Population based studies on utilisation of angiotensin converting enzyme inhibitors (ACEIs)

Seyed Hamidreza Mahmoudpour
PharmD, PhD candidate

Farmaco-epidemiologie & Klinische Farmacologie

Universiteit Utrecht

PREDICTION ADR

A. Patterns of ACEI prescriptions for different indications

B. Continuation of ACEI therapy, in spite of occurrence of angioedema

Background:

The first ACEI (captopril) came to the market in 1981

Indications:

- Hypertension
- heart failure
- myocardial infarction
- renal failure and nephropathy (diabetic & non-diabetic)

➢ The US: prescribed >150 million times per year since 2006[1]

➢ The Netherlands: ~ 9 million ACEI prescriptions in 2013 [2]

➢ The UK: Ramipril first antihypertensive medication in 2013 24 million prescriptions dispensed in community pharmacies [3]

1. National Prescription Audit PLUS. IMS.2014. http://www.imshealth.com Accessed 1 Dec 2014.2.
2. The drugs and medical devices Information Project (GIP). https://www.gipdatabank.nl Accessed 20 April 2015.
3. Croft K. Prescriptions Dispensed in the Community England 2003-13. Prescribing and Primary Care, Health and Social Care Information Centre; 9 July 2014. 110 p. http://www.hscic.gov.uk .

A) Patterns of ACEI prescriptions for different indications

- Discontinuation of ACEIs:
  - Stop because of ADR (19%)
  - Stop because of non-ADR reason (13.5%) [1]

- Switch of ACEIs:

  - PHARMO data:
    - ✓ 24% of ACEIs starters switched their therapy after 3 years and 75% of them switched to angiotensin receptor blockers (ARBs) [2]

  - CPRD data:
    - ✓ Longer follow up within hypertensive patients, total ACEIs switchers increased up to more than 40% [3]

INDICATION

1. Morimoto *et al* :Journal of Evaluation in Clinical Practice. 2003; 10(4): 499–509
2. Vegter *et al :* American Journal of Management Care. 2011;17(9):609-616
3. Burke *et al :* Journal of Hypertension 2006, 24:1193–1200

Objectives:

The aim of this study is to investigate whether the pattern of ACE-inhibitors use differ between indications in terms of persistence rate, continuation, discontinuation and switching to angiotensin receptor blockers (ARBs)

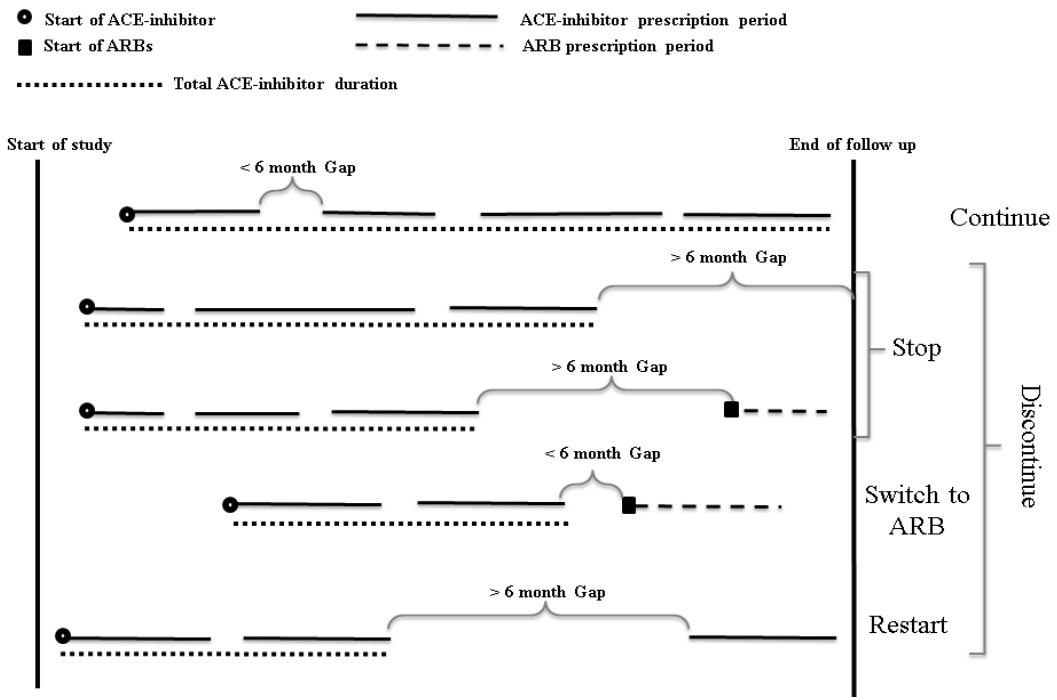
- ✓ Hypertension
- ✓ Heart failure
- ✓ Myocardial infarction (MI)
- ✓ Renal failure
- ✓ More than one indication
- ✓ Non of the above

