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TREAT: A Multicentre Cross-sectional Treatment Evaluation of Apparent Resistant hypertension in Belgium

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ABSTRACT

The goal of the TREAT study is to estimate the prevalence of true resistant hypertension in a Belgian setting of patients with apparent treatment resistant hypertension (aTRH) and to evaluate which determining factor of pseudo-resistant hypertension contributes the most to this prevalence.

TREAT is a single-visit, multicentric, non-interventional, cross-sectional survey. Inclusion criteria included: patients over 18 years receiving 3 or more antihypertensive molecules and referred to specialized hospital centers for aTRH.

A total of 201 eligible patients were included. Only 56.7% of the patients were treated with the guideline recommended triple combination therapy (i.e. renin–angiotensin–aldosterone system inhibitor, calcium channel blocker and thiazide (-like) diuretic), and only 23.4% were treated with the maximal recommended dose. WCH was present in 8.7% of the 115 patients with available ambulatory blood pressure recordings. Therapeutic adherence was self-reported as good by 80% of patients, while 20% reported poor or moderate adherence. In this cohort, the prevalence (95% CI) of true resistant hypertension was estimated at 21.9% (14.7%–30.6%).

Among patients referred to specialized centers for aTRH, about 3 out of 4 presented with pseudo-resistant hypertension. The occurrence of WCH and poor adherence appeared rather limited in our study, but half of the participants were polymedicated with non-recommended combinations of antihypertensive molecules. Inadequate dosing was observed in the majority of patients and a third was not using a single pill combination. Hence, pseudo-resistant hypertension seems to be mainly associated with the underuse of triple combination therapy and, most likely, with suboptimal dosing.

1 | Introduction

According to the WHO, high blood pressure (BP), “the silent killer”, is estimated to cause 10.8 million deaths yearly, about 19% of total annual mortality worldwide [1]. Since lowering elevated BP has been shown to reduce the risk of major cardio-

vascular (CV) events and death [2–4], BP control has become a crucial objective for physicians who have to deal with this disease. In fact, the Blood Pressure Lowering Treatment Trialists' Collaboration observed that a 5 mmHg reduction of systolic BP (SBP) reduces the risk of major CV events by about 10% [4].

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Depending on its grade and other factors such as the CV risk, the existence of a hypertension-mediated organ damage (HMOD) and/or comorbidities, hypertension can be effectively treated with lifestyle changes and medication; practical guidelines have set up several therapeutic strategies and algorithms [5–7]. The first step for achieving BP reduction in patients with slightly elevated BP, low CV risk and no HMOD, is the introduction of lifestyle changes such as losing weight, decreasing sodium intake, increasing physical activity, and adopting a healthy diet [6, 7]. When lifestyle changes alone appear not sufficient in these patients, and in patients with higher values of BP, increased CV risk and/or HMOD, medication is used [5, 7].

However, despite the established efficacy of antihypertensive treatments, some treated hypertensive patients are at the upper end of the CV risk spectrum: patients whose hypertension is resistant to antihypertensive treatment. Resistance to treatment is reported in 10%–20% of hypertensive patients [8, 9] but the prevalence studies of resistant hypertension have been limited due to variation in the definition used [6].

Hypertension is defined as resistant to treatment when the recommended treatment strategy fails to lower office SBP and diastolic BP (DBP) to <140 mmHg and/or <90 mmHg, respectively, in patients who have proven adherence to therapy. This has to be confirmed by ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) readings showing daytime BP values $\geq 135/85$ mmHg [7, 10]. The recommended therapeutic strategy includes appropriate lifestyle measures and treatment with optimal or best-tolerated doses of three or more drugs; the antihypertensive regimen should include a thiazide (-like) diuretic, an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), and a calcium channel blocker (CCB) [6]. Secondary causes of hypertension should also have been excluded.

When treatment resistant hypertension (TRH) is suspected in a patient, true TRH should be distinguished from what is called pseudo-resistant hypertension [11]. According to the ESC/ESH [5] the main causes of pseudo-resistant hypertension are (1) the so-called “white-coat phenomenon” which corresponds to elevated office BP while BP is controlled on ABPM or HBPM; (2) inadequate dosing of BP-lowering drugs since one of the criteria defining TRH is that antihypertensive drugs should be taken at the maximum or maximally tolerated dose; and (3) poor adherence to prescribed medicines, a frequent cause of pseudo-resistant hypertension that occurs in about 50% of patients and is directly related to the number of tablets prescribed [6]. When pseudo-resistance issues have not yet been ruled out as a potential cause for the ongoing high BP, the term « apparent treatment-resistant hypertension (aTRH) » is used [11].

