

# BMJ Open Therapy discontinuation or substitution in patients with cardiovascular disease, switching among different products of the same off-patent active substance: a 'real-world' retrospective cohort study

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## ABSTRACT

**Objective:** The present study investigated the effects of switching to different products of the same off-patent active substance (brand name or generic) on therapy discontinuation or substitution with another molecule of the same class, in patients with cardiovascular disease treated with statins and antihypertensives in a 'real-world' setting.

**Design:** A retrospective cohort study in a 'real-world' setting.

**Setting:** Analysis of data performed by integrating administrative databases that included approximately two million individuals who are assisted by the National Health System from three Local Health Units located in three different regions of Italy.

**Participants:** All patients aged  $\geq 18$  years with at least one prescription of simvastatin, ramipril or amlodipine in the period 1 January to 31 December 2010 were included and followed up for 2 years.

**Main outcome measures:** Prescription refills occurring during follow-up were evaluated. Frequency of discontinuation of therapy or substitution with another molecule of the same class (eg, from simvastatin to a different statin) during follow-up was identified.

**Results:** During follow-up, therapy discontinuation or substitution was found to be more frequent in patients switching to a different product of the same active substance compared with non-switching patients (11.5% vs 10.8% and 22.2% vs 20.8% ( $p=0.002$ ), respectively, in the simvastatin group; 4.0% vs 3.5% and 24.6% vs 22.7% ( $p<0.001$ ), respectively, in the amlodipine group). In the ramipril group, 8% of patients undertook a therapy substitution to another molecule; no trend towards a lower percentage of substitution was observed in the non-switching group, while 18% of patients discontinued treatment, with a significant difference in favour of patients not switching. These findings were partially confirmed by multivariate analysis.

**Conclusions:** Switches among products of the same active substance are quite common in patients with cardiovascular disease. Our study suggests that

## Strengths and limitations of this study

- This study, in a 'real-world' setting, is one of only a few studies to investigate clinical differences related to switching among different products of the same active substance in the cardiovascular setting. Until now, most research has focused only on comparing brand name and generic drugs.
- The sample size was relatively limited, and although we used three healthcare databases comprising a total of approximately two million individuals who are assisted by the National Health System in three regions of Italy, larger studies are needed to confirm and to enhance the generalisability of the findings, and in different populations.
- In common with other retrospective, observational studies, reasons for switch, non-adherence or discontinuation of treatment were not retrievable from the data set.

switching may expose patients to a higher risk of therapy discontinuation or substitution.

## INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death worldwide, accounting for approximately one-third of all deaths.<sup>1</sup> Combination therapy with antihypertensive drugs and serum cholesterol-lowering drugs is effective in prevention, and it is estimated that a high level of adherence to treatment will reduce the risk of CVD by approximately 80%.<sup>2</sup> A number of studies have demonstrated that patients often discontinue long-term treatment or take less than prescribed, and that such non-adherence reduces the potential preventive benefits.<sup>3</sup>

Many reasons contribute to patient non-adherence to medical therapy, such as ageing, comorbidities, poor relationship between patient and physician, poor memory and patients' low perception of disease severity.<sup>4</sup> In addition, the need to take several drugs concomitantly or other medication-related factors, may make remembering when to take each drug more difficult and increase the risk of possible side effects caused by adverse drug–drug interactions. Although medication side effects are probably not the main cause of poor adherence, as there seems to be little direct relationship between adherence and drug class,<sup>3</sup> they are also associated with treatment discontinuation, especially in the early treatment of hypertension.<sup>5–8</sup> Kronish *et al* showed that, in the clinical setting, adherence to diuretics and  $\beta$ -blockers is lowest and the highest adherence is to angiotensin II receptor blockers and ACE inhibitors.<sup>5</sup> Similarly, a retrospective study based on a cohort of 207 473 patients in Ontario found that treatment with ACE inhibitors showed the best therapy persistence and compliance, and  $\beta$ -blockers showed the worst compliance (all  $p < 0.001$ ).<sup>8</sup> Furthermore, some studies have demonstrated that switching between different products of the same active substance can have an impact on adherence to medication, because variation in packaging and pill appearance may reduce adherence, especially for chronic diseases.<sup>9–10</sup>

