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ORIGINAL ARTICLE

Systematic Data Monitoring and Analysis of Cardiovascular *Off-label* Prescriptions in Pediatrics: Focus on Angiotensin-Converting Enzyme Inhibitors (ACE-I) and Beta Blockers

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Abstract

Introduction Many efforts have been made to stimulate clinical trials (CTs) in pediatrics but most of the drugs are still authorized only in adults and used off-label in the pediatric population.

Aim To assess how widespread is the off-label prescription in Italy and to identify areas of unmet medical need by applying a model for the systematic collection and analysis of data.

Methods A study was performed using 2015 data from the Italian Medicines Utilization Monitoring Centre Health Database (OsMed). A study sample of 3,726,583 pediatric patients, was considered. Cardiovascular drugs were selected for this study. Assessment of the off-label use, the analysis of the pharmacovigilance signals, a bibliographic research and the analysis of ongoing CTs were carried out.

Results In 2015, 8,544 pediatric patients received treatment with a cardiovascular drug. Angiotensin converting enzyme inhibitors (ACE-I) followed by beta blockers agents are the most prescribed molecules. Eight molecules were selected and an in-depth analysis conducted. The PhV network showed only one record of adverse reaction as off-label in 2015. The results show several therapeutic areas of use in pediatrics.

Conclusion *Off-label* in pediatrics is largely widespread in Europe and US and our results show it is also present in Italy. Molecules selected are used *off-label* for therapeutic areas such as oncologic, hematological and rare diseases. Results of pharmacovigilance suggests underreporting. The analysis carried out in this study could be an open track for a systematic monitoring activity and of interest for prescribers, pediatricians and other healthcare professionals during the clinical practice.

Keywords Pediatric drugs · Off-label · Cardiovascular pediatric drugs · Pharmacovigilance (PhV)

1 Introduction

Medicinal products are not always used in accordance with the authorised therapeutic indications, populations, routes of administration, dosage and formulation in clinical practice and therefore they are considered *off-label*, even if used in accordance to international clinical guidelines. This approach continues to be widely exploited in particular areas such as in paediatrics [1–4]; this is mainly due to the fact that medicinal products are not tested in CTs in this population, as it also applies to other vulnerable populations, such as elderly people and pregnant women.

The extent of this phenomenon in Italy has not been studied yet. In the European Union, the Pediatric Regulation 1901/2006/EC [5] has brought about an increase in new drugs approved in particular areas such as rheumatology and infectious diseases [6]. However, of the number of authorised molecules appears too limited to date. In addition to ethical and sometimes economic factors, the pediatric population is eterogeneous and differences in pharmacokinetic and pharmacodynamic characteristics can be identified based on the different age groups [7, 8].

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Key Points

In the present manuscript, we perfectionate a model for the systematic collection of data on utilization of off-label drugs in pediatrics and performed an accurate literature research with the aim of describing this widespread phenomenon and identifying possible new areas of use in pediatrics related to unmet clinical need areas.

We analyzed data related to prescription drugs reimbursed by NHS in Italy for the pediatric population. Our results show that the prescription of off-label drugs is widely spread in this population and that the molecules considered for this research could be of interest in different therapeutic areas other than the cardiovascular one, such as for rare diseases or oncologic and hematological diseases. Only one ADR report is included in the national PhV network, suggesting possible underreporting for the selected molecules used off-label.

The study conducted could be of interest not only for decision makers but also for prescribers, pediatricians and other healthcare professionals during their clinical practice.

In Italy, according to the Law 648/96 and amendments [9–11], which states that the Italian Medicines Agency (AIFA) can drow up lists of drugs, whose *off-label* or unlicensed use is reimbursed by the Italian National Health Service (NHS), eleven lists of pediatric drugs were produced and are currently in place [12].

The goal of the study was to verify how wideapread this phenomenon is in Italy and to distinghish in which areas drugs are mostly prescribed outside the authorized indications in the pediatric population.

Moreover, for molecules proven to be used *off-label*, the reports recorded in the PhV network was assessed and a literature search was conducted to verify in which therapeutic areas are prescribed with the aim of identifying unmet clinical need, for which specific medicinal products are lacking and *off-label* use is widespread.

2 Methods

The approach consist in 5 steps as represented in Fig. 1.

Step 1. Pediatric prescription analysis

We considered data from the OsMed Health-DB Database [13] of anonymized pediatric prescriptions made by general praticioners, pediatricians and NHS specialists, reimbursed by NHS and supplied by public and private community pharmacies (1 January 2015 to 31 December 2015). The dataset recorded name of the molecule, Anatomical -Therapeutics -Chemical Classification System (ATC) till 5th level, number of patients to whom the molecule is prescribed, sex, age and defined daily doses (DDD).

Age was categorized into groups: infants and babies: 0–2 years; small children: 3–5 years; children: 6–11 years; adolescents: 12–17 years.

The prescriptions were divided according to first level ATC; total DDD of each ATC was considered and then selected the prescriptions for molecules covering the 75% of the total DDDs. This step was made necessary in order to avoid considering prescriptions for which a very small consumption was recorded, possibly related even to single prescriptions. We considered DDD, which is the assumed average maintenance dose per day for a drug used for its main indication in adults as an indicator of consumption also for the pediatric prescriptions, only at this stage.

We selected the ATC C (Cardiovascular System) for which results the highest number of prescribed molecules; among these the categories with the highest prevalence of use, ACE-Is and beta-blocker agents.

Step 2. Off-label use identification

For the selected categories our aim was that of identifying the possible *off-label* use in paediatrics so we assessed

Fig. 1 Approach used for the systematic data monitoring and analysis of off-label prescriptions in pediatrics
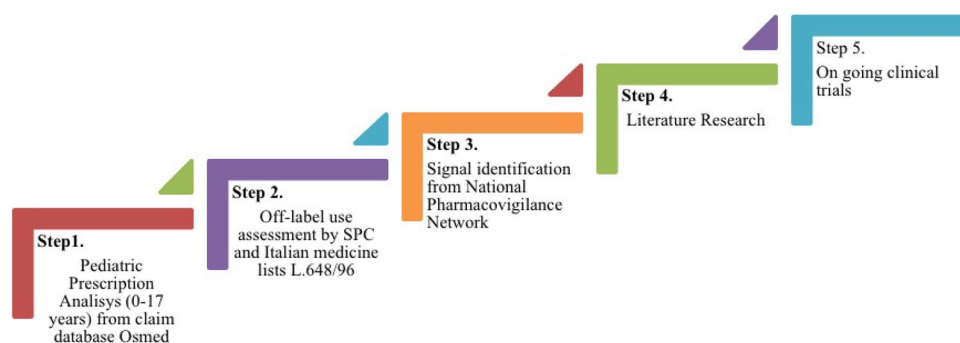
the summary of product characteristics (SmPC) authorized (September 2018).

Subsequently, was also verified the presence in the lists of *off-label* drugs reimbursed by NHS, referred to the Law 648/96 for pediatric use available on the AIFA website (March 2021).

Step 3. Pharmacovigilance signal detection

A search was performed from the national PhV network (period from 1 January 2014 to 31 December 2016) in order to identify possible new adverse drug reactions (ADRs) connected with the *off-label* use of ACE-Is and beta-blockers. We considered only the ADR reports of the pediatric population related to 2015 (to match with data of consumption) with *off-label* flagged records.

Step 4. Literature screening

Literature research of the studies related to the selected molecules in order to identify the therapeutic areas of utilization was performed.

The Medline database via PubMed was screened in September 2018, considering the last 5 years of human subheading. The search strategy relied on the term "Name of active substance" (i.e. atenolol) AND "Pediatric use" or its synonyms. For propranolol, studies concerning the use for approved indications for oral formulation in syrup (after the study period) were excluded and therefore the search was limited with the Boolean operator NOT, entering in the search string "propranolol" AND "pediatric use" NOT "hemangioma".

Study Eligibility

Included: containing children <18 years.

Excluded: Case reports, case series, letters, comments and studies falling outside the scope of the study were excluded. Reasons for exclusions: (1) related to galenic preparation; (2) studies describing the interaction of two or more drugs; (3) preclinical studies; (4) use on pregnant and/or lactating women; (5) drug utilization without comments on efficacy/safety; (6) studies presenting pooled data that did not allow extrapolating useful information. The rationale for the exclusion of case reports/series was made necessary to focus the attention on studies with higher scientific evidence.

Excluded studies were organized in a table with motivation of exclusion (Supplementary table S1).

Study selection

A review author (SMC) identified studies with the criteria for this review. The author included or excluded studies based on a first de-duplicated analysis recording motivation for exclusion. Discrepancies in the selection process were resolved between two authors (SMC and GC) by consensus.

Data Extraction

Data extraction was performed (SMC) using standardized forms also checked by GC. A chart review for each molecule was created, containing information on the study design, indication, comparator if used, study population and results.

Data Synthesis

A qualitative synthesis of the main features of the selected studies was undertaken and the key findings were tabulated (Supplementary table S2).

Step 5. Ongoing CTs

The evaluation of ongoing CTs was carried out by searching the "Clinicaltrial.gov" database [14] and selecting the name of the "active substance", the "pediatric population" (0–17 years) and the status of the study (December 2018).