After having applied a strict definition and excluded causes of secondary hypertension, the prevalence of true TRH is likely to be around 5% of treated patients [6]. Patients with true TRH are at higher risk of developing HMOD, chronic kidney disease (CKD), and premature CV events, emphasizing the critical importance of true TRH diagnosis to identify these high-risk patients and provide them with adequate treatment. Furthermore, adequate true TRH diagnosis allows the identification of patients with

pseudo-resistant hypertension, thus avoiding overtreatment of these patients.

In Belgium, no data exists on the prevalence of aTRH and true TRH. Many patients may be referred to specialized services for aTRH while having a pseudo-resistant hypertension.

The aim of the TREAT study (TReatment Evaluation of Apparent resistant hyperTension) is to assess in daily clinical practice the extent of pseudo-resistant and true TRH in a Belgian setting, in patients referred to specialized hospital centers for aTRH. A secondary objective is to evaluate which of the above-mentioned three determining factors of pseudo-resistant hypertension (white coat hypertension (WCH), inadequate dosing of the antihypertensive medication, poor adherence to therapy, contribute to this prevalence).

2 | Methods

TREAT is a single-visit, multicentric, non-interventional, cross-sectional survey of patients with suspected TRH. For this observational cross-sectional study, a random sample of specialist physicians from Belgian hospital centers where patients with aTRH are referred, were contacted to participate. Each specialist collected data from 10 consecutive patients seen in their clinical practice who met the inclusion criteria. These physicians were recruited over the entire geographical region of Belgium, ensuring a balanced geographical spread, in a period of 3 months (March 2020–June 2020).

Inclusion criteria were the following: men or women over 18 years, with office SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, receiving at least 3 antihypertensive molecules, and referred to specialized hospital centers (details of the molecules are available in Supplementary Material S1). Patients referred with confirmed secondary hypertension were not eligible for study participation.

Collected data: Existing data recorded in the daily practice of hospitals specializing in hypertension were collected. As the study data were collected at one specific moment in time, they constitute a cross-sectional overview of the studied population. The following individual data were extracted from the patients' medical records: demographics (age, gender, height and weight), concomitant CV risk factors/comorbidities (diabetes, previous CV events, renal disease, heart failure, dyslipidemia), office SBP and DBP, ABPM, HBPM, heart rate, number of years actively treated for high BP, antihypertensive treatment upon referral to hospital (pill burden, number of antihypertensive molecules, INN, brand name, therapeutic class and daily dose) and self-reported adherence to antihypertensive treatment.

Assessed parameters: No specific investigations or therapies were prescribed as part of this survey, aside from answering the Hill-Bone questionnaire if deemed useful by the specialist, so patients' care was not influenced. BP was measured according to the ESC/ESH 2018 Guidelines for the management of hypertension [5]. The following BP thresholds were applied: (i) Office BP levels $\geq 140/90$ mmHg; (ii) daytime ABPM BP levels $\geq 135/85$ mmHg; (iii) HBPM BP levels $\geq 135/85$ mmHg. The Hill-

Bone Scale [12] was used to assess adherence to the treatment. This 9-item tool is useful in conditions such as hypertension, diabetes, chronic obstructive pulmonary disease, and stroke [12]. It can be self-administered or interviewer-administered in less than 5 min, being then clinically useful. The Hill-Bone scale consists of 9 four-point Likert-type items (1 = *none of the time*, 2 = *some of the time*, 3 = *most of the time*, and 4 = *all the time*). The total scores on this subscale range from 9 to 36 with higher scores reflecting poorer adherence to antihypertensive drug therapy [12].

WCH was defined as BP that is, above the threshold for diagnosing hypertension in the office but below the threshold in home/ambulatory settings, for example, $\geq 140/90$ mmHg in office but $< 135/85$ mmHg at home/ambulatory daytime (or 24-h BP $< 130/80$ mmHg) [7].

