Patterns of Angiotensin-Converting Enzyme Inhibitors Prescribing for Various Indications: A Population-based Study

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Abstract

Aim: Angiotensin-converting enzyme inhibitors (ACE-inhibitors) are widely prescribed for several cardiovascular indications. This study investigated patterns of ACE-inhibitor use for various indications.

Methods: A descriptive, retrospective population-based study was conducted using data from the UK Clinical Practice Research Datalink. Patients starting ACE-inhibitors (2007-2014) were selected and ACE-inhibitor indications were retrieved from electronically recorded medical records. Stratified by indication, we distinguished between persistent and non-persistent ACE-inhibitor use, considering a six-month interval between two prescription periods as a maximum for persistent use. Five-year persistence rates for various indications were calculated using the Kaplan-Meier method and compared in a log-rank test. Non-persistent users were subdivided into three groups: 1) stop, 2) restart, and 3) a switch to an angiotensin II-receptor blocker (ARB). Patients who received ACE-inhibitors for hypertension who switched to other classes of antihypertensive medications were further investigated.

Results: In total, 254,002 ACE-inhibitor initiators were identified with hypertension (57.6%), myocardial infarction (MI) (4.2%), renal disease (RD) (3.7%), heart failure (HF) (1.5%), combinations of the above (17.2%), or none of the above (15.8%). Five-year persistence rates ranged from 43.2% (RD) to 68.2% (MI) ($p<0.0001$). RD and HF patients used ACE-inhibitors for the shortest time (average 23.6 and 25.0 months, respectively). For the non-persistent group, the percentage of switchers to ARBs ranged from 27.6% (RD) to 42.2% (MI) and the restarters ranged from 15.0% (HF) to 18.1% (group without indication).

Conclusions: Depending on the indication, there are various rates of ACE-inhibitor non-persistence. Patients with RD are most likely to discontinue treatment.

What is already known about this subject:

- ACE-inhibitors are widely prescribed for several cardiovascular indications including hypertension, heart failure, myocardial infarction, and renal failure.
- Although ACE-inhibitors are usually prescribed as maintenance therapy, studies have shown a non-persistence rate between 20 to 40 per cent.

What this study adds:

- Using real-world clinical practice data in a large UK population-based study, we showed that the patterns of use for ACE-inhibitors vary among indications for initiation.
- Patients who start ACE-inhibitors after a myocardial infarction are the most persistent users compared to those with hypertension and heart failure. Patients who start ACE-inhibitors for renal diseases are the least persistent group.

Introduction

ACE-inhibitors are one of the most frequently prescribed classes of medication. For instance, in 2013, ramipril (an ACE-inhibitor) was the first antihypertensive medication with more than 24 million prescriptions dispensed in community pharmacies in the United Kingdom (UK) [1]. ACE-inhibitors are commonly used to treat hypertension, heart failure (HF), myocardial infarction (MI), and renal disease (RD). It has been demonstrated that these drugs decrease cardiovascular disease morbidity and mortality, especially in patients with hypertension and HF [2-4]. Studies on the use of all antihypertensive medications have consistently shown that ACE-inhibitors have the second lowest risk of discontinuation (lowest are angiotensin II-receptor blockers [ARBs]) [5-9]. Nonetheless, a substantial number of patients discontinue ACE-inhibitor therapy, mainly because of adverse drug reactions (ADRs) [10]. A US cohort study of more than 2,200 outpatients who received ACE-inhibitors for the first time showed that 19% discontinued ACE-inhibitors due to ADRs (median follow-up 336 days) [11]. In a Dutch study on ACE-inhibitor use based on a pharmacy drug-dispensing database, Vegter *et al.* reported that approximately 24% of ACE-inhibitor starters switched their therapy within the first three years, and 75% of this group switched to ARBs [12]. In the UK, the percentage of ACE-inhibitor switchers increased to more than 40% in a large population-based cohort of newly diagnosed hypertensive patients including a subgroup of more than 36,000 ACE-inhibitor starters with a maximum of nine years of follow-up [13].

No study has investigated whether persistence with ACE-inhibitors differs among indications. A prior UK study showed that patients with MI were less likely to stop beta-blocker therapy than patients with HF or angina pectoris [14]. The aim of this

study is to investigate whether the pattern of ACE-inhibitor use differs by indication for persistence rate, stop, restart, or a switch to ARBs.