3 Results

Step 1

During 2015, the OsMed Health-DB database collected data on 4,944,184 (males: 2,655,507; females: 2,288,677) pediatric individuals (0–17 years).

The prescriptions for molecules covering the 75% of the total DDDs accounting for 3,726,583 (37.2% of total Italian pediatric population in 2015) are considered [15].

The study sample includes 14,2% children, 26,2% small children, 11,4% teenagers and 19,1% babies and infants 0–2 years; of the total population 54% are males and 46% females (Appendix Table 1).

ATC J (antinfective for systemic use 51%) and R (respiratory system 34%) were the most representative in the 2015 (Fig. 2).

Forty therapeutic/pharmacological subgroups (3rd level ATC) were prescribed for 68 active substances and 10 associations of two drugs (5th level ATC).

The study focused on drugs belonging to the ATC C and in particular on ACE-I and beta blocker agents. Moreover, the prescriptions highlight how the largest number of drug-therapeutic categories and prescribed active ingredients belong to the cardiological area: eight pharmacological classes (3rd level ATC) with 15 prescribed active substances (5th level ATC) belong to this 1st level ATC C.

8,544 pediatric patients into the study sample received a cardiovascular drug (56% male and 44% female).

2,836 (33,2%) pediatric received an ACE-I of which 59% were male. Half (52%) were aged 12–17 yrs, 28% 6–11 yrs, 11% 3–5 yrs and 8% 0–2 yrs.

Beta blockers are the most prescribed after ACE-Is. In total, at least one beta blocker was prescribed to 2,058 (25%) patients (0–17 yrs) of which 56% male. More than half (61%) of the sample was aged 12–17 yrs, 23% 6–11 yrs, while very low percentages related to patients 3–5 yrs and 0–2 yrs (9% and 7% respectively). The most prescribed molecule for children aged 0–2 yrs is captopril (Appendix Tables 2 and 3; Fig. 3).

Among ACE-Is, ramipril, enalapril and captopril were chosen for further analysis while among the beta-blockers bisoprolol, carvedilol, propranolol, atenolol and, finally, metoprolol were used (Appendix Table 4, Fig. 4).

Step 2

Ramipril, enalapril and captopril have no specific pediatric indication, suggesting *off-label* prescription.

For ramipril SmPC does not explicitly report the contraindication. However, states that use is not recommended in children and adolescents in the absence of sufficient efficacy and safety data.

For enalapril, although a pediatric posology is reported, the experience of use in CTs on hypertensive pediatric patients is limited. In addition, SmPC explains that it is not recommended in children for indications other than hypertension.

For captopril a pediatric dosage is reported but efficacy and safety in this population have not been fully established.

Furthermore, ramipril is not reimbursed by the NHS according to Law 648/96, while enalapril and captopril are reimbursed for hypertension, heart failure and proteinuria.

Bisoprolol, atenolol, metoprolol, carvedilol, and propranolol have no pediatric therapeutic indications; the use of bisoprolol and atenolol is not recommended as stated in SmPC due to the lack of pediatric experience. For carvedilol and metoprolol, there are no sufficient data on efficacy and safety. For propranolol (tablet), the dose related to the use in arrhythmias is in the SmPC while the use of this molecule is clearly contraindicated in pediatrics.

The NHS does not reimburse bisoprolol and atenolol. Carvedilol, propranolol and metoprolol are reimbursed for hypertension, carvedilol also for heart failure and propranolol for cardiomyopathy, tetralogy of fallot, hyperthyroidism, arrhythmias, migraine, portal hypertension and gastroesophagitis.

For the selected molecules proven to be *off-label* in Step 2, data of the PhV reports were analyzed.

Step 3

From the national PhV network, only one record of ADR was reported in 2015 in a pediatric patient who received propranolol as treatment for hemangioma at the dosage of 15 mg/die.

Propranol obtained an authorization in oral solution for infantile hemangioma but the PhV signals referres to the use of tablets, which are still not authorized for the pediatric population, as of today.

No other records were found in the PhV network for all the other selected molecules.

The ADR described includes "bradycardia, hypoglycaemia, unconsciousness, metabolic acidosis"; bradycardia is reported in the SmPC as common (1-9.9%) however
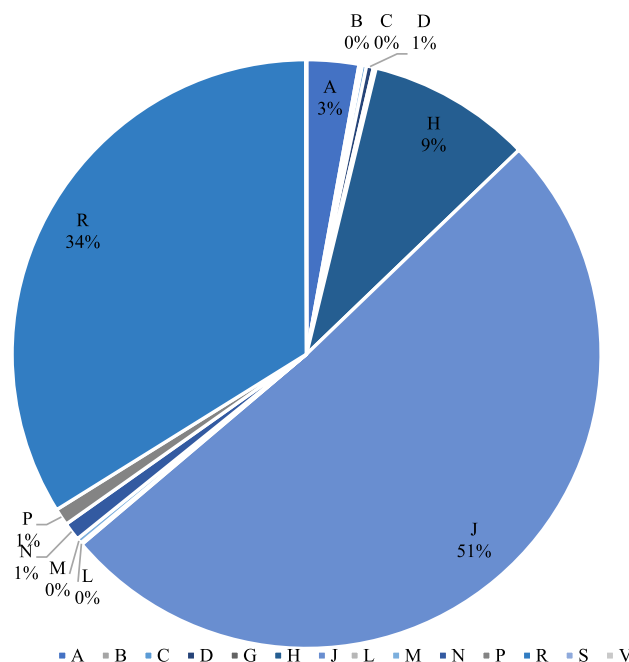

Fig. 2 Prescribed molecules in Italy for the year 2015 and collected by OsMed database, divided according to the ATC classification system. **A** Alimentary tract and metabolism, **B** Blood and blood forming organs, **C** Cardiovascular system, **D** Dermatologicals, **G** Genito-urinary system and sex hormones, **H** Systemic hormonal preparations, excluding sex hormones and insulins, **J** Anti-infectives for systemic use, **L** Antineoplastic and immunomodulating agents, **M** Musculoskeletal system, **N** Nervous system, **P** Antiparasitic products, insecticides and repellents, **R** Respiratory system, **S** Sensory organs, **V** Various

hypoglycaemia has been reported in infants and children with frequency not known. Today in a formulation suitable for pediatric use, the drug has a specific indication for childhood hemangioma.

Step 4

The original search identified 186 titles of which 48 references were selected for full-text assessment (Appendix table 5, AT5). In the original research the studies related to propranolol used for hemangioma were directly excluded. The remaining 138 papers were excluded in accordance with established criteria.

A total of 13 full texts [AT5.1–13] were deemed eligible for further assessment (Fig. 5); for the ACE inhibitors: 3 reviews, 4 randomized CTs and 6 observational/descriptive studies (AT5); while 35 full-texts [AT5.14–48] (Fig. 5) were related to beta blocker agents: 11 systematic reviews and meta-analysis, 10 CTs and 15 observational/descriptive studies (AT5).

ACE Inhibitors

Studies published on ramipril show 2 main possible uses in the pediatric population that could be considered effective

and safe: remission of proteinuric nephropathies in association with losartan [AT5.1] and post heart transplant vasculopathy [AT5.2]. The first study is observational while the second is a randomized CT. Ramipril appears to be a safe and effective antihypertensive early after heart transplant and does not significantly affect plaque progression during the first year. However, the number of pediatric patients compared to the enrolled population ($n=96$) is small ($n=7$; 12–19 yrs) on post heart transplant vasculopathy [AT5.2].

Literature on enalapril relates to its use for the treatment of univentricular heart and as a pharmacological support for the Fontan procedure [AT5.3]. This is a review considering one single study with enalapril *vs* placebo where enalapril did not show improvements in this condition.

Another use is for the treatment of anthracycline cardiotoxicity [AT5.4,5] that considered enalapril as a cardioprotective agent and conclude that enalapril can provide only temporary cardioprotection.

Hypertension after successful repair of aortic coarctationis is another use in which enalapril showed efficacy in the reduction of left ventricular myocardial infarction, however, it has caused adverse events (AEs) that led to discontinuation of treatment [AT5.6].

Other possible uses of enalapril are for the remission of proteinuric nephropathies in pediatric kidney transplant recipients and in chronic kidney disease (CKD). For the first condition, enalapril is used plus losartan showing it may be beneficial in kidney transplant recipients by decreasing blood pressure (BP) and proteinuria, but may be associated with serious AEs. From a retrospective analysis, its use could be associated with potentially life-threatening serious AE, including hyperkalaemia and acidosis [AT5.7].

Four studies were selected from literature on captopril. Captopril *vs* propranolol for infantile hemangiomas (IH), where propranolol shows a greater benefit than captopril [AT5.8].

The second study with captopril on pediatric with hypertension and obesity shows efficacy of the ACE-I in reducing urinary chemokine levels due to the chronic inflammatory state associated with obesity and contributing to the pathogenesis of hypertension [AT5.9].

Two more studies on enalapril and captopril evaluate the safety profile. One study shows that patients experiencing ACE-I associated acute kidney injury (AKI) have a significantly greater decrease in BP than patients who do not experience ACE-I associated AKI, suggesting that the risk and benefits of ACE-I in pediatric patients should be preventively evaluated before initiation of therapy [AT5.10,11].

