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

ARTICLE INFO

Article history:
Received 20 July 2015
Accepted 21 August 2015
Available online 25 August 2015

Keywords:
Angiotensin converting enzyme inhibitor
Adverse drug reaction
Prescribing pattern
Drug-induced angioedema

Angiotensin converting enzyme inhibitors (ACEis) are one of the most frequently used groups of medication worldwide, ramipril for instance was the first antihypertensive medication in 2013 with more than 24 million prescriptions dispensed in community pharmacies in the United Kingdom [1]. Life-threatening angioedema is the most severe adverse effect of ACEis with an incidence of approximately 0.2% which mostly occurs at the larynx or tongue [2] and less frequently at the gastrointestinal wall [3]. In patients continuing ACEi use after the first angioedema, the recurrence risk of ACEi-induced angioedema is high and the reaction is more severe [4]. Therefore, cessation of ACEi treatment after the first angioedema is highly recommended [5,6]. However, angioedema induced by ACEis can be misdiagnosed and there is a lack of systematic studies to evaluate the discontinuation of ACEi use after the occurrence of angioedema and the probability of a recurrent event. We therefore investigated ACEi continuation after a first angioedema and the risk of recurrent angioedema using data from the United Kingdom Clinical Practice Research Datalink (CPRD), a primary care electronic medical record database which covers almost 12 million patients in the UK and has been used in numerous drug safety studies; the details and validity of CPRD data has been published previously [7]. The protocol for this study was approved by the independent scientific advisory committee (ISAC) of CPRD. We defined a cohort of patients older than 45 years who newly started ACEi therapy between the 1st of January 2007 and the 1st of January 2014. Subjects were followed up until end of study, death or moving out of the practice area. The theoretical duration of an ACEi prescription was calculated as the quantity of medication prescribed divided by the number of daily doses extended by 10% of the duration of the prescription to take into account non-adherence. The first ever registered angioedema in the medical records for patients was assumed to be an ACEi related angioedema if it was registered during the ACEi use time window; two angioedema events registered within 7 days were classified as the same event. The cumulative incidence with 95% confidence interval (CI) of the first angioedema during ACEi use was calculated. Within the patients with a first ACEi-related angioedema we calculated the proportion of patients that continued ACEi use (received at least one ACEi prescription after the angioedema event) both overall and per year (2007 to 2013). After the first angioedema the cumulative incidences and Kaplan–Meier curves of the second events that happened either during or after ACEi exposure were calculated. All statistical analyses were performed using SPSS 20 (IBM SPSS Statistics for Windows Version 20.0. Armonk, NY: IBM Corp.).

The total cohort consisted of 267,612 ACEi starters, with a mean follow up time of 1197 days (SD 732) and mean ACEi use duration of 826 days (SD 743). There were 425 patients (52.9% male) with a first angioedema during ACEi use: cumulative incidence 0.16% (95% CI 0.15%–0.18%). Of those patients, in total 205 (48.2%) continued ACEis after the first angioedema; this proportion fluctuated between 32.1% and 52.8% from 2007 to 2013 (Fig. 1). Out of those 205 patients who continued ACEi therapy, 45 developed recurrent angioedema during ACEi exposure (cumulative incidence 21.9% (95% CI 16.8%–28.1%)) and in 4 patients the second angioedema occurred after discontinuation of the ACEi. In the 220 patients that did not receive a new ACEi prescription after the first angioedema, 28 developed a recurrent angioedema, cumulative incidence 12.7% (95% CI 8.9%–17.7%). Out of these 28 recurrent events, 9 occurred within the ACEi exposure time of the last prescription prior to the first angioedema. When it is assumed that these patients did not stop treatment after the first event, these 9 events were also ACEi-related recurrent angioedema and the cumulative incidence of recurrent angioedema in patients continuing ACEi would be 25.2% (95% CI 19.9%–31.4%); consequently in patients that discontinued ACEi use the cumulative incidence would be 9% (95% CI 5.8%–13.6%). The Kaplan–Meier curves

* Corresponding author at: Division of Pharmacoepidemiology and Clinical Pharmacology, Department of Pharmaceutical Science, Universiteitsweg 99, 3508 TB Utrecht, The Netherlands.
E-mail address: A.H.Maitland@uu.nl (A.H. Maitland-van der Zee).

http://dx.doi.org/10.1016/j.ijcard.2015.08.185
0167-5273/© 2015 Elsevier Ireland Ltd. All rights reserved.

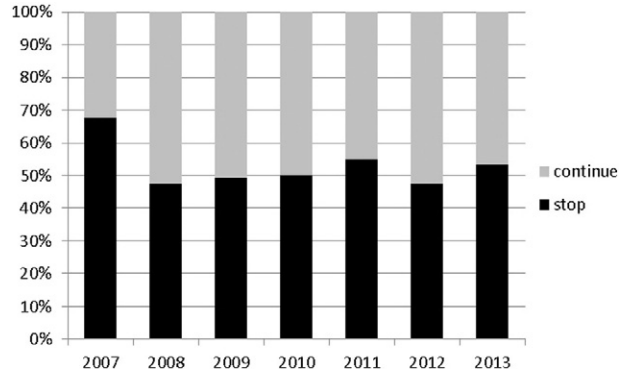

Fig. 1. The yearly percentage of patients who continued ACEi therapy after a first angioedema.

for risk of second angioedema, during ACEi exposure (totally 54 patients) and after ACEi exposure (totally 23 patients) are presented in Fig. 2 and are statistically significantly different (p-value < 0.001).