There is a perception among patients and physicians alike that frequent changes between branded and unbranded products (as well as between generics), all containing the same active substance, and especially if patients are older and on multidrug regimens, may cause patients to become anxious when the appearance of their drugs changes.<sup>11–13</sup> This can lead to an increased risk of patients making mistakes or double medicating, which flows on to increased drug non-adherence.<sup>14–15</sup>

Few studies have investigated clinical differences related to switching among different products of the same active substance in the cardiovascular setting. Until now, most research has focused only on comparing brand name and generic drugs.<sup>16–20</sup>

The aim of this study was to investigate the effects of switching to different products of the same off-patent active substance (brand name or generic) on therapy discontinuation or substitution with another molecule of the same class, in patients with CVD treated with statins and antihypertensives in a 'real-world' setting.

A version of this article has previously been published as a journal supplement in the Italian language.<sup>21</sup>

## METHODS

### Data collection

The data used for the analysis were obtained from the administrative databases of three local health units (LHUs), whose databases included a total population of about two million individuals who are assisted by the

National Health System, in the Italian regions of Lombardy, Lazio and Campania. We analysed the following archives: Assisted Subjects' Database, containing the personal data of patients; Medication Prescription database, containing all the information relating to individual prescriptions dispensed by the pharmacy, such as the International Nonproprietary Names (INN) for pharmaceutical substances, the Anatomical-Therapeutic-Chemical (ATC) code of the prescribed drug, the number of packages, the number of units per package, the dose, the brand name drug, the cost per unit and the date of the prescription; Hospital Discharge Database (SDO), containing information on each hospital discharge, in particular the date of admission and discharge, primary and secondary diagnoses coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The patient code in each database allowed electronic linking among all databases. To guarantee patient privacy, this patient code was transcoded into an anonymous univocal numeric code. No identifiers related to patients were provided to the researchers. According to the Italian law for confidentiality of data,<sup>22</sup> the study was notified to the Ethic Committees of each LHU.

### Cohort definition

The study was a retrospective cohort study including all patients aged  $\geq 18$  years that, between 1 January and 31 December 2010 (enrolment period), had at least one prescription of simvastatin (ATC code: C10AA01), ramipril (ATC code: C09AA05) or amlodipine (ATC code: C08CA01) as a brand name or generic prescription. The date of enrolment was defined as the earliest date within the enrolment period in which the patient had the last switch of medication or the last prescription in the case of a patient continuing with the same medication. Starting from this date, the individual patient was followed for 2 years (follow-up period). The patient cohorts were defined in the following way: non-switchers were defined as those patients who did not change medication, regardless of whether it was brand name or generic; switchers were defined as those patients who switched among different products of the same off-patent active substance (ie, from brand name to generic, from generic to brand name or from generic to another generic). The changes in dose and dosage form were not accounted for during switching. Data on baseline characteristics, including demographics, cardiovascular risk factors and receipt of more than one cardiovascular medication at the date of enrolment, were collected. The data on drug prescriptions and hospitalisations that occurred during the 12 months preceding the date of enrolment were analysed (characterisation period). The medication adherence in the year before the index date was also analysed. Adherence to therapy was determined by calculating the proportion of days covered according to the method used by Catalan and LeLorier.<sup>23</sup>

Only patients with at least one prescription of the index drug in the previous 12 months were included (to capture patients who could have made a change in therapy) and with at least two prescriptions at follow-up (to include patients with continuity of treatment). Patients treated with fixed combinations of the molecules under consideration (ramipril and diuretics (ATC code: C09BA05), perindopril and amlodipine (ATC code: C09BB04), ramipril and felodipine (ATC code: C09BB05), olmesartan and amlodipine (ATC code: C09DB02), simvastatin and ezetimibe (ATC code: C10BA02)) were excluded.

Patients transferred to another LHM during the follow-up period were excluded from the analysis.