Other studies confirmed a higher risk of renal ADRs with enalapril when used in pediatric patients [AT5.12,13]. A similar safety profile for nephrotoxicity aspects is also evident for captopril [AT5.12].

Beta Blockers

35 full texts were selected for beta blockers agents: bisoprolol, atenolol, metoprolol, propranolol and carvedilol These molecules are not authorized for pediatric use except for propranolol which obtained authorisation for childhood hemangiomas in the proliferative phase, in a different formulation than that prescribed in 2015.

Literature on bisoprolol and carvedilol [AT5.14,15,16] shows a main use for these molecules in the cardiologic area for the treatment of heart failure in congenital pediatric heart disease (CHD), hypertension and ventricular systolic dysfunction. Specifically, bisoprolol plus diuretic (hydrochlorothiazide) was studied in a CT and did not result in a significant reduction in systolic BP but did have an effect on diastolic BP [AT5.14].

For carvedilol there are studies evaluating its effectiveness in portal hypertension, in heart failure in patients who have had a Fontan intervention and in preventing heart failure in cancer survivors exposed at high doses of anthracyclines [AT5.16,28]. Of these two studies, the meta-analysis [AT5.16] demonstrated clinical outcome benefit of carvedilol in children with chronic heart failure.

For metoprolol five full texts were considered.

One metanalysis considers metoprolol, carvedilol and bisoprolol, showing a significant improvement of echocardiographic parameters in pediatric with systemic left ventricular failure. However, the use of beta blockers did not provide significant benefits in improving the ejection fraction in patients with right ventricular failure. Nonetheless, beta blockers may be effective to prevent the clinical deterioration of pediatric and congenital heart disease patients with heart failure [AT5.15].

Another possible use investigated in CT on BP shows that metoprolol compared with placebo significantly reduced systolic BP but not diastolic BP (low-quality evidence) [AT5.14].

Other three full texts investigate the use of this beta blocker on postural tachycardia syndrome (POTS) [AT5.17,18,19] as it is currently used for this condition. The studies considered the correlation of biomarkers (copeptin level, plasma norepinephrine levels and plasma C-type natriuretic peptide concentration) to therapeutic effectiveness of metoprolol on POTS.

Atenolol is studied in comparison with propranolol for hemangiomas and efficacy and safety was assessed both in proliferative and ulcerative hemangiomas [AT5.20–24]. Another indication is for Marfan syndrome, a rare connective tissue disease, involving heart and blood vessels, ligaments and skeletal system, eyes and lungs [AT5.25,26].

Another study evaluated the tolerability and efficacy of atenolol *vs* enalapril on 24-h BP and left ventricular mass index (LVMI) concluding that enalapril and atenolol are similarly effective in reducing BP but only enalapril demonstrated a significant reduction of LVMI. Moreover, enalapril

Fig. 3 Number of pediatric patients treated divided per age and selected molecule

Legend:
RAMIPRIL — ENALAPRIL — CAPTOPRIL — BISOPROLOL — METOPROLOL — CARVEDILOL — PROPRANOLOL — ATENOLOL
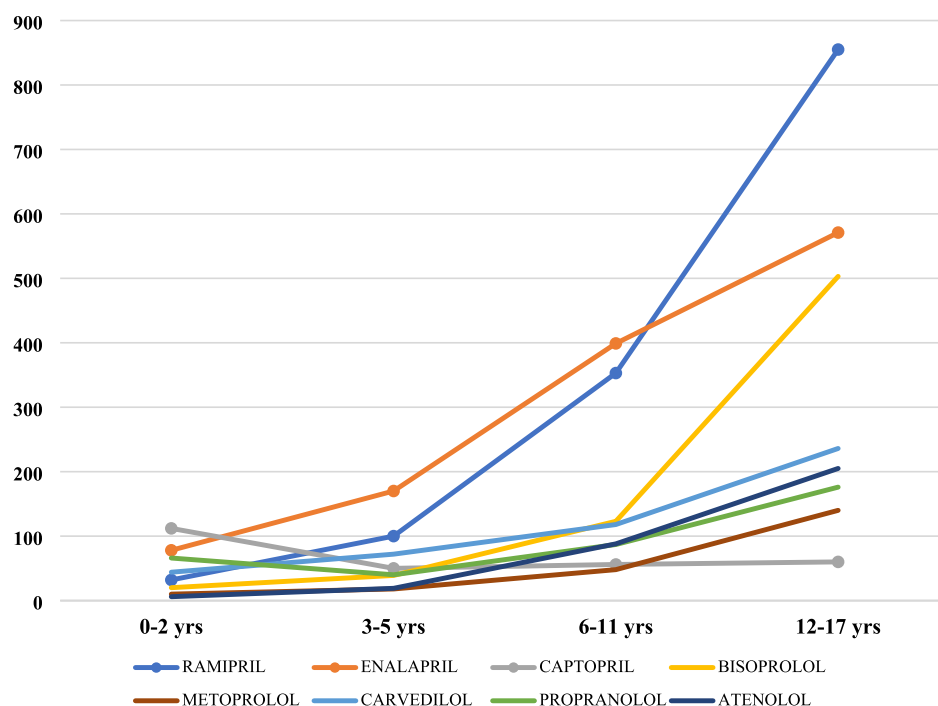
was not stopped for AE while 2 patients withdrew due to AE in the atenolol arm [AT5.6].

Twenty-two full texts focused on propranolol were considered for this manuscript.

One authorised indication for propranolol in adults is the prophylaxis of migraine which is also evaluated for pediatric use in five of the full texts selected [AT5.27–31]. Propranolol shows efficacy for the treatment of migraine and cyclic vomiting syndrome in children.

Four full texts focus on premature retinopathy (ROP) [AT5.32–35], a proliferative vitreo retinopathy, one of the most frequent causes of blindness in preterm infants. Possible AE attributed to oral propranolol raises concerns regarding the systemic administration of this drug.

One review focused on the possible use of propranolol for the reduction of the metabolic response following burn injures [AT5.36].

Three full texts evaluated the effects of propranolol for the primary prophylaxis in cirrhotic children and adolescents with portal hypertension and for thrombocytopenia. [AT5.38–40].

Four full texts consider the use of propranolol for supraventricular tachycardias compared to digossin also in combination with other antiarrythmics [AT5.41–44].

One manuscript on hypertrophic cardiomyopathy evaluating the use of beta blockers as first choice treatment in children [AT5.45].

One study evaluates the effect of propranolol on neuroblastoma, suggesting efficacy of the betablocker in this condition, in association to other treatments [AT5.46].

Another possible use of propranolol is studied for lymphatic malformations although not all patients benefit from this treatment [AT5.47]. Another use under evaluation for propranolol could be for the treatment of Paroxysmal Sympathetic Hyperactivity (PSH); the results are encorauging but more studies are needed in order to assess the possible remission of PSH [AT5.48].

Step 5.

For the same molecules selected, a research of ongoing CTs was conducted.

Eight ongoing CTs for ACE-Is and 27 for beta blockers (Supplementary table S2).

Three on ramipril: two investigate the use for Alport syndrome and the other one is on spontaneous Coronary Artery Dissection (SCAD).

Three on enalapril focus on the effect for pediatric heart failure, hypertension secondary to kidney transplant, atherosclerosis and lupus nephritis.

Two on captopril focus on the prevention of chemotherapy induced cardiotoxicity in children with bone tumors and acute myeloid leukemia and prevention of asymptomatic cardiovascular insult in Type 1 diabetic children.

Four on carvedilol: effect of carvedilol on exercise performance in Fontan patients and also in preventing heart failure in childhood cancer survivors, assessment of severity of portal hypertension and reversal of ventricular remodeling in childhood cancer survivors at risk for congestive heart failure (PREVENT-CHF).