Masked hypertension was defined as BP that is, below the hypertension diagnostic threshold in the office but above the hypertension diagnostic threshold in home/ambulatory settings, for example, $< 140/90$ mmHg in clinic but $\geq 135/85$ mmHg at home/ambulatory daytime (or 24-h BP $\geq 130/80$ mmHg) [7].

In this study, adequate dosing was defined as the maximum dose for hypertension recommended by the Belgian Centre for Pharmacotherapeutic Information (BCPI).

2.1 | Statistical Analysis

Data were summarized using proportions, means, standard deviations (SD), medians and interquartile ranges (IR). Differences in continuous or dichotomous variables between groups were evaluated using the Mann-Whitney *U* test or Fisher's exact test. The 95% confidence intervals for the prevalence of TRH were calculated according to the Clopper–Pearson exact method. Odds ratios in the analysis of the association between true TRH and patients characteristics were obtained by means of logistic regression models. Their 95% confidence intervals and *p*-values were based on Wald chi-square test. A Type I error level of 0.05 was chosen to indicate statistical significance. All analyses were performed with SAS software (release 9.4, Cary, NC, US).

3 | Results

A total of 25 physicians participated in the study and included 232 patients in the survey. A total of 21 centers located in various regions of the country, participated in the study. However, 7 patients were excluded since they were treated with less than 3 antihypertensive molecules and another 24 patients were found to be normotensive at the time of the study visit. The latter group included 5 patients with elevated ambulatory and/or home blood pressures, resulting in a 4.2% prevalence of masked hypertension. Hence, data of 201 patients were included in the present analyses.

3.1 | Baseline Characteristics

Table 1 depicts some general patient characteristics, the prevalence of comorbidities and a description of their BP characteristics.

About half of the study sample were men. The mean age of the population was around 65 years and 40% of patients were found to be obese. The majority of patients presented with comorbidities, mostly diabetes, prior CV events and renal failure. Comorbidities were more frequent in men than women. As can be expected, the large majority of patients were using antihypertensive medication for at least 5 years and half of the population for at least 10 years.

3.2 | Blood Pressure

Almost all patients (98.0%) were included because of a SBP exceeding the 140 mmHg threshold, while somewhat more than half of patients presented with diastolic hypertension as well. The same pattern was seen in the 115 (57.2%) patients with either ambulatory or home measured BP available. In about 90% of these patients, the 135 mmHg threshold for SBP was exceeded. Hypertension based on office measurements, was confirmed by ambulatory or home BP in 91.3% of cases, hence bringing the prevalence of WCH to 8.7%, this prevalence being somewhat higher in women (13.0%) than in men (5.0%), the difference however not being statistically significant ($p = 0.19$).

3.3 | Adherence to Prescribed Medicines

Treatment adherence was self-perceived as good in 80.0% of patients, moderate in 16.8% of patients and poor in 3.2% of patients, with men being slightly more compliant with their therapy than women (Table 2). Therapeutic adherence was assessed by the Hill-bone scale in 60% of the patients and revealed a median (IR) score of 10, reflecting high patient adherence.

3.4 | Use of BP-lowering Drugs and Dosing

As depicted in Table 3, only 56.7% were treated with the recommended triple therapy (renin-angiotensin-aldosterone system inhibitor (RAASi) + CCB + diuretic combination) and among these, only 41.2% did so at the appropriate dosage making an overall estimate of 23.4% of patients being managed in accordance with the 2023 ESH and the 2024 ESC hypertension guidelines [6, 7]. Overall, 73.1% of patients were using at least one single pill combination (SPC) (bi- or tri-therapy). As shown in Table 4, the use of the recommended triple therapy whether or not at the maximum dose, was significantly associated with age, previous CV events, and to a lesser extent with the presence of heart failure.

3.5 | Prevalence of True Resistant Hypertension

Finally, our most accurate assessment of the occurrence of true TRH, derived from a subsample of 114 patients with adequate data on all excluding qualifiers, is displayed in Table 5. After exclusion of patients with WCH, insufficient treatment intensity according to the current hypertension guidelines [6, 7], and those with poor therapeutic adherence, the prevalence of true TRH was estimated at 21.9% (14.7%–30.6%) with a markedly threefold higher prevalence in men ($p = 0.010$) compared to women. True TRH was also more common in obese patients, an association

TABLE 1 | Baseline characteristics of the study population.