Methods: Setting & design

- Study design: Retrospective cohort study
- Setting: Clinical practice research Datalink (CPRD)
- Study population: > 45 years, start ACEIs: Jan 1st 2007 Jan 1st 2014.
- index date: First ACEI prescription.
- Exclusion criteria: <12 months of prescription history before index date and <6 months after.
- Follow up duration: Death, moving out of study, or end date of study (Jan 1st 2014),
- Indication: Any time before or 1 year after start of ACEI based on the medical read codes

Methods: Prescription pattern

1. Continuation
2. Discontinuation of ACEIs → Stop / Switch to ARB / Restart



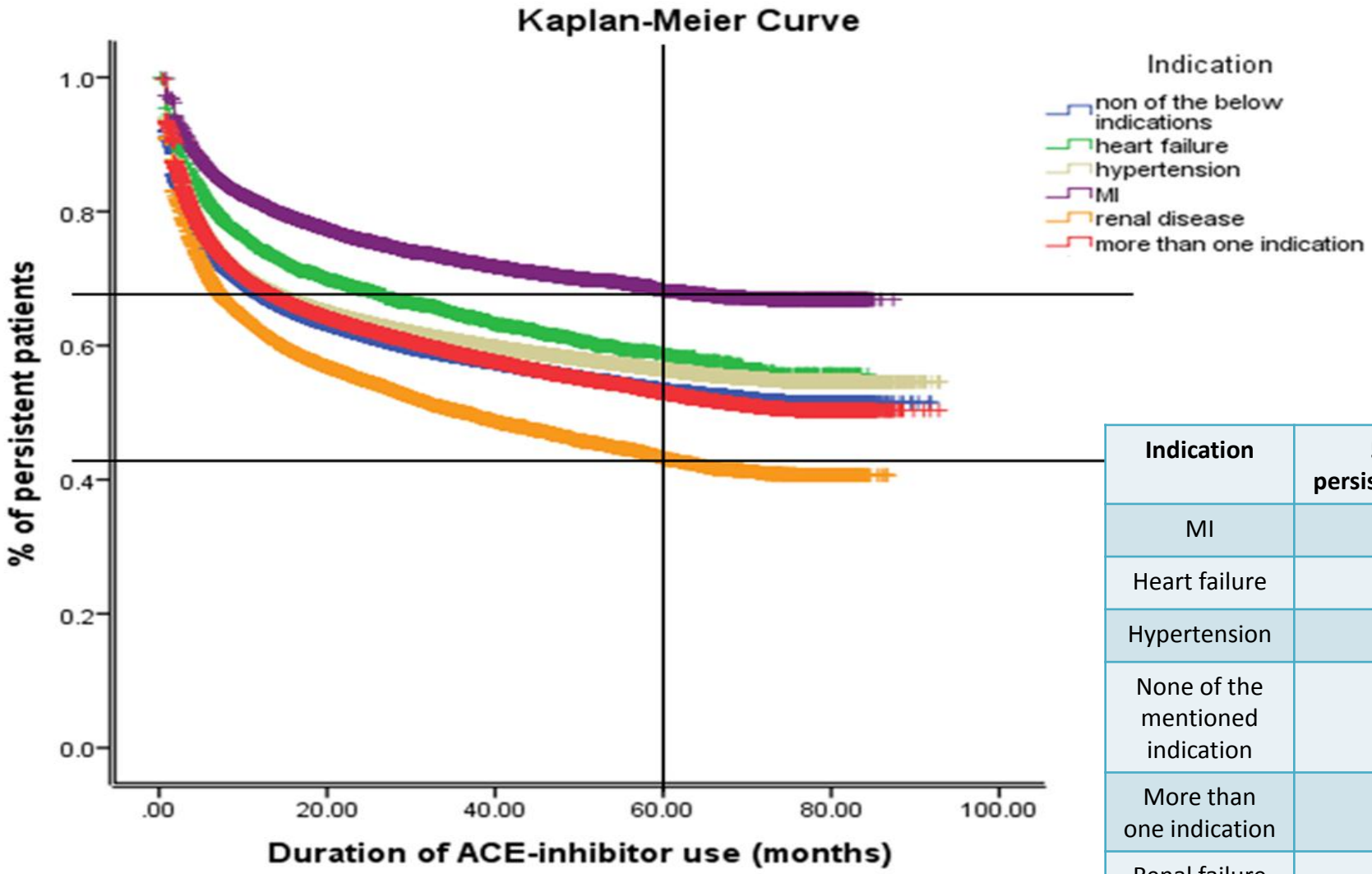
- 5-year persistence was calculated using the Kaplan-Meier method.
- Times to discontinuation were compared using the Log-Rank test.