Fig. 4 Most frequently prescribed cardiological active substances-ATC C, in 2015 from the OsMed database
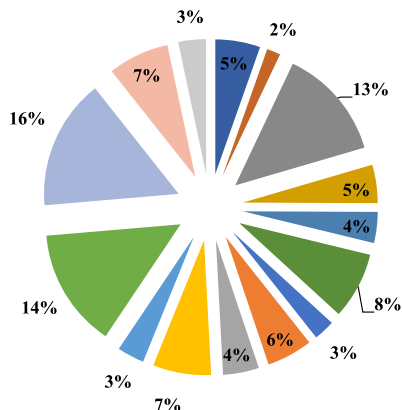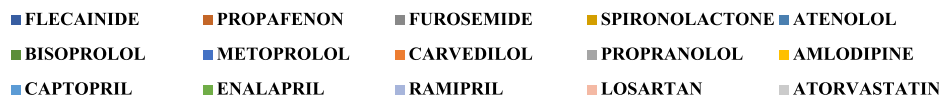
Fig. 5 ACE-I and Beta blockers agents: Study flow diagram
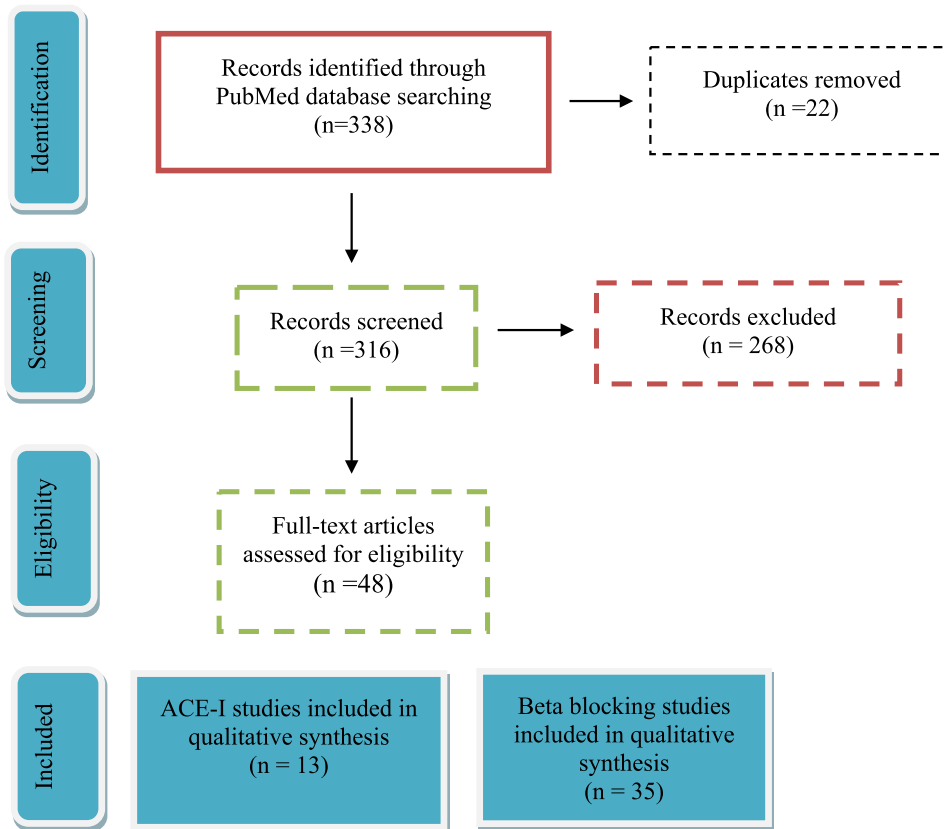
Twenty on propranolol: two on autism and spectrum disorder, six on infantile hemangioma and Kaposiform Hemangioendothelioma, one on ROP, one on reducing pediatric dental patients anxiety, three for severely burned children, two on pregnancy, one in lymphedema, one for metronomic treatment in children and adolescents with recurrent or progressive high risk neuroblastoma, one for variceal rebleeding in cirrhotic patients, one for hortostatic hypotension and one for hypertension secondary to kidney transplant.

Two on atenolol for hemangioma.

One on metoprolol on burned children.

For bisoprolol there are no ongoing CTs on *clinicaltrial.gov* at the time the research was conducted.

4 Discussion and Conclusions

Data on pediatric prescriptions in Italy for 2015, collected throught the national database OsMed divided on the ATC level, showed that the highest number of prescribed molecules belonged to the cardiovascular system. Among the most prevalent therapeutic categories of the ATC C, our study focused on eight molecules, three of which ACE-Is (ramipril, enalapril and captopril) and five beta-blockers (propranolol, atenolol, metoprolol, misoprolol and bisoprolol), involving approximately 4.900 patients.

These molecules show no pediatric authorization for the prescribed formulation and/or for the prescribed indication, showing that they are used *off-label* as confirmed throught an analysis of the SmPC.

Propranolol is authorized for the pediatric population as oral solution, but for the purpose of this study, we only considered the tablet formulation as prescribed in Italy, which is used *off-label*.

The analysis of the published studies has highlighted how the selected molecules could be used for a wide range of indications in real life, even for rare diseases and the analysis of the ongoing CTs showed, in same cases, the existence of clinical evidence supporting the use in this population.

ACE Inhibitors

Ramipril show two main possible uses in paediatrics for which is considered effective and safe: proteinuric nephropathies plus losartan [AT5.1] and post heart transplant vasculopathy [AT5.2]. Another emerging area concerns the treatment of Alport syndrome, a rare genetic condition for which ongloing studies are found suggesting future authorization developments.

Enalapril and captopril *off-label* are comprise in the Law 648/96 lists for arterial hypertension, heart failure and proteinuria.

Literature on enalapril is focused on the treatment of univentricular heart and as a support for the Fontan procedure, for which it could, however, be uneffective [AT5.3], as well as for the treatment of anthracycline cardiotoxicity [AT5.4,5]. In patients with aortic coarctation, enalapril showed efficacy in the reduction of LVMI, however, it has caused AE that led to discontinuation [AT5.6]. It also showed efficacy in reducing proteinuria, suggesting renoprotection in proteinuric kidney disease [AT5.10,11] and as for ramipril plus losartan has been studied for proteinuric nephropathies but is associated with potentially life-threatening serious AE [AT5.7].

Studies are ongoing investigating the use of ramipril and enalapril in different cardiological area (pediatric heart failure and hypertension secondary to kidney transplantation), and evaluating their use in atherosclerosis and lupine nephritis.

Literature on captopril is related to hemangiomas where, however, propranolol has a indication of use in the oral liquid formulation [AT5.8]. Captopril is effective in reducing urinary chemokine levels associated with obesity and contributing to the pathogenesis of hypertension [AT5.9]. Studies ongoing with captopril are focused on the prevention of cardiotoxicity related to chemotherapy and the cardioprotective action of captopril, simvastatin and levocarnitine in patients with type I diabetes.

There is little information on safety. Furthermore, the products are not always used in the formulation issued by the marketing authorization holder, therefore studies concerning the formulation and dosage manipulation have not been considered.

Nevertheless, the profile of highlighted AE requires further study. For enalapril, the literature reports hyperkalaemia (13%), increased serum creatinine (5%), hypotension (4%) and death (0.5%) in infants (first 120 days of life). Other published studies confirmed a higher risk of renal ADRs with enalapril when used in pediatric compared to all other medicines and to adults [AT5.12,13]. A similar safety profile for nephrotoxicity aspects is also evident for captopril [AT5.12].

Beta Blockers

After ACE-I, beta-blockers are the most prescribed (2,058 patients) with bisoprolol, atenolol,metoprolol, propranolol and carvedilol.Only propranolol is authorized for childhood hemangiomas in a different formulation than that prescribed in 2015. Although bisoprolol is the most prescribed molecule, it is not present in the Law 648/96 lists, while metoprolol, carvedilol and propranolol are reimbursed for arterial hypertension, whereas metoprolol is reimbursed for heart failure and propranolol for heart disease, arrhythmias, hyperthyroidism, migraine prophylaxis, portal hypertension at risk of varicose veins. Literature and ongoing CTs focus mostly on propranolol. Propranolol in adults is authorized for the prophylaxis of migraine also evaluated for pediatric use [AT5.30]. Other studies have evaluated its efficacy, safety and tolerability in comparison with pregabalin, topiramate and flunarizine, concluding that topiramate is more effective than propranolol, and that topiramate and propranolol are more effective than flunarizine [AT5.27–29].

Ongoing studies focus on ROP, a proliferative vitreo retinopathy, one of the most frequent causes of blindness in preterm infants. However, AE attributed to oral propranolol raise concerns on systemic use [AT5.32–36].

Metronomic treatment with low doses of chemotherapy, anti-angiogenetic and immunomodulating drugs for neuroblastoma are other area studied. Results have shown activity for propranolol and therefore that it could be considered in combination treatments [AT5.46]. Supraventricular tachycardia, hypertension due to paroxysmal sympathetic hyperactivity and portal hypertension are also considered.

Furthermore, the mechanisms underlying the use of propranolol in burn hypermetabolism are attributable to the increased efficiency of muscle protein synthesis [AT5.37]. Studies currently ongoing with propranolol are related to approaches in the field of autistic spectrum in combination with intensive behavioral intervention, in ROP, in patients with burn injuries, in a rare vascular neoplasia (Kaposiforme hemangioendothelioma) and neuroblastoma.

Bisoprolol [AT5.14,15] and carvedilol [AT5.16] are studied for heart failure in congenital pediatric heart disease, hypertension and ventricular systolic dysfunction. As for bisoprolol there are no active studies, while there are studies for carvedilol in portal hypertension, in heart failure in patients who have had a Fontan intervention to the heart and in preventing heart failure in cancer survivors exposed at high doses of anthracyclines.

Atenolol in comparison with propranolol in proliferative and ulcerative hemangiomas demonstrated efficacy and safety [AT5.20,23,24] as for Marfan syndrome, a rare connective tissue disease, involving heart and blood vessels, ligaments and skeletal system, eyes and lungs [AT5.25,26].

One suspected ADR related to propranolol was recorded in 2015 despite a population considered of approximately 4.900 patients. Though wide use could suggest an acceptable safety profile, the safety analysis indicates a possible underreporting, also considering that *off-label* use is more likely to be implicated in ADR occurring [16]. This implies that awareness and information campaigns would be appropriate to stimulate adequate reporting.

The present study has some limitations: although the *off-label* use is proven, there is still missing information on the actual indication of use from the data collection. Currently this information cannot be extrapolated from the available databases. However, this information could be monitored in the future, if systematic monitoring is started. A further limitation is the absence of prescription data referring to hospital drugs whose *off-label* use may be of economic and financial interest, in addition to scientific relevance, due to the impact on the NHS expenditure.The study demonstrates that pediatric patients are still treated in an *off-label* setting even when in accordance to international guidelines which nonetheless implies the resposability of the treatments on clinicians.