## Study population

### Cardiovascular risk

Patients were classified as being at high cardiovascular risk if they had cardiovascular treatment or hospitalisation for diabetes. For each patient, hospitalisations related to diabetes were identified by the ICD-9-CM code: 250 (primary discharge reasons); and/or cardiovascular risk factors (previous hospitalisation for ischaemic heart disease (acute myocardial infarction (ICD-9-CM: 410) acute cardiac ischaemia (ICD-9-CM: 411), old myocardial infarction (ICD-9-CM: 412), angina pectoris (ICD-9-CM: 413), chronic cardiac ischaemia (ICD-9-CM: 414)); heart failure (ICD-9-CM: 428); cerebral haemorrhage (ICD-9-CM: 431); cerebral artery occlusion (ICD-9-CM: 434); transient cerebral ischaemia (ICD-9-CM: 435); cerebral circulatory disorders (ICD-9-CM: 436); atherosclerosis (ICD-9-CM: 440); other peripheral vascular disease (ICD-9-CM: 443); chronic renal failure (ICD-9-CM: 585); coronary angioplasty (ICD-9-CM procedure: 0066, 360)); and/or the presence of at least two prescriptions of anti-diabetic drugs (ATC code: A10). All other patients were classified as being at moderate cardiovascular risk.

### Drug treatments

Patients were also characterised by the strategy of treatment at baseline with lipid-lowering drugs (ATC code: C10) and antihypertensive drugs (ATC codes: C02, C03, C07, C08, C09).

### Data analysis at follow-up

During the follow-up period, the discontinuation or the first substitution of therapy was identified. Discontinuation of therapy was defined as the absence of prescriptions of the same therapeutic class (ATC group) as the index molecule in the last quarter of observation. A substitution of therapy was defined as a change to a different active substance of the same therapeutic class (ATC group) (ie, switching from simvastatin to a different statin). A switch among different products of the same active substance was identified by INN.

### Statistical analysis

Continuous variables were reported as mean±SD and compared using Student's *t*-test; categorical variables

were reported as absolute numbers and percentages and compared using the  $\chi^2$  test.

Discontinuations of therapy and substitution with another molecule of the same class were analysed by multivariate analysis using Cox proportional hazards models; covariates considered in the models were: age, male sex, high cardiovascular risk, cardiovascular treatments, change of formulation in the period of characterisation.

The analysis of Schoenfeld residuals (scaled and unscaled) was conducted to assess the proportionality of risk.

*p* Values<0.05 were considered statistically significant. All analyses were performed using STATA V.12.0 SE.

## RESULTS

### Simvastatin

A total of 38 183 patients treated with simvastatin, 17 642 male (46%), mean age 68.3±10.7 years, were included in the analysis. A total of 9392 (25%) patients were classified as being at high cardiovascular risk, while 30 467 (80%) received concomitant cardiovascular treatments (table 1).

Switches among different products occurred in 39% of patients treated with simvastatin. Switcher patients were mainly men with high cardiovascular risk; this cohort of patients was slightly younger than that of non-switcher patients, but the difference was statistically significant. With regard to switchers, a little over half carried out one switch only during the characterisation period, with 8% having four switches or more (table 2). Among patients enrolled, the non-switching and switching groups showed a similar percentage of adherence during the characterisation period (34.2% vs 33.5% (*p*=0.133), respectively).

In the follow-up period, 4232 (11%) patients undertook a therapy substitution with another molecule; a significantly lower percentage of substitution was observed in the group that did not switch to a different product of the same active substance (table 3).

In the same period, 8153 (21%) patients discontinued treatment; a significantly lower percentage of discontinuation was observed for non-switching patients (table 3). These findings were partially confirmed by multivariate analysis (table 4): the group that switched to a different product of the same active substance showed a higher probability of discontinuation (HR=1.087, 95% CI 1.040 to 1.136, *p*<0.001) and a higher, but not significant, probability of substitution of therapy (HR=1.059, 95% CI 0.996 to 1.126, *p*=0.068).