Results:

- Totally 254,002 ACEI starters were included in the study.

Characteristics	Heart failure 1.5%	Hypertension 57.6%	Myocardial infarction 4.2%	Renal disease 3.7%	More than one indication 17.2%	None of the mentioned indications 15.8%	Total 100%
Mean age [1] (years)[SD]	72.1[11.8]	62.7[11.0]	64.1[11.1]	72.6[11.0]	73.4[10.8]	64.1[11.5]	65.3 [11.9]
Sex (%male)	60.1%	50.1%	76.2%	43.5%	45.0%	58.0%	51.5%
Mean follow up (months) [SD]	35.2 [20.9]	43.7[22.2]	39.2[21.9]	41.8[22.6]	43.7[23.0]	39.1[21.9]	42.6 [22.4]
Mean ACE-inhibitor duration (months) [SD]	25.0 [21.5]	28.8[25.1]	30.5[23.3]	23.6[23.3]	28.1[25.1]	24.9 [23.2]	27.9 [24.7]
Percentage of death	21.5%	4.2%	7.1%	13.8%	15.4%	7.4%	7.3%

Results:



Indication	5-year persistence rates
MI	68.2%
Heart failure	58.6%
Hypertension	56.4%
None of the mentioned indication	53.4%
More than one indication	53.0%
Renal failure	43.2%

Results:

Total (N=254,002) 100%	Persistent (N=153,212) 60.3%	
	Non-persistent (N=100,794) 39.7%	Stop(N=45,676) 45.3%
		Switch to ARB (N=37,421) 37.1%
		Restart(N=17,693) 17.6%

indication	Non-persistent (%)
Heart failure (N=3,762)	33.4%
Hypertension (N= 146,275)	39.4%
Myocardial infarction (N= 10,639)	26.4%
Renal failure (N= 9,299)	49.2%
More than one indication (N= 43,753)	41.6%
None of the mentioned indication (N= 40,274)	40.5%

- In total: MI lowest 26.4 & renal failure highest 49.2% probability to discontinue.
- Restart: not different considerably from 15% in heart failure to 18.1% in the non of mentioned group
- Within non-persistent: switching to ARBs ranged from 27.6% in renal disease to 42.2% in MI

Conclusion & Suggestion:

- In total population, 40% stop ACEI therapy
  - 37% of them switch to ARBs

preventable [1]

- Different indications ⟶ different rates of ACEI discontinuation.

- Renal failure & heart failure are most likely to discontinue treatment.

1. Mahmoudpour *et al* :International Journal of Clinical Pharmacy. 2015 Jul 10 DOI 10.1007/s11096-015-0159-3

B) Continuation of ACEI therapy, in spite of occurrence of angioedema

- Life-threatening angioedema
- incidence ≈ 0.2%
- mostly larynx or tongue[1]
- Continuing ACEI after angioedema ↑ recurrence risk
- reaction is more severe [2]

1. Inman *et al* :Post-marketing surveillance of enalapril. I: Results of prescription-event monitoring. BMJ. 1988; 297:826-829.
2. Brown et al :Recurrent angiotensin-converting enzyme inhibitor--associated angioedema. JAMA 1997; 278:232-233.