In reviewing the number of drugs with pediatric labeling, pediatric indications, and/or pediatric dosing recommendations, it is clear that a prescriber's choice of agents might be significantly limited if only agents with labeling, indications and dose recommendations were used [17].

This is due to the fact that the majority of the drugs used in this population are currently off-label, which means that they are not authorized by the regulatory agency for use in pediatrics. The clinical choices for the treatment of this population respresents, after a patient based clinical appropriate assessing an essential approach to field the gap of an important unmet medical need, but cannot be only the a clinician responsibility that of using *off-label* drugs.

A multi-pronged approach is needed and a proficuous debate could help develop paths of shared responsabilties among all interested parties.

In this context, this pilot study could be a useful track opener to consolidate a monitoring activity and also for prescribers and other healthcare professionals during their daily clinical practice supporting awareness of *off-label* use in pediatrics.

Appendix

See Tables 1, 2, 3, 4 and 5.

Table 1 Age and gender distribution in the study sample

Age (years)	Male (n)	Female (n)	Male + Female (n)	%
0	59.193	47.084	106.277	2.9
1	172.403	136.313	308.716	8.3
2	164.122	134.412	298.534	8.0
0–2 y	**395.718**	**317.809**	**713.527**	**19.1**
3	176.255	152.711	328.966	8.8
4	184.249	161.514	345.763	9.3
5	161.636	139.750	301.386	8.1
3–5 y	**522.140**	**453.975**	**976.115**	**26.2**
6	134978	113.711	248.689	6.7
7	110.810	92.997	203.807	5.5
8	103.629	85.375	189.004	5.1
9	96.456	80.342	176.798	4.7
10	100.239	81.703	181.942	4.9
11	95.403	76.612	172.015	4.6
6–11 y	**641.515**	**530.740**	**1.172.255**	**14.2**
12	85.944	69.347	155.291	4.2
13	83.092	64.684	147.776	4.0
14	77.697	60.118	137.815	3.7
15	75.840	63.667	139.507	3.7
16	73.868	67.267	141.135	3.8
17	72.679	70.483	143.162	3.8
12–17 y	**469.120**	**395.566**	**864.686**	**11.4**
Total	**2028.493**	**1698.090**	**3726.583**	**100**

Table 2 Most commonly prescribed medications in the study sample, belonging to ATC C

3rd level ATC		% Male (n)	% Female (n)	0–2 y	3–5 y	6–11 y	12–17 y	% Male + Female (n)	DDD	DDD (%)
C09A	Ace inhibitors, plain	59 (1677)	41 (1159)	8 (222)	11 (320)	28 (808)	52 (1486)	33 (2836)	459.409	49%
C07A	Beta blockers agents	56 (1151)	44 (907)	7 (146)	9 (188)	23 (464)	61 (1260)	25 (2058)	124.975	13%
C03C	High-ceiling diuretics	53 (612)	47 (536)	30 (345)	17 (192)	24 (282)	29 (329)	13 (1148)	93.961	10%
C08C	Selective calcium channel blockers with mainly vascular effects	60 (361)	40 (236)	6 (38)	12 (73)	29 (171)	53 (315)	7 (597)	84.140	9%
C01B	Antiarrhythmics	53 (317)	47 (284)	7 (44)	11 (67)	33 (200)	48 (290)	7 (601)	70.969	8%
C09C	Angiotensin II receptor blockers (arbs), plain	63 (398)	37 (229)	1 (4)	7 (46)	32 (200)	60 (377)	7 (627)	62.936	7%
C03D	Potassium-sparing agents	30 (117)	70 (276)	15 (58)	12 (49)	15 (59)	58 (227)	5 (393)	27.401	3%
C10A	Lipid modifying agents, plain	51 (144)	49 (140)	8 (22)	13 (38)	21 (61)	57 (163)	3 (284)	20.245	2%
Pediatric patients		**56 (4777)**	**44 (3767)**	10,3 (879)	11,3 (973)	26.3 (2245)	52 (4447)	**100 (8544)**	**944.037**	**100%**

Table 3 Number of pediatric patients treated divided per molecule, gender and age

Active substance	Number of patients	Males	Females	0–2 yrs	3–5 yrs	6–11 yrs	12–17 yrs
Ramipril	1340	809	531	32	100	353	855
Enalapril	1218	713	505	78	170	399	571
Captopril	278	155	123	112	50	56	60
Bisoprolol	685	380	305	20	39	123	503
Carvedilol	470	273	197	44	72	118	236
Propranolol	369	177	192	66	40	87	176
Atenolol	318	196	122	6	19	88	205
Metoprolol	216	125	91	10	18	48	140

Table 4 Most prescribed active substances belonging to ATC C divided according to gender

ATC	Pharmacological cathegory	Active substance	M	F	TOT.	%
C03B	Antiarrhythmics	Flecainide	252	209	461	5,4%
		Propafenone	65	75	140	1,6%
C03C	Higher acting diuretics	Furosemide	612	536	1148	13,4%
C03D	Potassium-sparing agents	Spironolactone	117	276	393	4,6%
						0,0%
C07A	Beta blockers agents, selective	Atenolol	196	122	318	3,7%
		Bisoprolol	380	305	685	8,0%
		Metoprolol	125	91	216	2,5%
	Alfa and beta-adrenegic receptors	Carvedilol	273	197	470	5,5%
	Beta blockers agents, non selective	Propranolol	177	192	369	4,3%
C08C	Selective blockers calcium channels with prevalent vascular effect	Amlodipine	361	236	597	7,0%
						0,0%
C09A	ACE-Inhibitors	Captopril	155	123	278	3,3%
		Enalapril	713	505	1218	14,3%
		Ramipril	809	531	1340	15,7%
C09C	Angiotensine II antagonists	Losartan	398	229	627	7,3%
C10A	HMG-CoA reductase inhibitors	Atorvastatin	144	140	284	3,3%

Table 5 Research of published studies on ACE-I and on beta blockers agents

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
RAMIPRIL + ENALAPRIL	1	Ruggenenti P. et al. *Achieving remission of proteinuria in childhood CKD.* Pediatr Nephrol. 2017 Feb;32(2):321–330.	Observational, longitudinal, cohort study	Proteinuric chronic nephropathies	Ramipril and losartan 2.48±1.37 mg/m² and 0.61±0.46 mg/kg daily	–	20 children; mean (±SD) age at inclusion was 13.8±2.8 years	Combination therapy with maximum approved doses of ACE inhibitors and ARBs may achieve proteinuria remission with kidney function stabilization or even improvement in a substantial proportion of children with proteinuric nephropathies and is safe.
	2	Fearon WF. et al. *Angiotensin-Converting Enzyme Inhibition Early After Heart transplantation.* J Am Coll Cardiol. 2017 Jun 13;69(23):2832–2841	Multicenter, double-blind, randomized clinical trial	Cardiac allograft vasculopathy (CAV) after HT	Ramipril mean dosage 13.8 ± 7.7 mg	Placebo-controlled trial	96;7 pediatric patients (12 to 19 years old)	Ramipril does not slow development of epicardial plaque volume but does stabilize EPC levels and improve microvascular function, which have been associated with improved long-term survival after HT.
ENALAPRIL	10	Hari P. et al. *Effect of enalapril on glomerular filtration rate and proteinuria in children with chronic kidney disease: a randomized controlled trial.* Indian Pediatr. 2013 Oct;50(10):923–8. Epub 2013 Mar 5.	Open-label, single-center, randomized controlled trial	Treatment on decline in glomerular filtration rate and reduction in proteinuria in children with chronic kidney disease	Enalapril single bedtime dose of 0.4 mg/kg	Placebo	41; 20 (8.4 ± 4.3) enalapril, 21(9.5 ± 4.7) no enalapril	Enalapril is effective in reducing proteinuria in children with CKD and might be renoprotective in proteinuric CKD.

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
	7	Sakalli H. et al. *Acidosis and hyperkalemia caused by losartan and enalapril in pediatric kidney transplant recipients*. Exp Clin Transplant. 2014 Aug;12(4):310–3.	Retrospective analysis (losartan and enalapril)	Hypertension, and proteinuria after kidney transplant	31 pt losartan (50 mg/d, oral) + enalapril (5 or 10 mg daily, oral) and 12 patients (39%) also were treated with amlodipine (5 or 10 mg daily, oral).		31; 14 ± 4 (4 to18)	Losartan and enalapril may be beneficial in pediatric kidney transplant recipients by decreasing blood pressure and proteinuria, with maintenance of stable graft function, but may be associated with serious adverse events including hyperkalemia and life-threatening acidosis.
	4	Franco VI, Lipshultz SE. *Cardiac complications in childhood cancer survivors treated with anthracyclines*. Cardiol Young. 2015 Aug; 25 Suppl 2:107–16	Review: 1.Silber JH et al. *Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines*. J Clin Oncol 2004; 22: 820–828. 2. Lipshultz SE et al. *Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer*. J Clin Oncol 2002; 20: 4517–4522).	Treatment for cardiac problems caused by anthracy-cline chemotherapy for childhood cancer		Placebo		1. One study found that treatment with enalapril resulted in an early decrease in left ventricular end systolic wall stress; 2. However, Lipshultz et al. found that these beneficial effects of enalapril on the cardiac function were transient and were largely related to how changes in blood pressure reduced left ventricular wall stress. 3 Thus, the long-term effects of enalapril as a cardio protectant are yet to be determined.