	All N = 201	Women N = 98	Men N = 102
Age (years)	64.7 (12.6)	66.6 (12.4)	63.0 (12.6)
Body mass index (kg/m ²)	29.7 (5.8)	29.3 (6.0)	30.0 (5.7)
Body mass index ≥ 30 kg/m ²	40.0% (78)	33.3% (31)	46.1% (47)
Treatment duration ≥ 5 years	78.8% (126)	83.5% (66)	74.1% (60)
Treatment duration ≥ 10 years	51.3% (82)	58.2% (46)	44.4% (36)
No comorbidities (%)	33.8% (68)	40.8% (40)	26.5% (27)
Diabetes (%)	33.8% (68)	26.5% (26)	41.2% (42)
Prior cardiovascular event (%)	31.3% (63)	26.5% (26)	36.3% (37)
Heart failure (%)	10.0% (20)	8.2% (8)	11.8% (12)
Renal disease (%)	26.9% (54)	24.5% (24)	29.4% (30)
Other comorbidities (%)	23.9% (48)	21.4% (21)	26.5% (27)
Office SBP (mmHg)	162.7 (17.7)	163.5 (18.7)	161.8 (16.8)
Office SBP ≥ 140 mmHg (%)	98.0% (197)	98.0% (96)	98.0% (100)
Office DBP (mmHg)	87.1 (13.0)	84.5 (13.8)	89.5 (11.9)
Office DBP ≥ 90 mmHg (%)	55.8% (111)	49.5% (48)	61.4% (62)
Ambulatory or home BP available (%)	57.2% (115)	55.1% (54)	58.8% (60)
Ambulatory or home SBP (mmHg)	154.2 (18.4)	156.5 (20.1)	152.0 (16.8)
Ambulatory or home SBP ≥ 135 mmHg (%)	90.4% (103)	87.0% (47)	93.2% (55)
Ambulatory or home DBP (mmHg)	87.0 (12.8)	85.8 (13.5)	88.0 (12.3)
Ambulatory or home DBP ≥ 85 mmHg (%)	56.1% (64)	49.1% (26)	61.7% (37)
Ambulatory or home SBP/DBP ≥ 135/85 mmHg (%)	91.3% (105)	87.0% (47)	95.0% (57)
White coat hypertension (%)	8.7% (10/115)	13.0% (7/54)	5.0% (3/60)

Note: Cell entries are mean (SD) or % (n).

TABLE 2 | Adherence to antihypertensive therapy among study patients.

	All N = 201	Women N = 98	Men N = 102
Self-reported adherence			
Poor% (n)	3.2% (6)	5.6% (5)	1.1% (1)
Moderate % (n)	16.8% (31)	22.2% (20)	11.7% (11)
Good % (n)	80.0% (148)	72.2% (65)	87.2% (82)
Hill-bone medication adherence score ^a	10 (9–14)	11 (9–15)	10 (9–13)

Note: Hill-bone medication adherence scale available in n = 121 patients. Cell entries are mean (SD) or % (n).

^a Median (interquartile range).

being however at borderline significance in multivariate analysis (Table 6).

4 | Discussion

This multicentric cross-sectional study aimed to assess the true prevalence of TRH in a Belgian cohort and identify the most

TABLE 3 | Use of antihypertensive therapy.

	All N = 201	Women N = 98	Men N = 102
Using SCP (%)	73.1% (147)	71.4% (70)	74.5% (76)
Using triple therapy 2023 ESH and 2024 ESC guidelines ^a	56.7% (114)	54.1% (53)	59.8% (61)
Of whom at maximum dose	41.2% (47)	32.1% (17)	49.2% (30)
Using triple therapy 2023 ESH and 2024 ESC guidelines at maximum dose	23.4% (47)	17.3% (17)	29.4% (30)

^a Renin-angiotensin-aldosterone system inhibitor (RAASi), calcium channel blocker (CCB) and diuretic.

common contributors to pseudo-resistance. Our findings confirm that the majority of patients referred for aTRH do not meet the criteria for true resistance. Only 21.9% of the study population fulfilled the definition of true TRH after exclusion of WCH, suboptimal therapy, and poor adherence, highlighting the significant burden of pseudo-resistance in clinical practice. These findings align with previous data suggesting that a substantial

TABLE 4 | Characteristics of patients complying to the 2023 ESH and the 2024 ESC guidelines on triple therapy.^a