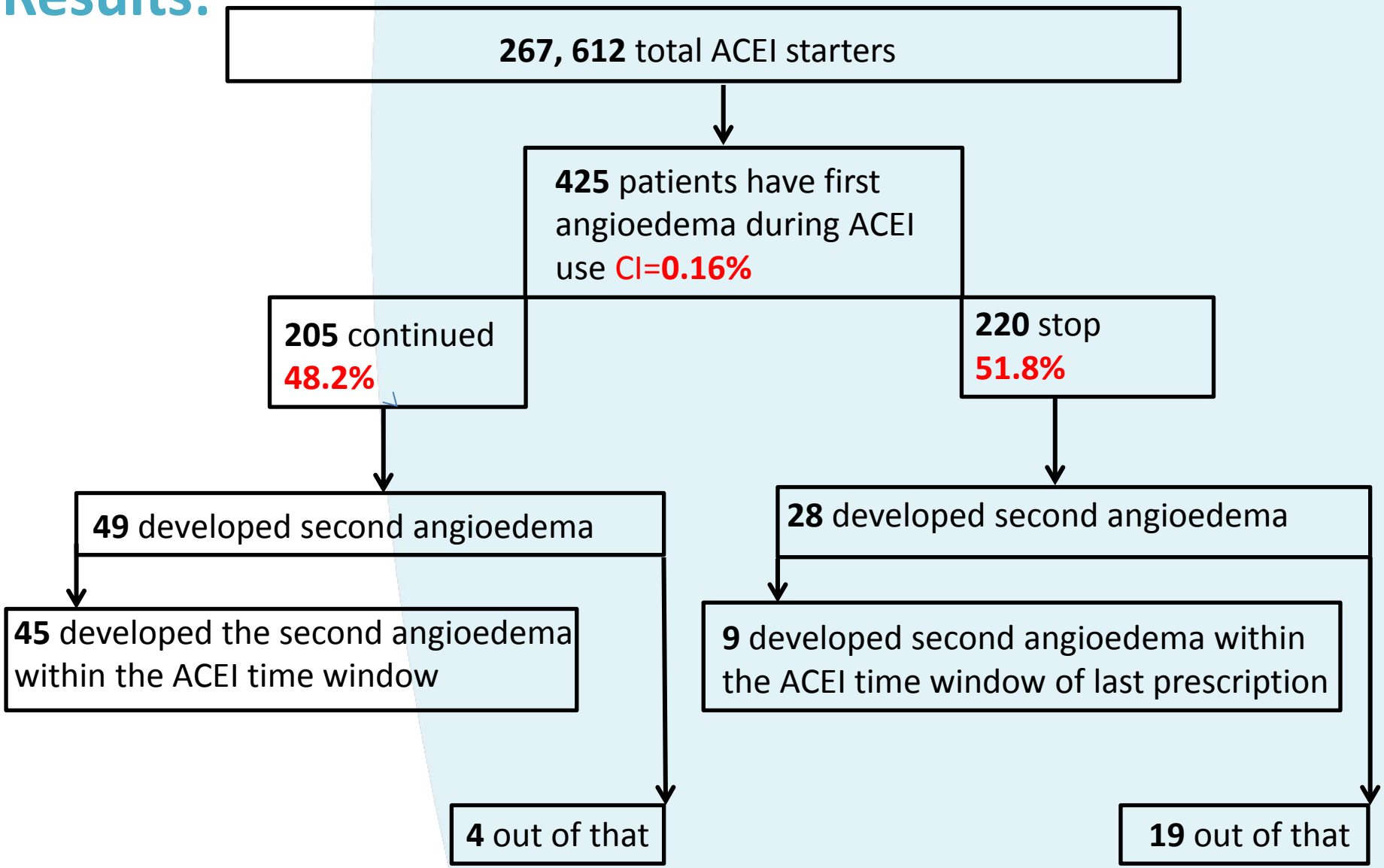
Objectives:

The aim of this study is to evaluate the discontinuation of ACEI use after the occurrence of angioedema and the probability of a recurrent event