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
	6	Di Salvo G. et al. *Atenolol vs enalapril in young hypertensive patients after successful repair of aortic coarctation. J Hum Hypertens.* 2016 Jun;30(6):363–7.	Single-centre, prospective, randomized, open-label study	Hypertension patients after successful repair of aortic coarctation	Atenolol 0.5–2mg/kg, once a day) or enalapril (0.08–0.6mg/kg, once a day)	Atenolol	51 patients (13± 3.9 years, age range: 6–20 years;	Enalapril, significantly reducing 24-h SBP and LVMI, two factors generally associated with increased cardiovascular morbidity and mortality, should be the preferred treatment for hypertensive young patients after successful repair of isolated AoC.
	3	Oldenburger NJ. et al. *Drug therapy in the prevention of failure of the Fontan circulation: a systematic review.*Cardiol Young. 2016 Jun;26(5):842–50.	Systematic review (only one RCT -cross-over, double-blinded, placebo-controlled)	Prevention of failure of the Fontan circulation	Enalapril (0.2–0.3 mg/kg daily (max 15 mg))	Placebo	21 (14.5 ± 6.2 (8–27)	No change in blood pressures, HR, respiratory rates, VO2 max, or O2 saturations Side-effects: no difference in enalapril versus placebo.
	5	Cheuk DK. et al. *Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer.* Cochrane Database Syst Rev. 2016 Aug 23;(8):CD008011.	Review (RCT o CT): 1.Silber JH et al. *Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines.* J Clin Oncol 2004; 22: 820–828.	Treatment for cardiac problems caused by anthracycline chemotherapy for childhood cancer	0.093 mg/kg/d for enalapril patients and 0.1 mg/kg/d for placebo patients	Placebo	135; ≤ 18 ys	The drug had no significant beneficial effect on important outcomes and was associated with side effects such as dizziness and fatigue.
	13	Ku LC. et al. *Safety of Enalapril in Infants Admitted to the Neonatal Intensive Care Unit.* Best Pharmaceuticals for Children Act—Pediatric Trials Network Steering Committee. Pediatr Cardiol. 2017 Jan;38(1):155–161.	Retrospective study	Safety of enalapril in young infants		–	662 infants; median gestational age 30 weeks (25th, 75th percentiles: 27, 36)	The overall risk for AEs and the risks for hyperkalemia and elevated serum creatinine associated with enalapril exposure are greatest during postnatal ages <30 days and with longer exposures after controlling for gestational age

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
ENALAPRIL + CAPTOPRIL	12	Lindle KA. et al. *Angiotensin-converting enzyme inhibitor nephrotoxicity in neonates with cardiac disease.* Pediatr Cardiol. 2014 Mar;35(3):499–506.	Retrospective analysis (enalapril and captopril) of clinical databases	Nephrotoxicity	Enalapril: 0.08 ± 0.007 mg/kg preterm; 0.08 ± 0.003 terms. Captopril: 0.07 ± 0.009 mg/kg preterm n and 0.13 ± 0.019 mg/kg term neonates		206; age (days) preterm (17.0 ± 1.1) term(16.4 ± 0.5)	Nearly 42 % of all patients showed renal risk, with approximately 30 % demonstrating renal failure. The premature neonates were more likely to experience ACEi-related renal failure
	11	Ghazi P. et al. *Hypotension as the etiology for angiotensin-converting enzyme (ACE) inhibitor-associated acute kidney injury in pediatric patients.* Pediatr Cardiol. 2014 Jun;35(5):767–70.	Case–control study (1:4) (enalapril and captopril)	Hypotension between patients with acute kidney injury		–	100; age pt 6.5 (1.6–186) control 5.8 (1.4–185)	Pediatric patients who experience ACE inhibitor-associated AKI have a significantly greater decrease in blood pressure than patients who do not experience such injury.

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
CAPTOPRIL	9	Övünç Hachamdioğlu D. et al. *Elevated Urinary T Helper 1 Chemokine Levels in Newly Diagnosed Hypertensive Obese Children.* J Clin Res Pediatr Endocrinol. 2015 Sep;7(3):175–82.	Prospective study	Hypertension in obesity children	Captopril in a dose of 12.5 mg every 12 hours, titrated as needed, with a maximum daily dose of 100 mg	The hypertensive obese group was divided into two subgroups, patients treated with captopril ($n=9$) and controlled using lifestyle changes only ($n=15$).	73; Twenty-four hypertensive obese (mean age 13.1), 27 healthy (mean age 11.2) and 22 non-hypertensive obese (mean age 11.5) children	The results of this study suggest that Th1-mediated inflammation is active in children with obesity and hypertension, and that antihypertensive therapy involving captopril and/or lifestyle changes can reverse this condition.
	8	Zaher H. et al. *Propranolol versus captopril in the treatment of infantile hemangioma (IH): A randomized controlled trial.* J Am Acad Dermatol. 2016 Mar;74(3):499–505. 2015 Dec 11.	Double-blind, randomized clinical trial	Treatment of infantile hemangioma (IH)	Propranolol at a dose of 2 mg/kg/d Captopril at a dose of 0.5 to 1 mg/kg/d.	Propranolol	65; 30 1–14 months [mean 6.36–3.27 months]-35 1.5–13 months [mean 5.86–2.98 months]	Propranolol shows greater benefit than captopril in the treatment of IH. No serious side effects were experienced by any patient in the propranolol group; mild diarrhea occurred in 3 patients and was managed accordingly. Four patients in the captopril group showed signs suggestive of cardiac side effects (hypotension,dizziness) on follow-up examination.

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
BISOPROLOL + METOPROLOL	14	Chaturvedi S. et al. *Pharmacological interventions for hypertension in children.* Cochrane Database Syst Rev. 2014 Feb 1;(2):CD008117.	Review (21 RCT)	Hypertension	Combination bisoprolol and hydrochlorothiazide (2.5mg or 10mg plus 6.25 mg) (Sorof 2002); Extended-release metoprolol 0.2mg/kg to2.0mg/kg (Batisky2007).	Placebo	94 pt bisoprolol/ hydrochlorothiazide 140 patients metoprolol; 1–18 years	Beta blocker/diuretic combination (Bisoprolol/hydrochlorothiazide,one trial, *n* =94)when compared with placebo, did not result in a significant reduction in systolic blood pressure but did have an effect on diastolic blood pressure. Metoprolol when compared with placebo significantly reduced systolic blood pressure but not diastolic blood pressure (low-quality evidence).
BISOPROLOL + CARVEDILOL+METOPROLOL	15	Cho MJI. *Effects of beta-blockers for congestive heart failure in pediatric and congenital heart disease patients: a meta-analysis of published studies.* Minerva Cardioangiol. 2015 Dec;63(6):495–505.	Meta-analysis	Congestive heart failure in children				Beta blocker therapy reduces the incidence of clinical worsening and improves Left Ventricular functional parameters.
CARVEDILOL	16	Prijic S. *Beta-Blockers (Carvedilol) in Children with Systemic Ventricle Systolic Dysfunction - Systematic Review and Meta-Analysis.* Rev Recent Clin Trials. 2014;9(2):68–75.	Meta-analysis (8 prospective/observational)	Systemic Ventricle Systolic Dysfunction				Meta-analysis demonstrated clinical outcome benefit of carvedilol in children with chronic heart failure
PROPRANOLOL	27	Fallah R. et al. *Topiramate and propranolol for prophylaxis of migraine.* Indian J Pediatr. 2013 Nov;80(11):920-4	Single-blinded randomized clinical trial	Prophylaxis of Migraine	50 treated with 3 mg/kg/d of topiramate (TPM) and another group of 50, were treated with 1 mg/kg of propranolol	Topiramate	100; 10,34 ± 2,31 years	Topiramate is more effective than propranolol for pediatric migraine prophylaxis

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
	45	Östman-Smith I. *Beta-Blockers in Pediatric hypertrophic cardiomyopathies. Rev Recent Clin Trials. 2014;9(2):82–5.*	Review	Hypertrophic Cardiomyopathies	>4.5 mg/kg/day propranolol			Beta-blocker therapy is without any doubt the treatment of choice for patients with heart failure caused by hypertrophic cardiomyopathy, but the dose needs to carefully titrated on an individual basis for maximum benefit. The dose required is surprisingly large in infants with heart failure due to HCM
	40	Hornik CP. et al. *Comparative effectiveness of digoxin and propranolol for supraventricular tachycardia in infants.* Pediatr Crit Care Med. 2014 Nov;15(9):839–45.	Retrospective cohort study	Supraventricular tachycardia	Digoxin ranged between 4 mcg/kg/day to 12 mcg/kg/day for 95% of all infants, while propranolol was ≥3 mg/kg/day	Digoxin	342 infants exposed to digoxin and 142 infants exposed to propranolol	In hospitalized infants with SVT without pre-excitation or significant congenital heart disease, SVT recurrence was more common when infants received prophylaxis with propranolol compared with digoxin.
	28	Topcu Y. et al. *The Paediatric migraine disability assessment score is a useful tool for evaluating prophylactic migraine treatment.* Acta Paediatr. 2014 Nov;103(11): e484–9.	Observational	Prophylaxis of Migraine	Propranolol 20–40 mg/day (10 pt); flunarizina 5–10mg/day (13pt); topiramate 1–2mg/kg/Day(18pt)	35 control no treatment	44 treated and 35 control. 88; aged between 6-17 years.	Topiramate, propranolol and flunarizine significantly decreases PedMISAS