### Ramipril

A total of 32 111 patients treated with ramipril, 18 493 male (58%), mean age 66.9±12.8 years, were included in the analysis. Of these, 6898 (21%) patients were classified as being at high cardiovascular risk, while 25 261 (79%) were receiving additional cardiovascular treatments (table 1). Switches among different products

Table 1 Characteristics of the enrolled patients

Category	Simvastatin			Ramipril			Amlodipine		
	Non-switchers	Switchers	p Value	Non-switchers	Switchers	p Value	Non-switchers	Switchers	p Value
Total	23 180 (61)	15 003 (39)		22 799 (71)	9312 (29)		26 823 (72)	10 644 (28)	
Patient characteristics									
Age, years	68.5±10.7	68.0±10.6	<0.001	67.0±12.7	66.8±13.0	0.203	68.3±11.7	68.1±11.8	0.137
Male sex	10 469 (45.2)	7173 (47.8)	<0.001	12 876 (56.5)	5617 (60.3)	<0.001	14 126 (52.7)	6213 (58.4)	<0.001
High CVR	5494 (23.7)	3898 (26.0)	<0.001	4873 (21.4)	2025 (21.7)	0.470	4983 (18.6)	2143 (20.1)	<0.001
Additional treatments	18 539 (80.0)	11 928 (79.5)	0.265	17 868 (78.4)	7393 (79.4)	0.044	23 793 (88.7)	9588 (90.1)	<0.001

Values are N (%) or mean±SD.  
CVR, cardiovascular risk.

occurred in 29% of patients treated with ramipril. Switcher patients were mainly men and the difference was statistically significant. The switching group showed a higher percentage of adherence than the non-switching group during the characterisation period (48.9% vs 46.6% ( $p=0.001$ ), respectively).

With regard to switchers, again, a little over half (55%) carried out one switch only, during the characterisation period, and few (6%) had four switches or more (table 2). In the follow-up period, 2496 (8%) patients undertook a therapy substitution to another molecule; no trend towards a lower percentage of substitution was observed in the group that did not switch to a different product of the same active substance (table 3). In the same period, 5677 (18%) patients discontinued treatment, with a significant difference in favour of patients not switching to a different product of the same active substance (table 3). These findings were confirmed by multivariate analysis (table 4): there was essentially no difference between groups in terms of probability of substitution (HR=0.973, 95% CI 0.892 to 1.062,  $p=0.540$ ), while the non-switching group showed a significantly lower probability of discontinuation of therapy (HR=1.163, 95% CI 1.100 to 1.230,  $p<0.001$ ).

### Amlodipine

A total of 37 467 patients treated with amlodipine, 20 339 male (54%), mean age 68.2±11.7 years, were included in the analysis. Of these, 7126 (19%) patients were classified as being at high cardiovascular risk, while 33 381 (89%) were receiving additional cardiovascular treatments (table 1). Switches among different products occurred in 28% of patients treated with amlodipine. Switcher patients were mainly men with high cardiovascular risk; the difference was statistically significant. Among patients enrolled, switcher patients showed a lower percentage of adherence during the characterisation period than non-switcher patients (42.2% vs 43.8% ( $p=0.007$ ), respectively). With regard to switchers, just over half (54%) carried out one switch only during the characterisation period and 7% had four switches or more (table 2). In the follow-up period, 1369 (4%) patients undertook a therapy substitution to another molecule; a significantly lower percentage of substitution was observed in the group that did not switch to a different product of the same active substance (table 3). In the same period, 8707 (23%) patients discontinued treatment; a significantly lower probability of discontinuation was observed for patients not switching to another product of the same active substance (table 3). These findings were confirmed by multivariate analysis (table 4): the switcher group showed a higher probability of discontinuation (HR=1.124, 95% CI 1.074 to 1.177,  $p<0.001$ ) and substitution of therapy (HR=1.179, 95% CI 1.043 to 1.333,  $p=0.008$ ).

### DISCUSSION

In accordance with previous studies,<sup>24–28</sup> this retrospective analysis in a ‘real-world’ setting shows that age,

**Table 2** Annual frequency of switches

Simvastatin		Ramipril		Amlodipine	
Switches (N)	Patients (%)	Switches (N)	Patients (%)	Switches (N)	Patients (%)
1	7842 (52)	1	5112 (55)	1	5710 (54)
2	4062 (27)	2	2501 (27)	2	2871 (27)
3	1917 (13)	3	1116 (12)	3	1300 (12)
4	805 (5)	4	413 (4)	4	563 (5)
≥5	377 (3)	≥5	170 (2)	≥5	200 (2)

gender, cardiovascular risk and more than one cardiovascular medication on the date of enrolment could play a role in the discontinuation of therapy. A number of factors may interact to affect adherence to therapies for chronic conditions. These have been categorised by the WHO as social and economic-related factors, health system/healthcare team-related factors, condition-related factors and patient-related factors.<sup>15</sup> Since poor adherence has a significant negative impact on health outcomes and healthcare costs, and imposes a substantial burden on patients and health systems, 'increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments'.<sup>29</sup>