Methods: Setting, Design & Analyses

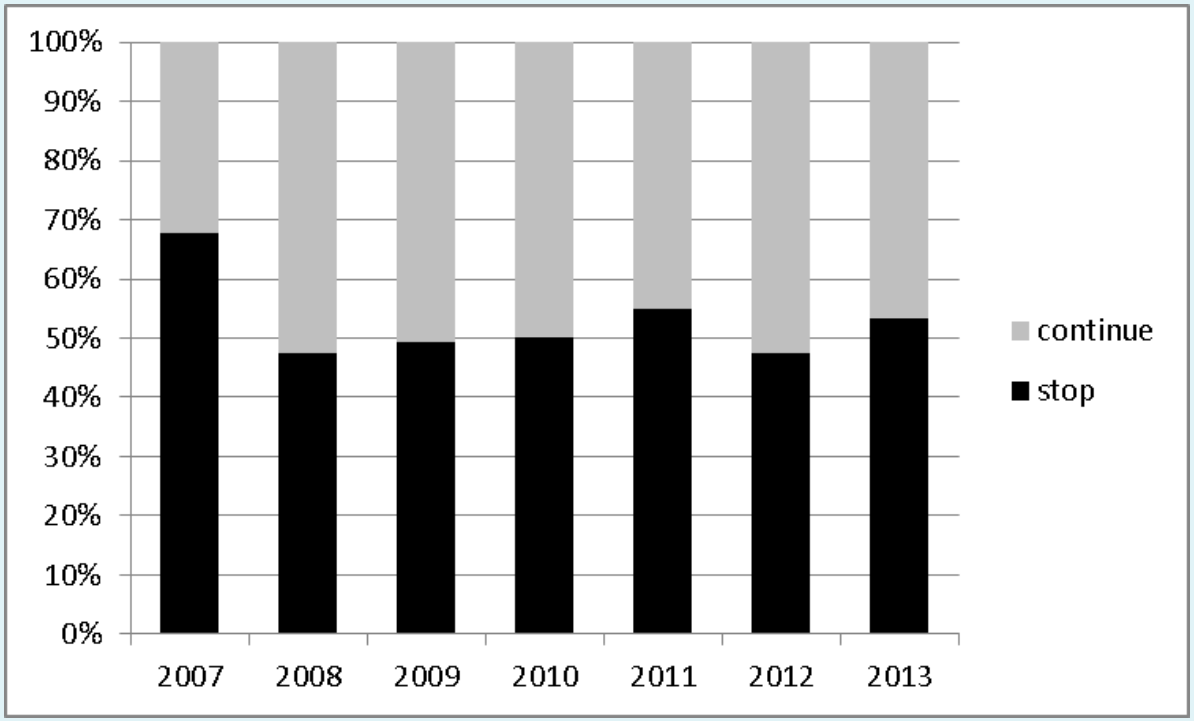
- Setting: Clinical practice research Datalink (CPRD)
- Prescription duration: Quantity of medication divided by the number of daily doses extended by 10% for non-adherence.
- The first ever registered angioedema during ACEI use time window
- Two angioedema within 7 days were classified as the same event
- Cumulative incidence (CI) of angioedema
- Continued ACEI : Received at least one ACEI prescription after the angioedema event
- Kaplan-Meier curves of the second events

Results:


267, 612 total ACEI starters
425 patients have first angioedema during ACEI use CI=**0.16%**
205 continued **48.2%**
220 stop **51.8%**
49 developed second angioedema
28 developed second angioedema
45 developed the second angioedema within the ACEI time window
9 developed second angioedema within the ACEI time window of last prescription
4 out of that
19 out of that