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
	32	Bührer C, Bassler D. *Oral Propranolol: A New Treatment for Infants with Retinopathy of Prematurity?* Neonatology. 2015;108(1):49–52.	Review (a.Makhoul IR, et al. Oral propranolol versus placebo for retinopathy of prematurity: a pilot, randomised, double-blind prospective study. Arch Dis Child 2013; 98: 565–567. b. Filippi L, et al. Oral propranolol for retinopathy of prematurity: risks, safety concerns, and perspectives. J Pediatr 2013; 163: 1570–1577.	Treatment for Infants with Retinopathy of Prematurity	a. propranolol (starting dose: 0.5 mg/kg/day, divided in 3 doses, incrementally increased to 1.5 mg/kg/day) or placebo b. 2 mg/kg/ day in 4 divided doses in infants 26–31 weeks' gestational age at birth; 1 mg/kg/day in 4 divided doses in infants 23–25 weeks' gestational age	Placebo	20 infants with a gestational age of 24–28 weeks 2 preterm infants with a gestational age of 23–31 weeks	So far, therapies for proliferative retinopathies have been based on local interventions, and exploring the possibilities of systemically administered drugs has become an exciting area of research. Hopefully, it will also lead to improved long-term outcome of infants with ROP.
	36	Núñez-Villaveirán T. et al. *Systematic review of the effect of propranolol on hypermetabolism in burn injuries.* Med Intensiva. 2015 Mar;39(2):101–13.	Review	Burn injuries	Propranolol (4–6 mg/kg/day p.o.)			Propranolol reduces the hypermetabolic response. In pediatric burn patients.
	29	Bakhshandeh Bali M. et al. *Comparison of propranolol and pregabalin for prophylaxis of childhood migraine: a randomised controlled trial.* Acta Med Iran. 2015;53(5): 276–80.	Randomized clinical trial	Prophylaxis of Childhood Migraine	Pregabalin (PGB) capsules (50 to 75 mg/day) and Propranolol (PRL) tablets with a dose of 10 to 20 mg/day divided in 2 doses	Pregabalin	99 children; 46 pregabalin from 5 to 15 years (mean, 9.95±2.4 years) and 45 patients age ranging from 5 to 15 years (mean, 9.81±2.7 years).	There was a significant difference between these two groups according to headache frequency reduction (P=0.04). Pregabalin efficacy in reducing the frequency and duration of pediatric migraine headache is considerable in comparison with propranolol.

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
	37	El-Karaksy HM. Et al. *Extrahepatic portal vein obstruction in Egyptian children.* J Pediatr Gastroenterol Nutr. 2015 Jan;60(1):105–9.	Observational study	Extrahepatic portal vein obstruction	The median starting dose was 15 (IQR 10) mg/day. The median adjusted dose was 1 (IQR0.3) mg/kg		69 patients. 1 month to 12 years (median 2.5 years, interquartile range 5);	This large study demonstrates the efficacy of propranolol in the reduction of gastrointestinal bleeding in children with EHPVO.
	41	Barton AL. et al. *Efficacy and safety of high-dose propranolol for the management of infant supraventricular tachyarrhythmias.* J Pediatr. 2015 Jan;166(1):115–8. 101.	Retrospective cohort study	Supraventricular tachycardia	Propranolol total daily dose of 3.6 ± 1.0 mg/kg/day.	Digoxin	287; Patients <1 year of age	High-dose propranolol is safe and reasonably successful in the treatment of infant SA. Inpatient control may be a predictor of continued outpatient efficacy.
	38	Poddar U. et al. *β-Blocker therapy ameliorates hypersplenism due to portal hypertension in children.* Hepatol Int. 2015 Jul;9(3):447–53.	CT	Hypersplenism due to portal hypertension	Long-acting propranolol (1.5–2 mg/kg/day).		51 consecutive children (mean age 11.5 ± 3.0 years)	Propranolol corrects thrombocytopenia and makes liver biopsy possible in almost two-thirds of cases by reducing splenic sequestration through splenic artery vasoconstriction.
	42	Moffett BS. Et al. *Efficacy of digoxin in comparison with propranolol for treatment of infant supraventricular tachycardia: analysis of a large, national database.* Cardiol Young. 2015 Aug;25(6):1080–5.	Comparative study	Supraventricular tachycardia	Dose ranging from 1 to 4mg/kg/ day divided every 6–8 hours. High doses (13mg/kg/day)	Digoxin	374; neonates	Digoxin or propranolol may be equally efficacious for inpatient treatment of infant supraventricular tachycard
	47	Definet AM. *Pediatric lymphatic malformations: evolving understanding and therapeutic options.* Pediatr Surg Int. 2016 May;32(5):425–33.	Review	Lymphatic malformations	-			Propranolol is routinely used for infantile hemangiomas, and recent studies have shown its efficacy in the treatment of some LMs, although not all patients respond to treatment

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
	39	Pimenta JR. et al. *Evaluation of primary prophylaxis with propranolol and elastic band ligation in variceal bleeding in cirrhotic children and adolescents.*Arq Gastroenterol. 2016 Oct-Dec;53(4):257–261.	Cohort study	Primary prophylaxis with β-blocker in cirrhotic children and adolescents with portal hypertension	The dosage of propranolol used at the pediatrics studies were 1 mg/kg/day to 2 mg/kg/day	-	26 cirrhotic patients median of 7.9 years old (25%–3 / 75%–13–17 started beta blocker prophylaxis	All of the patients that had upper gastrointestinal bleeding in this study were under propranolol prophylaxis. The use of propranolol showed a high number of contraindications and side effects, requiring referral to endoscopic prophylaxis.
	33	Korkmaz L. et al. *The Efficacy of Propranolol in Retinopathy of Prematurity and its Correlation with the PlateletMass Index.* Curr Eye Res. 2017 Jan; 42(1):88–97.	Randomized clinical trial	Rethinopathy of prematurity	0,5mg/ Kg/6 hours	Normal Saline	171 preterm neonates divided in three Rop group (stage 0, 56; stage 1, 62; stage 2, 53)	No significant differences between control group and propranolol in stage 0–1; in stage 2 a significant difference was found in terms of PMI value
	48	Pozzi M. *Paroxysmal Sympathetic Hyperactivity in Pediatric Rehabilitation: Pathological Features and Scheduled Pharmacological Therapies.*J Head Trauma Rehabil. 2017 Mar/Apr;32(2):117–124.	Retrospective cohort study.	Paroxysmal Sympathetic Hyperactivity	Average dose, mg/kg per day NR (1.12 ± 0.99) remission (1.28 ± 1.01)		23	Results should be interpreted carefully regarding causal relationships and drug doses and combinations, but they encourage further studies on the use of propranolol and diazepam to favor PSH remission.
	43	Bolin EH. Et. al. *Propranolol Versus Digoxin in the Neonate for Supraventricular Tachycardia (from the Pediatric Health Information System).* Am J Cardiol. 2017 May 15;119(10):1605–1610.	Retrospective cohort study	Supraventricular Tachycardia		Digoxin	2,657 neonates identified with a median gestational age of 37 weeks (interquartile range 34 to 39).	The use of propranolol is associate with greater survival compared with digoxin

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
	46	Berthold F. *Metronomic therapy has low toxicity and is as effective as current standard treatment for recurrent high-risk neuroblastoma.* Pediatr Hematol Oncol. 2017 Aug;34(5):308–319.	CT	Neuroblastoma			23;	Results suggest propanolol having an effect on NB. Thus, propanolol could be considered in combination treatment on patientes with NB.
	34	Sanghvi KP. et al. *Prophylactic propranolol for prevention of ROP and visual outcome at 1 year (PreROP trial).* Arch Dis Child Fetal Neonatal Ed. 2017 Sep;102(5): F389–F394.	Randomized clinical trial	Prevention of retinopathy of prematurity (ROP)	Propranolol prophylaxis (0.5 mg/kg/ dose every 12 hours)	Placebo	109 preterm neonates of ≤32 weeks of gestation with postnatal age ≤8 days old.	Prophylactic propranolol in the prescribed dose of 1 mg/kg/day showed a decreasing trend in all outcomes of ROP though statistically not significant.
	35	Kaempfen S. et al. *Beta-blockers for prevention and treatment of retinopathy of prematurity in pretermin fants.* Cochrane Database Syst Rev. 2018 Mar 2;3.	Meta-analysis (three randomised trials) a.Sanghvi KP. et al. 2017; b.Korkmaz L. et al. 2017; c.Filippi L, et al)	Prevention and treatment of retinopathy of prematurity (ROP)	a. Propranolol prophylaxis (0.5 mg/kg/ dose every 12 hours) b. 0,5mg/ kg/6hours c. 2 mg/kg/day in 4 divided doses in infants 26–31 weeks' gestational age at birth; 1 mg/ kg/day in 4 divided doses in infants 23–25 weeks' gestational age	Placebo or no treatment	366; preterm babies.	Prophylactic oral administration of beta-blockers compared to placebo or no treatment may reduce the risk of progression to stage 3 ROP in preterm infants without ROP or confirmed stage 2 or lower ROP without plus disease and may decrease the risk of requiring laser therapy or anti-VEGF agents.