The data of this study also show that, for the same active substance, a change of product (regardless of whether it is a brand name or generic drug) increases the risk of discontinuation of therapy and of substitution with another molecule of the same class. Our findings were confirmed by multivariate analysis, where the switcher group showed a higher probability of discontinuation and probability of substitution for amlodipine and simvastatin users. Instead, among ramipril users, there was essentially no difference between groups in terms of probability of substitution while a higher probability of discontinuation was confirmed by multivariate analysis.

Our findings are comparable with those reported by Ghate *et al.*,<sup>30</sup> who found that switching among warfarin formulations, including substituting a generic for another generic, might expose patients with atrial fibrillation to a higher risk of thrombotic and bleeding events than those remaining on the same formulation.

There is a lot of published evidence about switching from branded to generic medicines, specifically regarding the role of prescribers and pharmacists in the opportunity for generic drug use and generic substitution, as well as concerning the acceptance by patients of generic substitution by health providers.<sup>31–32</sup> According to Italian law (Patent Law and the Health Law Regulations in Italy, Decree 95/2012), all pharmacists in Italy are required to offer patients the opportunity to substitute a prescribed non-generic, interchangeable medicinal product with a less expensive generic alternative, unless the prescriber states specifically that the prescription is

non-substitutable. At the same time, the patient can decline the substitution of a medicinal product.

However, a previous study exploring the effect of generic substitution showed that physician-induced switching from brand name to generic ramipril does not negatively affect the refill compliance of patients.<sup>16</sup>

In contrast, at present only a few studies have estimated the frequency and effects of substitution between different products of the same active substance in a clinical practice setting. Previous analyses suggest that patients switching statin therapy showed significantly poorer compliance and higher risk of death or major cardiovascular events when compared with controls who did not switch.<sup>33–35</sup>

Moreover, as observed in other studies, this study indicates that age, sex and the presence of cardiovascular risk were associated significantly with the presence of switching to a different product of the same active substance.<sup>36</sup>

In addition, our results are also comparable with others that focused on different chronic therapies, such as a recent study by Kesselheim *et al* showing that changes in pill colours and shapes increased the risk of non-adherence among patients with epilepsy.<sup>37</sup> The possibility that variation in packaging and pill appearance, as well as in the shape and colour of either box or tablet, may affect adherence is a reason for concern.

However, we cannot exclude the possibility that other potential determinants can play a key role in a reduction of patients' adherence. Observational studies<sup>38–40</sup> have demonstrated a relationship between age, gender, cardiovascular risk factors, more than one cardiovascular medication and a suboptimal adherence to therapy; our findings are in agreement with these previous analyses. The majority of the published studies showed that age was related to adherence, although a few researchers found age not to be a factor causing non-adherence. New evidence suggests that older age is not related to poorer medication adherence to cardiovascular medication. A recent systematic search of the bibliographic database MEDLINE and all Cochrane databases, analysing the relationship between age and medication adherence in adult patients with chronic heart failure (CHF), showed that older age alone is not related to poorer medication adherence compared with younger patients

**Table 3** Therapy discontinuation and substitution in switcher and non-switcher patients

	Simvastatin			Ramipril			Amlodipine		
	Switch			Switch			Switch		
	No	Yes	p Value	No	Yes	p Value	No	Yes	p Value
Total, N (%)	23 180 (61)	15 003 (39)		22 799 (71)	9312 (29)		26 823 (72)	10 644 (28)	
Therapy substitution or discontinuation									
Substitution, N (%)	2506 (10.8)	1726 (11.5)	0.037	1785 (7.8)	711 (7.6)	0.571	943 (3.5)	426 (4.0)	0.026
Discontinuation, N (%)	4826 (20.8)	3327 (22.2)	0.002	3885 (17.0)	1792 (19.2)	<0.001	6089 (22.7)	2618 (24.6)	<0.001

with CHF.<sup>41</sup> Our study does not support this concern. Several studies also attempted to hypothesise plausible reasons for poorer compliance among elderly patients. Elderly patients may have problems with vision, hearing and memory. In addition, they may have more difficulties in following therapy instructions due to cognitive impairment or other physical difficulties, such as having problems in swallowing tablets, opening drug containers, handling small tablets, distinguishing colours or identifying markings on drugs.<sup>42</sup>