Methods

Setting

The data for this study were obtained from the Clinical Practice Research Datalink (CPRD), formerly known as General Practice Research Database (GPRD), which contains computerized information from almost 700 UK primary care practices. At the time of this study, CPRD included clinical records of close to 12 million patients. Validity data and a detailed description of the CPRD have been described earlier [15, 16].

The protocol for this study was reviewed and approved by the UK independent scientific advisory committee (ISAC), protocol number: 14_030R. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Study cohort

A descriptive, retrospective population-based study was conducted with patients aged 45 years and older who initiated ACE-inhibitor therapy between 1 January 2007 and 1 January 2014. To be eligible for the study, patient data had to include at least 12 months of valid prescription history before starting an ACE-inhibitor and at least six months of valid prescription data after starting so ACE-inhibitor persistence could be evaluated. Assessment of validity was performed using general practitioner prescription data for any medication prescribed for the study participants.

Follow-up

Subjects were followed through the study period, time of death, or the date they moved outside the practice area. Subject mortality data are available through an established link between CPRD and the UK office for national statistics. The cohort

entry date was the date of the patient's first ACE-inhibitor prescription. To categorize patients according to the indication for ACE-inhibitor initiation, we assessed whether patients had a diagnosis (based on relevant Read codes in electronic medical records) of hypertension, HF, MI, or RD prior to the cohort entry date or in the first year thereafter. Patients with more than one indication and patients for whom we could not retrieve any of the above indications within that period were classified in separate categories. The category of more than one indication was further subdivided based on the number and combination of indications (supplementary table S1). Both the average follow-up time and duration of ACE-inhibitor use were calculated for each indication.

Prescription patterns

According to the prescription data, starters with ACE-inhibitors were divided into two main categories.

1. *Persistent group*: patients who started ACE-inhibitors and continued until the end of follow-up. A maximum six-month time interval between two prescription periods was acceptable for this definition. This time interval has been shown to be a better indicator of ADRs in comparison to a three-month interval [10]. Even if a patient is hospitalized (usually no longer than one month) or has a stock of the medication, they are expected to return for a refill of their prescription within this time period.
2. *Non-persistent group*: patients who stopped receiving ACE-inhibitor prescriptions for at least six months after the theoretical end date of their previous ACE-inhibitor prescription. The discontinuation date was defined as the theoretical end date of the last ACE-inhibitor prescription and calculated by dividing the quantity of prescribed medications by the

number of daily doses. The non-persistent group was divided into three mutually exclusive subgroups according to the treatment pattern after ACE-inhibitor discontinuation (Figure 1).

A. *Stop group*: Patients who stopped their ACE-inhibitors and never restarted by the end of the study period and also had not started ARBs within six months after the theoretical end date of their last ACE-inhibitor prescription.

B. *Switch to ARBs group*: Patients who stopped their ACE-inhibitors and started ARBs within six months after the theoretical end date of their last ACE-inhibitor prescription. For patients with hypertension, a switch to another antihypertensive medication (beta blocker, diuretic, calcium channel blocker, or other antihypertensive such as alpha blocker, vasodilator, or centrally acting antihypertensive) was also investigated.

C. *Restart group*: patients who stopped or switched their ACE-inhibitors according to the above definitions, but during the study follow-up time, who had then restarted ACE-inhibitor therapy.

Statistical analyses:

General characteristics for all ACE-inhibitor starters were reported separately for each indication (hypertension, HF, MI, RD, more than one indication, and none of the above). Five-year persistence rates and the time to discontinuation among the various indications were calculated and compared using the Kaplan-Meier method and a log-rank test, respectively. Patients who started with an ACE-inhibitor and had a follow-up time of less than six months were excluded since, these patients would have automatically been placed in the persistent group due to the definition of persistence. This result could have unrealistically increased the estimation of the proportion of

persistent patients. To evaluate the influence of these exclusions, we performed a sensitivity analysis in which excluded patients were analysed once as persistent ACE-inhibitor users and once as non-persistent users. All statistical analyses were performed using SPSS 20 (IBM SPSS Statistics for Windows Version 20.0. Armonk, NY: IBM Corp)