This large population based study shows that in the UK almost half of ACEi-related angioedema cases, despite the guidelines [8], continue ACEi treatment which is associated with a high risk of recurrent angioedema. The probability to develop angioedema for patients who continue ACEis after a first event is between 137 and 158 times higher compared to new ACEi users and up to 2.8 times higher compared to patients who discontinued ACEi use. The main limitation of the study is that the diagnosis of angioedema was recorded by general practitioners and that we were not able to verify whether the angioedema was indeed caused by the use of an ACEi.

Considering the growing numbers of ACEi users, the high percentage of patients continuing an ACEi after a first angioedema event and the high risk of recurrent angioedema in these patients, physicians should be more aware of the serious risks of continuation of ACEi therapy after the occurrence of angioedema. This is particularly relevant because recently it has been shown that angioedema itself can potentially harm the heart and coronary arteries [9,10].

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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.

References

[1] K. Croft, Prescriptions dispensed in the community England 2003–13, Prescribing and Primary Care. , Health and Social Care Information Centre, 9 July 2014 (110 pp. Available on http://www.hscic.gov.uk).
[2] W.H. Inman, N.S. Rawson, L.V. Wilton, G.L. Pearce, C.J. Speirs, Postmarketing surveillance of enalapril. I: results of prescription-event monitoring, BMJ 297 (1988) 826–829.
[3] M.U. Khan, M.A. Baig, R.A. Javed, et al., Benazepril induced isolated visceral angioedema: a rare and under diagnosed adverse effect of angiotensin converting enzyme inhibitors, Int. J. Cardiol. 118 (2007) e68–e69.
[4] N.J. Brown, M. Snowden, M.R. Griffin, Recurrent angiotensin-converting enzyme inhibitor-associated angioedema, JAMA 278 (1997) 232–233.
[5] M. Cicardi, L.C. Zingale, L. Bergamaschini, A. Agostoni, Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment, Arch. Intern. Med. 164 (2004) 910–913.
[6] L. Beltrami, A. Zanichelli, L. Zingale, R. Vacchini, S. Carugo, M. Cicardi, Long-term follow-up of 111 patients with angiotensin-converting enzyme inhibitor-related angioedema, J. Hypertens. 29 (2011) 2273–2277.
[7] A. Matcho, P. Ryan, D. Fife, C. Reich, Fidelity assessment of a clinical practice research datalink conversion to the OMOP common data model, Drug Saf. 37 (2014) 945–959.
[8] A.P. Kaplan, M.W. Greaves, Angioedema, J. Am. Acad. Dermatol. 53 (2005) 373–388 (quiz 389–92).
[9] N.G. Kounis, A. Mazarakis, C. Bardousis, N. Patsouras, 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. 198 (2015) 83–84.
[10] G. Lippi, R. Buonocore, F. Schirosa, G. Cervellin, Cardiac troponin I is increased in patients admitted to the emergency department with severe allergic reactions. A case–control study, Int. J. Cardiol. 194 (2015) 68–69.

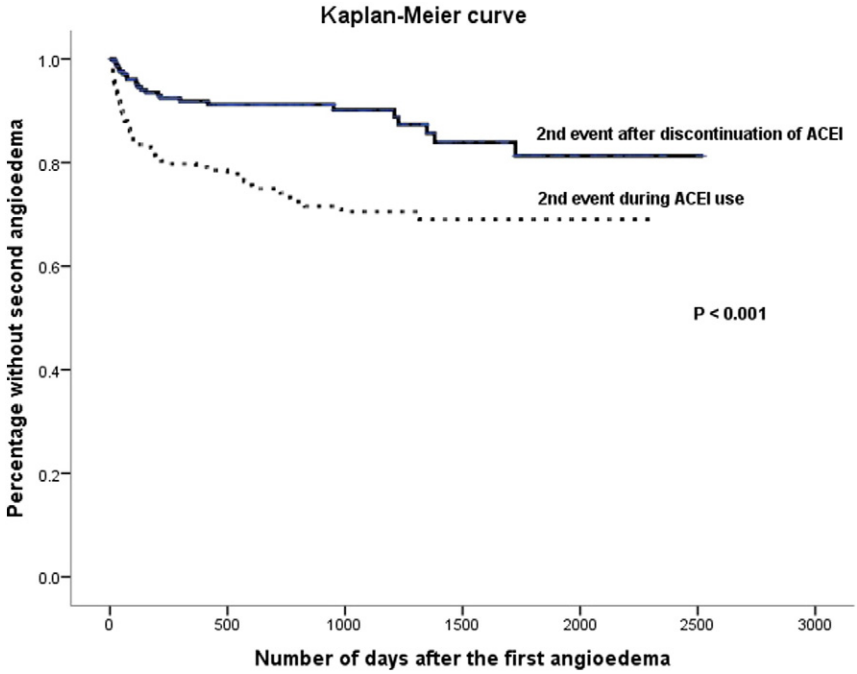

Fig. 2. Comparing the rate of second angioedema during and after ACEi exposure. Abbreviations: ACEi = angiotensin converting enzyme inhibitor.