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
	30	Donnet A, Redon S. *Cyclic Vomiting Syndrome in Children*. Curr Pain Headache Rep. 2018 Mar 19;22(4):30.	Review	Cyclic vomiting syndrome	It is recommended to start with low initial doses, and increase incrementally, titrating to effect			Propranolol is the second treatment showing efficacy in literature (based on Lee LY et al, The management of cyclic vomiting syndrome: a systematic review. Eur J Gastroenterol Hepatol. 2012 Sep;24(9):1001–6.)
PROPRANOLOL	31	Saito Y et al. *Reconsideration of the diagnosis and treatment of childhood migraine: A practical review of clinical experiences*. Brain Dev. 2017 May;39(5):386–394.	Review	Prophylaxis of Childhood Migraine			$n = 154$ patients (76 males and 78 females) age of ≤15 years	Possible use of propranolol for preventive therapy of migraine in children
PROPRANOLOL + ATENOLOL	44	Guerrier K, et al. *Variation in Antiarrhythmic Management of Infants Hospitalized with Supraventricular Tachycardia: A Multi-Institutional Analysis*. Pediatr Cardiol. 2016 Jun;37(5):946–52.	Retrospective study	Supraventricular Tachycardia			Propranolol (n = 234),	In this study, we found that propranolol was the most frequently prescribed antiarrhythmic medication. These findings are similar to those reported by Seslar et al. [13] and Wong et al. [10] and not unexpected given that propranolol has been proven to be a safe and effective antiarrhythmic treatment for infant SVT prophylaxis [14–16]. The study does not report data related to atenolol

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
ATENOLOL	26	Singh MN, Lacro RV. *Recent Clinical Drug Trials Evidence in Marfan Syndrome and Clinical Implications.* Can J Cardiol. 2016 Jan;32(1):66–77.	Review	Prophylactic treatment of aortic enlarge- ment in Marfan syndrome	In the Pediatric Heart Network trial some patients were responsive to doses of 1 mg/ kg/d, butoth- ers required doses as high as 4 mg/kg/d or 250 mg/d toachieve a similar heart rate response.			The Pediatric Heart Net- work trial showed that atenolol and losartan each reduced the rate of aortic dilation
	20	de Graaf M. et al. *Treat- ment of infantile hae- mangiomas with ateno- lol: comparison with a historical propranolol group.* Plast Reconstr Aesthet Surg. 2013 Dec;66(12):1732–40.	Prospective comparison of atenolol group with historical propranolol group	Infantile hemangio- mas	Atenolol from 0.5 mg/kg /day to max 3 mg/ kg/day propra- molol mean dose 3 mg/kg/ day	Propranolol	58 (28 pro- pranolol, 30 atenolol); mean age 6.4 mos	Compared with a historical control group treated with propranolol, the effects of atenolol seem to be similar and less frequently associated with severe side effects
	21	Ábarzúa-Araya A. et al. *Atenolol versus propranolol for the treat- ment of infantile heman- giomas: a randomized controlled study.* J Am Acad Dermatol. 2014 Jun;70(6):1045–9.	Randomized con- trolled trial	Infantile hemangio- mas	Atenolol from1 mg/kg/day; propranolol 2 mg/kg/day	Propranolol	23 (13 pro- pranolol, 10 atenolol); mean age 5.3 mos	Atenolol appears to bea s effective as propranolol

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
	25	Lacro RV et. *Pediatric Heart Network Investigators Atenolol versus losartan in children and young adults with Marfan's syndrome.* N Engl J Med. 2014 Nov 27;371(22):2061–71.	Randomized trial	Aortic-root dissection in Marfan's syndrome	Atenolol (at an initial dose of 0.5 mg/kg) to a maximum dose of 4.0 mg /kg. Losartan (at an initial dose of 0.4 mg/kg) to a maximum dose of 1.4 mg /kg/day	Losartan	608 participants, 6 months to 25 years of age (mean [±SD] age, 11.5±6.5 years in the atenolol group and 11.0±6.2 years in the losartan group)	Among children and young adults with Marfan's syndrome who were randomly assigned to losartan or atenolol, we found no significant difference in the rate of aortic root dilatation between the two treatment groups over a 3-year period.
	22	Bayart CB, Brandling-Bennett HA. *Beta-blockers for childhood vascular tumors.* Curr Opin Pediatr. 2015 Aug; 27(4):454–9.	Review (comprise the papers de graaf 2013 and Abarxua 2014)	Infantile hemangiomas	-			See specific papers
	23	Ji Y. et al. *Oral atenolol therapy for proliferating infantile hemangioma: A prospective study.* Medicine (Baltimore). 2016 Jun;95(24): e3908.	Prospective, single cohort	Infantile haemangiomas	Atenolol (at an initial dose of 0.5 mg/kg) to a maximum dose of 1.0 mg /kg/day		76 all treated with atenolol; 5 to 20 Weeks	Atenolol is effective and safe for 24 weeks.
	24	Bayart CB. et al. *Atenolol Versus Propranolol for Treatment of Infantile Hemangiomas During the Proliferating Phase: A Retrospective Noninferiority Study.* Pediatr Dermatol. 2017 Jul;34(4): 413—421	Retrospective noninferiority study	Infantile Hemangiomas	Initial dose of atenolol (0.25 mg/kg) administered in clinic Send home on atenolol 0.5 mg/kg/day (BID dosing)	Propranolol	80; 27 treated with atenolol and 53 with propranolol-median mos 3 (0–8)	Atenolol is at least as effective as propranolol in treating IHs.

Table 5 (continued)

Active substance	Ref.	Study reference and year of publication	Study design	Therapeutic indication	Medication (dose)	Comparator	Number of patients (and age)	Main results (as reported by authors)
METOPROLOL	17	Zhao J. et al. *Usefulness of plasma copeptin as a biomarker to predict the therapeutic effectiveness of metoprolol for postural tachycardia syndrome in children.* Am J Cardiol. 2014 Aug 15;114(4):601–5	Case control study	Postural tachycardia syndrome (POTS)	metoprolol was 0.5 mg/kg daily, twice a day	Control	49 children with POTS (7 to 16 years old) and 25 normal controls (11 to 13 years old).	The plasma copeptin level was higher in children with POTS than controls but was lower for responders than for non-responders to metoprolol therapy. Plasma copeptin is a suitable biomarker to predict the therapeutic effectiveness of metoprolol.
	18	Zhang Q. et al. *Orthostatic plasma norepinephrine level as a predictor for therapeutic response to metoprolol in children with postural tachycardia syndrome.* J Transl Med. 2014 Sep 10;12:249	Case control study	Postural tachycardia syndrome (POTS)	metoprolol was 0.5 mg/kg daily, twice a day	Control	27; mean age, 11 +/- 6 years, ranging from 6 years to 15 years	Orthostatic plasma norepinephrine level of > 3.59 pg/ml was an indicator of the effectiveness of metoprolol therapy for POTS in children and adolescents
	19	Lin J. et al. *Plasma C-type natriuretic peptide as a predictor for therapeutic response to metoprolol in children with postural tachycardia syndrome.* PLoS One. 2015 Mar 26;10(3):e0121913	Case control study	Postural tachycardia syndrome (POTS)	metoprolol (12.5 mg, twice/day)	Control	34 POTS l [aged (11.7 ± 2.0) years, 27 healthy aged (11.4 ± 1.7) years	Of great significance are the findings that plasma concentrations of CNP could predict the efficacy of metoprolol in treating POTS, which provided an important steppingstone for the individualized treatment of POTS

Declarations

Funding and Competing Interests There are no competing interests to declare. The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Availability of data and material (data transparency) The data that support the findings of this study are available from corresponding author. Restrictions apply to the availability of these data, which were used under license for this study.

Disclosure The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the Italian Medicines Agency or their Committee. LP has consulted for AbbVie USA; Acadia USA; BCG Switzerland; Boehringer Ingelheim International GmbH; Compass Pathways, UK; Ferrer Spain, EDRA-LSWR Publishing Company, Italy; Inpeco SA Lab Automation Company, Switzerland; Johnson & Johnson USA; NeuroCog Trials USA; Otsuka USA, Pfizer Global USA; PharmaMar Spain; Takeda, USA and VeraSci USA.

Authors' contributions SMC carried out the analysis on the Osmed Database data, the bibliographical search, screened studies for inclusion, recorded the motivation for the exclusion of any study considered, performed data extraction and analysis, and drafted the manuscript; GC participated in the discussion related to the selection process in case of discrepancies, checked the forms containing the data extraction, revised the manuscript. NL revised the manuscript. LP and AM provided methodological advice and revised the manuscript. All authors read and approved the final manuscript.

Ethics Statement Given the nature (not clinical) of the study, exclusively based on the administrative anonymous data with no disclosure of confidential/sensitive information, approval by an ethics committees and informed consent were not required, in accordance with the local legislation and institutional requirements.

Consent for publication Not applicable.

Consent for participate Not applicable.

Code availability Not applicable.

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