Results

There were 276,973 eligible patients who had started with an ACE-inhibitor during the study period. A total of 22,971 patients (8.2%) were excluded from the main analyses due to a less than six-month follow-up time. Table 1 presents the general characteristics of the remaining 254,002 patients (51.5% male) at the first date of ACE-inhibitor prescription. Table 1 also includes the average follow-up time, average duration of ACE inhibitor use, and proportions of deceased patients during follow-up; all were stratified by indication. The majority of participants had started with an ACE-inhibitor because of hypertension (57.6%) and the smallest group was for HF (1.5%). The patient group with more than one indication was 17.2%, and 90.1% of these participants had hypertension as one indication. Patients who started an ACE-inhibitor for HF and RD were approximately nine years older than patients with an MI or hypertension.

The highest percentages of death were for patients with HF (21.5%) or more than one indication (15.4%). The mean duration of ACE-inhibitor use was longest for those who had had an MI (30.5 months) and shortest for those with HF (25.0 months) or RD (23.6 months) (see Table 1).

Table 2 shows the patterns of ACE-inhibitor use by indication. In the total study population, 60.3% of ACE-inhibitor starters continued till the end of study follow-up. For the 100,790 non-persistent patients, 45.3% stopped their ACE-inhibitor (did not

switch to ARBs within six months and never restarted ACE-inhibitors), 37.1% switched to ARBs, and 17.6% restarted their ACE-inhibitors after at least six months of discontinuation.

Patients who started an ACE-inhibitor for MI had the highest probability of remaining on their initial ACE-inhibitor treatment (73.6%). Patients who started an ACE-inhibitor for RD were most likely to discontinue (49.2%). More than half (54.5%) of the non-persistent patients with RD actually stopped and did not restart ACE-inhibitors or switch to ARBs. This was the highest percentage for this behaviour among all indications.

Study participants who switched from ACE-inhibitors to ARBs ranged from 27.6% (RD) to 42.2% (MI). For patients with hypertension, out of 24,206 patients who stopped ACE-inhibitor and did not restart or switch to ARBs, 17.2% switched to calcium channel blockers which was the highest percentage, followed by a switch to diuretics (6.3%), a combination of antihypertensives (5.0%), or beta blockers (3.6%). The same pattern was observed for patients with hypertension combined with other indications (10.0% switched to calcium channel blockers, 6.3% to diuretics, 3.3% to a combination of antihypertensives, and 3.2% to beta blockers).

Kaplan-Meier curves of ACE-inhibitor use for various indications are presented in Figure 2. Five-year persistence rates for indications included in this study were 68.2% (MI), 58.6% (HF), 56.4% (hypertension), 53.4% (no mentioned indication), 53.0% (more than one indication), and 43.2% (RD) (log-rank p-value <0.0001).

Sensitivity analyses, including the 22,971 patients with less than six months of follow-up, changed the crude percentages for the non-persistent patients for all indications. For example, in the MI group, the percentage of non-persistent patients change from 26.4% to 34.4% (excluded patients included as non-persistent patients)

and to 23.6% (excluded patients included as persistent patients). Detailed results of sensitivity analyses are presented in supplementary table S2.

Discussion

This study demonstrated that patterns of ACE-inhibitor use and persistence differ among indications. Patients with RD discontinued their ACE-inhibitor therapy more frequently and used ACE-inhibitors for a shorter time period than those with other indications. Five-year non-persistence rates ranged between 31.8% (MI) to 56.8% (RD).

Hypertension, RD, and HF are three main indications of ACE-inhibitors previously studied for drug utilisation patterns. Although ACE-inhibitors are well tolerated compared to other antihypertensive medications, the problem of poor persistence still exists for patients with hypertension. For example, a one-year discontinuation rate for lisinopril (ACE-inhibitor) consumers in the US and Australia with hypertension was reported to be more than 30% [17, 18].