However, the underlying reasons for poor adherence are not fully understood, and there may be many reasons behind these behaviours, some of which relate to the perceptions that physicians, pharmacists and patients may have of drugs and therapies. Nevertheless, the clinical consequences that may result from these perceptions are important and should be considered. Establishing better physician–patient communication, improving patient education and maintaining regular follow-up and review of patients' progress may be as important as other factors in encouraging adherence and lead to improved health outcomes and enhanced patient safety.<sup>15</sup> This includes addressing patients' perceptions about the medications they are prescribed and understanding that they may find routine changes in the name and appearance of long-term medications challenging.

Our analysis has several limitations inherent to any observational study. First, the study was performed using the administrative databases, and the reasons for switch, non-adherence or discontinuation of treatment in the patients were not retrievable from the data set. Also, no information on the role of the prescribers regarding switching within the same class or the role of the counselling pharmacist when substituting and dispensing drug packages was available to us. A second limitation is a relatively limited sample size. Although in our study we used the healthcare databases of Lombardy, Lazio and Campania, three Italian Regions localised from north to south of Italy, including data for a total population of about 2 million and considering that we have focused our analysis among users of simvastatin, ramipril and amlodipine, larger studies are needed to confirm and to enhance the generalisability of the findings, and in different populations. Third, our study did not include an outcome analysis and the evaluation of the clinical consequences of switching was beyond the scope of this work.

Despite these limitations, our study indicates that in a 'real-world' setting, changes among different products of the same active substance, including switching brand name to generic, generic to another generic and generic to brand name, are quite common among patients with CVD. Our findings suggest that switching to a different product of the same off-patent active substance, brand name or generic may expose patients to a higher risk of therapy discontinuation or substitution than continuing treatment with the same product.

**Table 4** Multivariate analysis of predictors of risk of therapy discontinuation and substitution

Variable	Simvastatin					
	Substitution			Discontinuation		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	0.993	0.990 to 0.995	<0.001	1.001	0.999 to 1.004	0.194
Male sex	1.116	1.050 to 1.186	<0.001	0.921	0.882 to 0.963	<0.001
High CVR	1.107	1.034 to 1.185	0.004	0.962	0.914 to 1.013	0.140
Additional CV treatments	1.064	0.984 to 1.152	0.121	0.821	0.778 to 0.867	<0.001
Switch to different product of the same substance	1.059	0.996 to 1.126	0.068	1.087	1.040 to 1.136	<0.001
	Ramipril					
	Substitution			Discontinuation		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.003	1.000 to 1.006	0.072	1.005	1.002 to 1.007	<0.001
Male sex	0.938	0.865 to 1.017	0.119	0.950	0.900 to 1.002	0.058
High CVR	1.158	1.057 to 1.269	0.002	0.866	0.811 to 0.926	<0.001
Additional CV treatments	1.521	1.360 to 1.700	<0.001	0.806	0.757 to 0.857	<0.001
Switch to different product of the same substance	0.973	0.892 to 1.062	0.540	1.163	1.100 to 1.230	<0.001
	Amlodipine					
	Substitution			Discontinuation		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.019	1.013 to 1.024	<0.001	1.006	1.004 to 1.008	<0.001
Male sex	0.807	0.719 to 0.907	<0.001	0.870	0.834 to 0.909	<0.001
High CVR	1.247	1.091 to 1.424	0.001	0.879	0.831 to 0.929	<0.001
Additional CV treatments	1.935	1.514 to 2.474	<0.001	0.959	0.897 to 1.025	0.215
Switch to different product of the same substance	1.179	1.043 to 1.333	0.008	1.124	1.074 to 1.177	<0.001

CV, cardiovascular; CVR, cardiovascular risk.

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**Ethics approval** For this type of study, formal consent is not required. However, to guarantee patient privacy, no personal identifiers were provided to the researchers. According to the Italian law for confidentiality of data, the study was notified to the Ethic Committees of each local health unit.

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