	Using triple therapy 2023 ESH and 2024 ESC guidelines			Significance ^b
	No N = 87	Yes Not at max dose N = 67	At max dose N = 47	
Female (%)	51.7% (45)	53.7% (36)	36.2% (17)	<i>p</i> = 0.248
Age (years)	66.8 (11.5)	65.7 (13.4)	59.5 (12.0)	<i>p</i> = 0.0072
Body mass index (kg/m ²)	28.9 (5.8)	30.0 (5.9)	30.5 (5.7)	<i>p</i> = 0.172
Body mass index ≥ 30 kg/m ² (%)	32.9% (27)	40.3% (27)	52.2% (24)	<i>p</i> = 0.103
Treatment duration ≥ 5 years	81.4% (57)	72.5% (37)	82.1% (32)	<i>p</i> = 0.422
Treatment duration ≥ 10 years	47.1% (33)	52.9% (27)	56.4% (22)	<i>p</i> = 0.623
No comorbidities (%)	35.6% (31)	31.3% (21)	34.0% (16)	<i>p</i> = 0.855
Diabetes (%)	28.7% (25)	34.3% (23)	42.6% (20)	<i>p</i> = 0.271
Prior cardiovascular event (%)	39.1% (34)	32.8% (22)	14.9% (7)	<i>p</i> = 0.015
Heart failure (%)	9.2% (8)	16.4% (11)	2.1% (1)	<i>p</i> = 0.041
Renal disease (%)	24.1% (21)	34.3% (23)	21.3% (10)	<i>p</i> = 0.226
Other comorbidities (%)	19.5% (17)	23.9% (16)	31.9% (15)	<i>p</i> = 0.277
Office SBP (mmHg)	161.0 (15.4)	162.1 (20.1)	166.5 (17.8)	<i>p</i> = 0.121
Office DBP (mmHg)	86.2 (12.7)	86.2 (12.5)	89.9 (14.2)	<i>p</i> = 0.504
Ambulatory or home SBP (mmHg)	150.6 (16.1)	155.5 (18.7)	156.4 (20.2)	<i>p</i> = 0.546
Ambulatory or home DBP (mmHg)	85.3 (10.1)	85.5 (18.7)	90.5 (15.1)	<i>p</i> = 0.408
Hill-bone medication adherence score ^a	11 (9–15)	10 (9–14)	10 (9–14)	<i>p</i> = 0.868

^aRenin-angiotensin-aldosterone system inhibitor (RAASI), calcium channel blocker (CCB) and diuretic.^bAccording to Fisher's exact test or the Mann-Whitney U test.**TABLE 5** | Prevalence of true resistant hypertension.

	All	Women	Men
Number of patients with data available on ambulatory/home BP, therapeutic adherence and use of triple therapy ^a (2023 ESH and 2024 ESC guidelines)	N = 114	N = 54	N = 59
White coat hypertension	N = 11	N = 7	N = 4
Not using triple therapy at max dose (Not using triple therapy)	N = 78 (N = 37)	N = 42 (N = 21)	N = 35 (N = 15)
Not adherent	N = 25	N = 19	N = 6
True resistant hypertension	25/114	6/54	19/59
Prevalence (95% CI)	21.9% (14.7%–30.6%)	11.1% (4.2%–22.6%)	32.2% (20.6%–45.6%)

Note: Gender was unknown in 1 patient.

^aRenin-angiotensin-aldosterone system inhibitor (RAASI), calcium channel blocker (CCB) and diuretic.

proportion of patients referred for aTRH may not have true TRH and that the prevalence increases with increasing CV risk [11, 13].

Among the various contributors to pseudo-resistance, suboptimal treatment regimens, more specifically the underuse of guideline-recommended triple combination therapy, emerged as the most prevalent. Less than 60% of patients were treated with the recom-

mended combination of a RAASI, a CCB, and a thiazide (-like) diuretic, and only 23.4% were receiving these at their maximally recommended doses. This finding underscores the gap between guideline recommendations and clinical practice. Suboptimal dosing was significantly associated with older age, history of CV events, and heart failure, potentially reflecting physician hesitancy in prescribing higher doses in patients perceived as frail or vulnerable.

TABLE 6 | Prevalence of true resistant hypertension in relation to patients characteristics.