Several socio-demographic factors have been shown to be associated with non-persistence to antihypertensive therapy (e.g., sex, co-medications, comorbidities, and even demographic characteristics of the geographic location) [19, 20], which can eventually result in poor clinical outcomes [21]. A Dutch study showed that the putative ACE-inhibitor-related cough can affect patient compliance (20% higher compliance for patients without a putative cough); however, the precise cause of ACE-inhibitor discontinuation could not be retrieved directly [22]. In the early 2000s, two studies using the same population (Régie de l'assurance maladie du Québec administrative database) showed that among patients with hypertension (and specifically ACE-inhibitor users), those patients who had more risk factors for cardiovascular events were more persistent with their drug therapy than patients with

less risk factors [23, 24]. Patients who start ACE-inhibitors for RD are more susceptible to adverse effects like renal function deterioration or hyperkalemia (in addition to the common side effect of coughing) because of a combination of drug action and disease complications. Therefore, it is not uncommon to recommend that patients with RD discontinue (permanently or temporarily) their ACE-inhibitors [25]. It has also been shown that older age in patients with hypertension is associated with a higher risk of non-persistence to ACE-inhibitors [26]. In our study, the mean age of patients with RD was higher than patients with other conditions, which could potentially have influenced the higher non-persistence rate in this group.

ACE-inhibitors are one of the main medications used in HF management and large population-based studies have demonstrated that drug adherence is significantly associated with increased survival time in these patients [27]. Recently, it has been shown in the US that medication adherence for patients with HF decreases during the first few months after hospitalization [28]. A 2015 French study showed that the pharmacological management of HF in elderly patients is not optimal [29]; however a 2015 systematic review of 17 studies (162,727 patients) found that older age alone is not related to the poor medical management in patients with HF [30]. In our study, patients with HF were the third oldest group and had the highest mortality rate. This might explain the average time-limited use of ACE-inhibitor in this group.

Our study demonstrates that patients who start ACE-inhibitors for RD and HF have a higher probability of stopping and should have improved follow-up and monitoring by health care providers to achieve the full benefit of ACE-inhibitors. We suggest either pharmacists or physicians contact patients who have discontinued relevant medication (specifically ACE-inhibitors) without clear justification, to improve persistence and thus, patient outcomes [31, 32].

More studies are needed to address the issue of whether or not ACE-inhibitor discontinuation is inevitable or can be managed by a dose adjustment, addition of a new class of medication, or other interventions.

The main strength of this population-based study was the large number of patients who can be considered as representative of all ACE-inhibitor starters in the UK. Valid data for at least 18 months (12 months before and six months after the first ACE-inhibitor prescription) was an acceptable follow-up time to identify new users and define usage and persistence patterns.

One of the limitations of this study was that the indications for ACE-inhibitor use were based on electronic medical records registered by general practitioners. These diagnoses were not validated, so misclassifications cannot be ruled out. That said, a recent study compared CPRD codes for renal replacement therapy and decreased kidney function with external data sources in the UK (Health Survey for England and UK Renal Registry). The authors found an acceptable validity when comparing the prevalence of the abovementioned kidney diseases in the CPRD with external data sources [33]. Another recent study could not find significant prognostic differences between patients with HF who were recorded in CPRD primary care data alone and those who were recorded both in hospital admission and primary care data [34]. Unequal follow-up time for all patients could potentially be another limitation. However, we tried to decrease the variation between patient follow-up times by excluding patients with very short follow-up times (less than six months of follow-up after ACE-inhibitor initiation).

In conclusion, this UK study demonstrated that for all patients with various indications for ACE-inhibitors a relatively high percentage of patients will stop or switch their therapy, with the highest proportion of stoppers within patients with RD.

The main cause of non-persistence to ACE-inhibitors within these patients needs to be further investigated.

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Author contributions

S.H.M. performed the analysis and wrote the manuscript; P.C.S. managed the data; S.H.M., P.C.S., F.W.A., A.d.B., and A.H.M interpreted the results; F.W.A., A.d.B., and A.H.M. designed the research and critically revised the manuscript. S.H.M., P.C.S., F.W.A., A.d.B., and A.H.M have given final approval of the version to be published.

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Table 1: General characteristics of included patients stratified by indications (N= 254,002 patients).