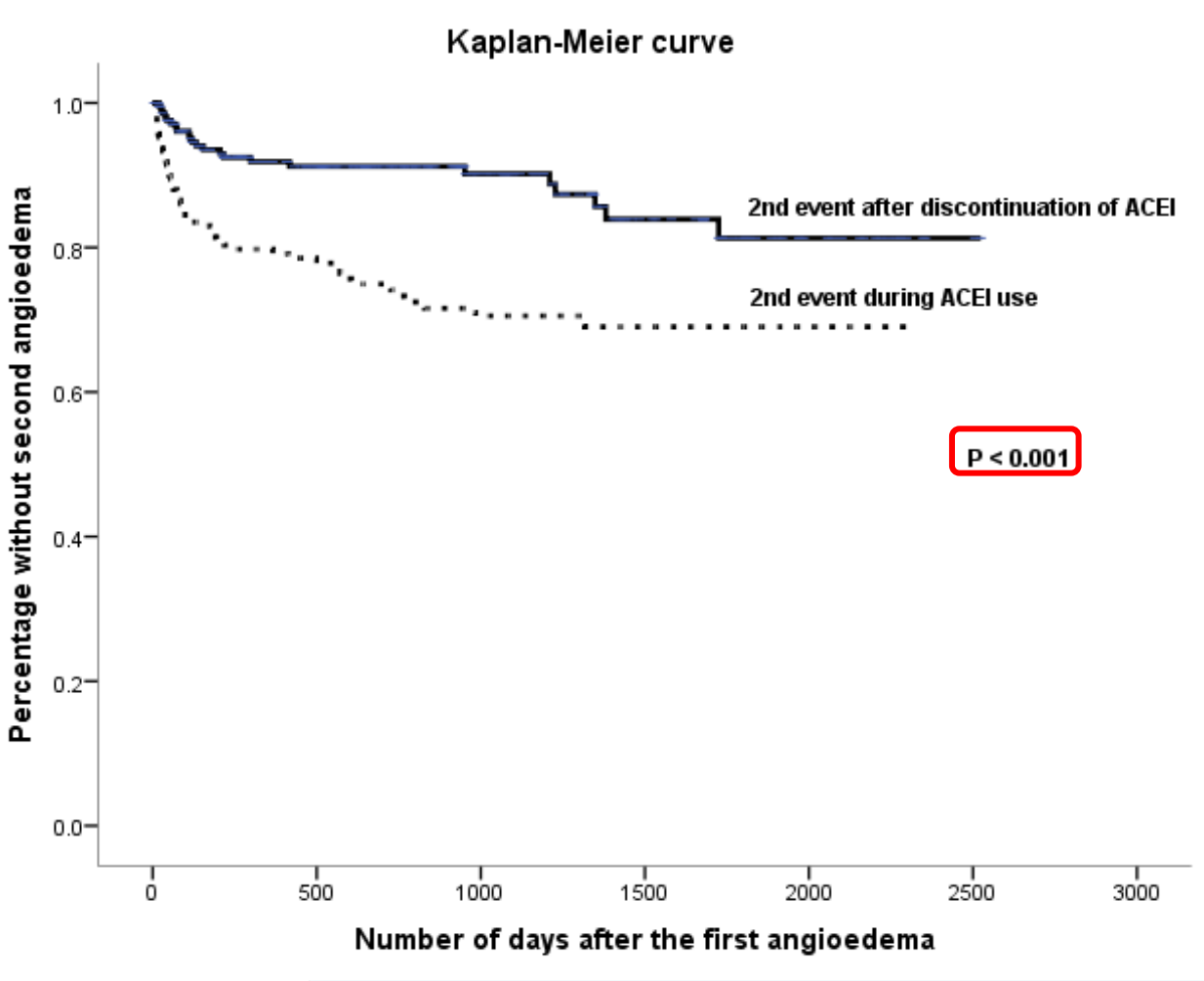
Results:

The yearly percentage of patients who continued ACEI therapy after a first angioedema



Results:

Comparing the rate of second angioedema during and after ACEI exposure



Conclusion & Suggestion:

- Almost half of ACEI-related angioedema cases, continue ACEI treatment
- High risk of recurrent angioedema up to 158 times higher for continuous users
- This is particularly relevant because recently it has been shown that angioedema itself can potentially harm the heart and coronary arteries[1] [2]

1. Kounis *etal*. The heart and coronary arteries as primary target in severe allergic reactions: Cardiac troponins and the Kounis hypersensitivity-associated acute coronary syndrome. Int J Cardiol 2015; 198:83-84.
2. Lippi G *etal*. Cardiac troponin I is increased in patients admitted to the emergency department with severe allergic reactions. A case-control study. Int J Cardiol 2015; 194:68-69.

Future plan:

A. Comorbidities/co-medications associated with ACEI switching/angioedema

B. Clinical outcome after switching of ACEI therapy to ARBs

Acknowledgments:

Prof. Folkert W Asselbergs
Prof. Anthonius de Boer
Dr. Ingrid Terreehorst
Dr. Patrick C Souverein
Dr. Anke-Hilse Maitland-van der Zee

International Journal of Cardiology 201 (2015) 644–645

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Continuation of angiotensin converting enzyme inhibitor therapy, in spite of occurrence of angioedema

Seyed Hamidreza Mahmoudpour [a], Folkert W. Asselbergs [b], Ingrid Terreehorst [c], Patrick C. Souverein [a], Anthonius de Boer [a], Anke H. Maitland-van der Zee [a,*]

[a] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, The Netherlands
[b] Department of Cardiology, Division Heart and Lungs, University Medical Centre Utrecht, The Netherlands
[c] Department of Otorhinolaryngology, Academic Medical Center, Amsterdam, The Netherlands

Acknowledgments

This research is part of the PREDICTION-ADR project that has received funding from the European Commission's Seventh Framework Programme (FP7) under Grant Agreement No. 602108. The funding source had no involvement in study design, analysis and interpretation of data and the writing of the report.