	% True resistant hypertension	Odds Ratio (95% CI), <i>p</i> -value ^a	
		Univariate	Multivariate
All	21.9% (25/114)		
Sex			
Female	11.1% (6/54)	1	1
Male	32.2% (19/59)	3.80 (1.39–10.42), <i>p</i> = 0.010	3.58 (1.15–11.16), <i>p</i> = 0.028
Age			
< 65 years	27.8% (15/54)	1	1
≥ 65 years	17.5% (10/57)	0.55 (0.22–1.37), <i>p</i> = 0.20	0.70 (0.24–2.06), <i>p</i> = 0.51
Body mass index			
< 30 kg/m ²	15.2% (10/66)	1	1
≥ 30 kg/m ²	32.6% (14/43)	2.70 (1.07–6.83), <i>p</i> = 0.036	2.56 (0.92–7.08), <i>p</i> = 0.071
Treatment duration			
< 10 years	21.7% (10/46)	1	
≥ 10 years	20.0% (10/50)	0.90 (0.34–2.41), <i>p</i> = 0.83	^b
Diabetes			
No	18.3% (13/71)	1	1
Yes	27.9% (12/43)	1.73 (0.70–4.24), <i>p</i> = 0.23	1.39 (0.47–4.11), <i>p</i> = 0.55
Prior CV event			
No	26.6% (21/79)	1	1
Yes	11.4% (4/35)	0.36 (0.11–1.13), <i>p</i> = 0.080	0.31 (0.09–1.13), <i>p</i> = 0.075
Heart failure			
No	23.1% (24/104)	1	1
Yes	10.0% (1/10)	0.37 (0.04–3.07), <i>p</i> = 0.37	0.34 (0.03–3.40), <i>p</i> = 0.36
Renal disease			
No	20.5% (16/78)	1	1
Yes	25.0% (9/36)	1.29 (0.51–3.28), <i>p</i> = 0.59	1.75 (0.56–5.46), <i>p</i> = 0.34

^aaccording to logistic regression models.^btreatment duration not included in the multivariate model because of missing values.

Interestingly, male sex was independently associated with true TRH, and a trend towards higher rates in obese individuals was seen. These findings are consistent with known risk profiles for TRH although the sex-difference is usually not this large [14].

Contrary to some prior studies, we observed a relatively low prevalence of WCH (8.7%) and lower self-reported non-adherence (20.0%) [15, 16]. An underestimation of WCH is possible as ABPM was only available in 57% of participants. The use of the Hill-Bone scale confirmed generally moderate to good adherence, but this tool is subject to the limitations of self-reporting and could underestimate the number of patients with poor adherence. Other limitations of this study include its cross-sectional design and the reliance on a single-visit assessment, which may not fully capture long-term adherence or BP variability. In addition, no data on lifestyle, such as smoking and in particular salt consumption were collected and secondary HT was excluded

if known, but was not systematically verified in all patients included.

Our findings underscore the critical need for systematic medication review and optimization prior to confirming a diagnosis of TRH. Particularly, ensuring the use of the recommended triple combination therapy at adequate doses in single-pill combinations to enhance adherence, may substantially reduce the number of patients incorrectly labelled as treatment-resistant.

In conclusion, our study highlights that pseudo-resistant hypertension is highly prevalent among patients referred for aTRH, largely due to suboptimal treatment strategies rather than poor adherence or white coat effect. A structured, stepwise approach to evaluating aTRH, emphasizing medication optimization, remains essential to avoid overtreatment and ensure accurate diagnosis.

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Ethics Statement

This study was conducted in accordance with Belgian regulations regarding retrospective studies (2004 guidance). As the study was observational and based on routinely collected data from general practice medical records, formal approval by an ethics committee was not required.

Consent

Patient informed consent was not required, as the study was observational, retrospective in nature, and relied solely on anonymized data routinely recorded in medical practice.

Conflicts of Interest

Bregt Van Nieuwenhuyse and Mathilde Chabot are employees of Servier BeLux. The other authors declare no conflicts of interest related to this work.

Data Availability Statement

The data that support the findings of this study are available upon request from the corresponding author Sofie Brouwers.

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No previously published material, figures, or tables were reproduced in this article.

Trial Registration

This study is registered with the ISRCTN registry under the identifier ISRCTN33435469.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File 1: jch70230-sup-0001-SupMat.docx