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], (SDM)	72.1 [11.8] (-0.58)	62.7 [11.0] (reference)	64.1 [11.1] (-0.08)	72.6 [11.0] (-0.63)	73.4 [10.8] (-0.69)	64.1 [11.5] (-0.08)	65.3 [11.9]
Sex (%male)	60.1%	50.1%	76.2%	43.5%	45.0%	58.0%	51.5%
Mean follow-up [2] (months) [SD], (SDM)	35.2 [20.9] (0.27)	43.7 [22.2] (reference)	39.2 [21.9] (0.14)	41.8 [22.6] (0.05)	43.7 [23.0] (0)	39.1 [21.9] (0.14)	42.6 [22.4]
Mean ACE-inhibitor duration (months) [SD], (SDM)	25.0 [21.5] (0.11)	28.8 [25.1] (reference)	30.5 [23.3] (-0.04)	23.6 [23.3] (0.15)	28.1 [25.1] (0.01)	24.9 [23.2] (0.11)	27.9 [24.7]
Death	21.5%	4.2%	7.1%	13.8%	15.4%	7.4%	7.3%

[1] recorded at the first ACE-inhibitor prescription date
[2] minimum requirement of a six-month follow-up after ACE-inhibitor initiation
SD: Standard deviation, SDM: Standardized difference between means as compared to the hypertension group as the most common indication

Table 2: Patterns of ACE-inhibitor use stratified by indication.

Indication (Patients)	Pattern (N) Percentage	
Heart failure (n= 3,762)	Persistent (n= 2,507) 66.6%	
	Non-persistent (n= 1,255) 33.4%	Stop (n= 561) 44.7%
		Switch to ARB (n= 506) 40.3%
		Restart (n= 188) 15.0%
Hypertension (n= 146,275)	Persistent (n= 88,632) 60.6%	
	Non-persistent (n= 57,643) 39.4%	Stop [1] (n= 24,206) 42.0%
		Switch to ARB (n= 23,271) 40.4%
		Restart (n= 10,166) 17.6%
Myocardial infarction (n= 10,639)	Persistent (n= 7,826) 73.6%	
	Non-persistent (n= 2,813) 26.4%	Stop (n= 1,200) 42.7%
		Switch to ARB (n= 1,187) 42.2%
		Restart (n= 426) 15.1%
Renal disease (n= 9,299)	Persistent (n= 4,727) 50.8%	
	Non-persistent (n= 4,572) 49.2%	Stop (n= 2,493) 54.5%
		Switch to ARB (n= 1,262) 27.6%
		Restart (n= 817) 17.9%
More than one indication (n= 43,753)	Persistent (n= 25,555) 58.4%	
	Non-persistent (n= 18,198) 41.6%	Stop [2] (n= 8,399) 46.2%
		Switch to ARB (n= 6,650) 36.5%
		Restart (n=3,149) 17.3 %
None of the mentioned indications (n= 40,274)	Persistent (n= 23,965) 59.5%	
	Non-persistent (n= 16,309) 40.5%	Stop (n= 8,817) 54.1%

		Switch to ARB (n= 4,545) 27.9%
		Restart (n= 2,947) 18.1%
Total (n=254,002)	Persistent (n=153,212) 60.3%	
	Non-persistent (n=100,790) 39.7%	Stop (n= 45,676) 45.3%
		Switch to ARB (n= 37,421) 37.1%
		Restart (n=17,693) 17.6%

