity
  - Seamless integration with health care delivery
  - Focus on needs of all rheumatologists
    - removal of “hassle” factor,
    - early warning system for AE,
    - patient education, reinforcement of informed consent, information resource for other health care providers

# Operational Lessons Learned

- Does not work with “ad hoc” funding model
- Administrators/managers don’t understand “clinical ops” and/or we do not communicate the concept adequately
- Capture of outcomes should be integrated into work-flow
- Needs to be rheumatologist designed, owned, and delivered

# The End

- What you have heard is the ‘End of the Beginning’
- We are now entering a new era of biologic therapy
- Long term effects of reference biologics are still unknown
- Subsequent entry biologics are here
- New biologic therapies with different targets are being developed
- Oral agents are here – Tofacitinib

# The End

- Costs of these agents is a growing concern
- We are becoming aware of insurance companies interfering with care
  - trying to direct patients to be treated with certain agents as a first choice!
  - Demanding more and more data before approving therapies

# The End

- Subsequent entry biologics (SEBs) present new challenges
- Are they cheaper and if so by how much?
- We do not know how effective they are in the ‘longer’ term
  - Only a small cohort of patients have been studied in RA and AS
- Concerns have been raised about their immunogenicity

# The End

- Tracking products may be difficult
- Generic names will be unhelpful
- WHO organisation has INN system (International Non-proprietary Names)
  - Will not be helpful unless protocol is changed
- Suggestions that brand names be used when prescribing products
- Can lead to issues when giving educational talks where brand names are disallowed!

# The End

- In Europe the EMA has proposed that biosimilars should be monitored through pharmacovigilance programs
- HPB also has intimated that these agents need to be monitored through such programs
- The FDA, in its musings, about also considers monitoring of follow-on-biologics to be important

# The End

- Monitoring patient populations is important
- To date we have been focused primarily on patients with RA
  - Patients with other conditions need to be monitored
- EMA has guidelines on how to develop this type of program
- We have a well developed system in this province
- It is unique across the country and the world
- Funding however is needed to maintain this program