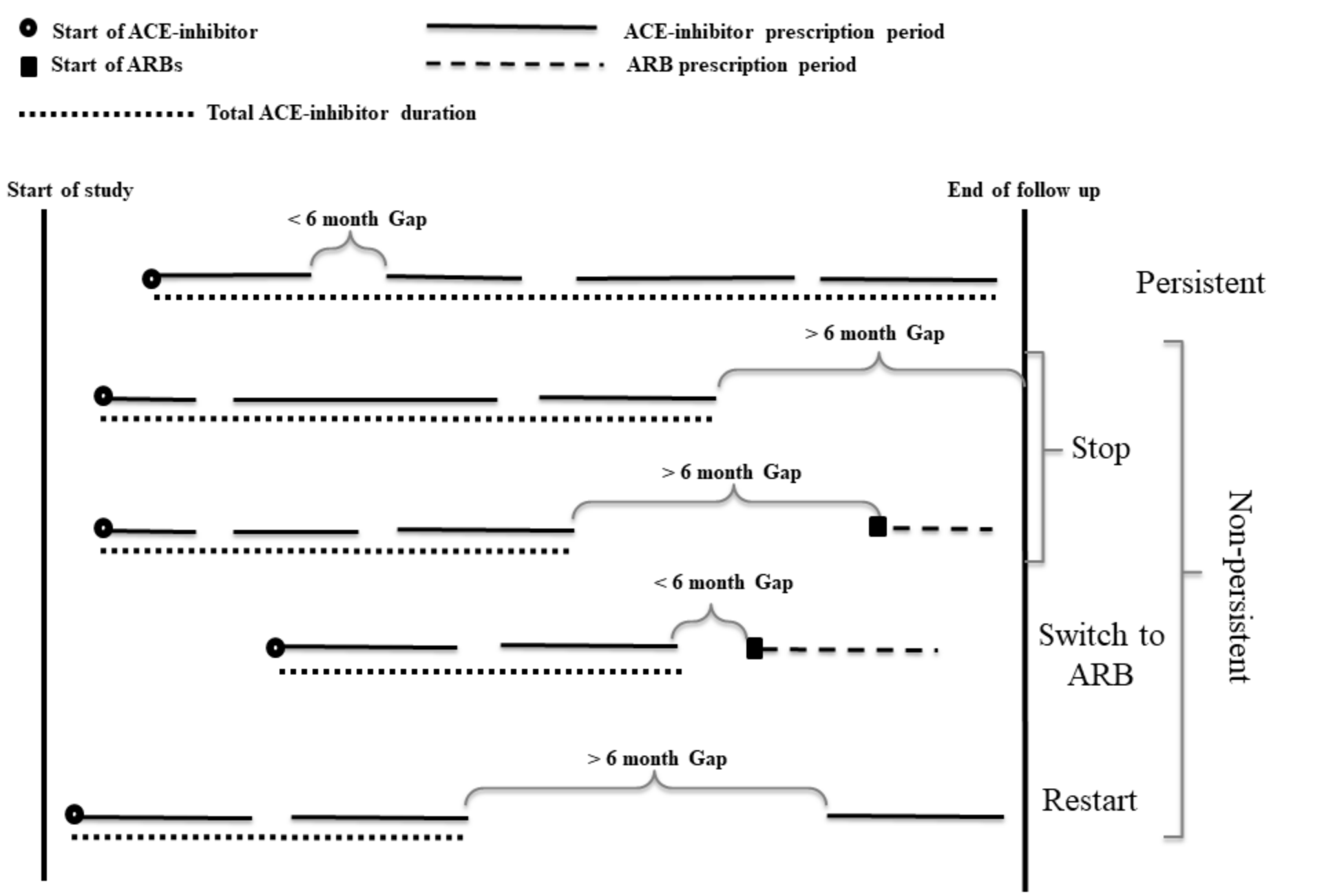
[1] switched to calcium channel blockers (17.2%), diuretics (6.3%), combination of antihypertensives (5.0%), beta blockers (3.6%), and other antihypertensives (0.1%).

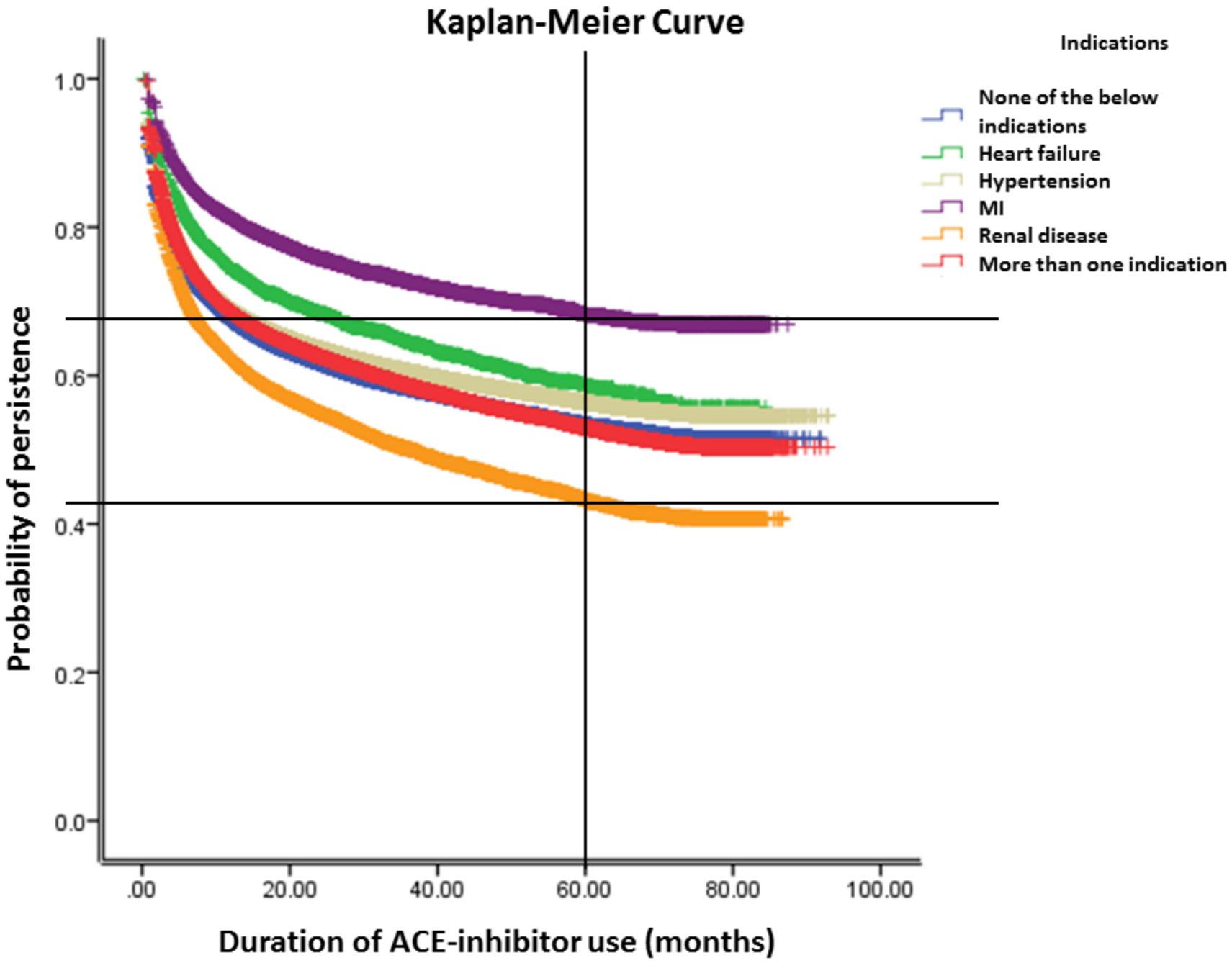
[2] Two subgroups: a) more than one indication including hypertension (90.5%) and b) not including hypertension (9.5%). Group A per cent switched to calcium channel blockers (10.0%), diuretics (6.3%), combination of antihypertensives (3.3%), beta blockers (3.2%), and other antihypertensives (0.3%).

Figure legends

Figure 1: Definition of ACE-inhibitor use patterns.

Figure 2: Comparison of non-persistence rates of ACE-inhibitor use for various indications.


Start of ACE-inhibitor
Start of ARBs
ACE-inhibitor prescription period
ARB prescription period
Total ACE-inhibitor duration
Start of study
End of follow up
< 6 month Gap
Persistent
> 6 month Gap
Stop
> 6 month Gap
Non-persistent
< 6 month Gap
Switch to ARB
> 6 month Gap
Restart


Kaplan-Meier Curve
Indications
None of the below indications
Heart failure
Hypertension
MI
Renal disease
More than one indication
Probability of persistence
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
80.00
100.00
Duration of ACE-inhibitor use (months)

Supplementary Table 1: Detailed retrieved diagnoses for patients who had more than one indication, the percentage of deceased patients in each category, and patterns of ACE-inhibitor use (N= 43,753 patients).

	Two indications						Three indications				Four indications	Total
Indication (N) Percentage of total	HF&HTN **(2,377) 5.4%**	HF&MI **(1,068) 2.4%**	HF&RD **(1,194) 2.7%**	HTN&MI **(4,641) 10.6%**	HTN&RD **(28,674) 65.5%**	MI&RD **(1,524) 3.5%**	HF&HTN&MI **(586) 1.3%**	HF&HTN&RD **(1,254) 2.9%**	HF &MI&RD **(365) 0.9%**	HTN&MI&RD **(1,734) 4.0%**	HF&HTN&MI&RD **(336) 0.8%**	**43,753 100%**
Percentage of death within each category	**23.8%**	**18.9%**	**33.8%**	**11.9%**	**12.1%**	**16.1%**	**27.1%**	**34.4%**	**38.1%**	**22.8%**	**38.7%**	**15.4%**
Persistent (N) Percentage	**(1,619) 68.1%**	**(764) 71.5%**	**(693) 58%**	**(3,122) 67.3%**	**(15,902) 55.5%**	**(900) 59.1%**	**(404) 68.9%**	**(745) 59.4%**	**(222) 60.8%**	**(984) 56.7%**	**(200) 59.5%**	**(25,555) 58.4%**
Non-persistent (N) Percentage	**(758) 31.9%**	**(304) 28.5%**	**(501) 42%**	**(1,519) 32.7%**	**(12,772) 44.5%**	**(624) 40.9%**	**(182) 31.1%**	**(509) 40.6%**	**(143) 39.2%**	**(750) 43.3%**	**(136) 40.5%**	**(18,198) 41.6%**
Stop	**42.8%**	**39.2%**	**51.5%**	**39%**	**46.3%**	**52.1%**	**42.9%**	**55%**	**45.4%**	**47.3%**	**55.9%**	**46.2%**
Switch to ARB	**41.6%**	**43.4%**	**32.1%**	**42.9%**	**36.2%**	**32.5%**	**42.9%**	**28.1%**	**39.2%**	**33.9%**	**28.7%**	**36.5%**
Restart	**15.6%**	**17.4%**	**16.4%**	**18.1%**	**17.5%**	**15.4%**	**14.2%**	**16.9%**	**15.4%**	**18.8%**	**15.4%**	**17.3 %**

HF: Heart failure, HTN: Hypertension, MI: Myocardial infarction, RD: Renal disease, ARB: angiotensin II-receptor blocker.
For the last row (stop, switch to ARB and, restart), percentages are presented from the total non-persistent patients.

Supplementary Table 2: Detailed results from the sensitivity analyses including the 22,971 patients with less than six months of follow up time.

Indication	Main analyses (n=254,002)	Sensitivity analyses including all as non-persistent (n=276,973)	Sensitivity analyses including all as persistent (n=276,973)
Heart failure	Persistent (n= 2,507) 66.6%	Persistent (n= 2,507) 56.9%	Persistent (n= 3,154) 71.5%
	Non-persistent (n= 1,255) 33.4%	Non-persistent (n= 1,902) 43.1%	Non-persistent (n= 1,255) 28.5%
Hypertension	Persistent (n= 88,632) 60.6%	Persistent (n= 88,632) 56.3%	Persistent (n= 99,901) 63.4%
	Non-persistent (n= 57,643) 39.4%	Non-persistent (n= 68,912) 43.7%	Non-persistent (n= 57,643) 36.6%
Myocardial infarction	Persistent (n= 7,826) 73.6%	Persistent (n= 7,826) 65.6%	Persistent (n= 9,123) 76.4%
	Non-persistent (n= 2,813) 26.4%	Non-persistent (n= 4,110) 33.4%	Non-persistent (n= 2,813) 23.6%
Renal disease	Persistent (n= 4,727) 50.8%	Persistent (n= 4,727) 46.6%	Persistent (n= 5,564) 54.9%
	Non-persistent (n= 4,572) 49.2%	Non-persistent (n= 5,409) 53.4%	Non-persistent (n= 4,572) 45.1%
More than one indication	Persistent (n= 25,555) 58.4%	Persistent (n= 25,555) 54.1%	Persistent (n= 29,005) 61.4%
	Non-persistent (n= 18,198) 41.6%	Non-persistent (n= 21,648) 45.9%	Non-persistent (n= 18,198) 38.6%
None of the mentioned indications	Persistent (n= 23,965) 59.5%	Persistent (n= 23,965) 52.4%	Persistent (n= 29,436) 64.3%
	Non-persistent (n= 16,309) 40.5%	Non-persistent (n= 21,780) 47.6%	Non-persistent (n= 16,309) 35.7%